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11. REFERENCES
1. Introduction

In the 1980's and early 1990's the treatment of the critically ill patient was seen to be becoming increasingly expensive with little evidence of improvement in outcome [1]. A number of studies had however started to investigate the effects of specific treatment in some of the sickest groups of patients [2], and some of that work has now resulted in advances in the treatment of patients with adult respiratory distress syndrome [3] and sepsis and septic shock [4]. There does however appear to be a large group of critically ill patients who are excluded from this type of analysis. This group comprises an increasing number of high risk surgical cases. These are being undertaken increasingly as techniques originally pioneered in a healthy population are expanded to include patients who are more elderly with coexisting diseases. These high risk patients have a higher mortality and morbidity rate and frequently die from multiple organ dysfunction syndrome (MODS), a syndrome that once established has proved largely resistant to therapeutic intervention.

This group of high risk surgical patients therefore appeared to be a fruitful group to investigate therapeutic intervention to improve outcome. Initial studies attempted to define the features present in patients that might predict a good outcome. Studies concentrated on cardiorespiratory changes as new technology allowed these to be measured more simply by bedside techniques [5]. Subsequently, in common with other areas of critical care where physiological goals of therapy were set to match the state of normality, the physiological patents of the survivors were selected to become goals of therapy themselves [6]. This thesis, as its central theme, reviews the results of case series and randomised studies in this area.

At the same time that this pragmatic approached to the treatment of high-risk surgical patients was being defined, based on the attainment of predefined goals for treatment; scientific and clinical investigation was advancing in understanding of the pathophysiology and causes of MODS. This work allowed a theoretical link between treatment targeted to various cardiorespiratory parameters and a reduction in the
incidence of MODS in the patients to whom it had been applied. Subsequently additional work has attempted to refine the techniques that can be used in this area by suggesting different targets for therapy and less-invasive monitoring interventions. This thesis also reviews these areas of scientific and technical work.

1.1 Outline of Thesis

During the perioperative period there are a large number of physiological changes. These are the result of a number of factors such as surgical manipulation and positioning, activation of inflammation, anaesthetic drugs and intra- and extra-vascular fluid shifts. Some patients will have a good physiological reserve and there will be little change in measured physiological parameters, while in others there may be great changes resulting in alterations of tissue perfusion. Patterns of physiological changes that are seen in the survivors and non-survivors of surgery and to the consequences for tissue perfusion are reviewed in Chapter 3: Physiological changes in the perioperative period. Poor tissue perfusion is one of the major causes of MODS and the association between surgery, tissue hypoperfusion, MODS and surgical mortality is reviewed in Chapter 4.3: Multiple organ dysfunction syndrome and the surgical patient.

Knowing the physiological changes that occur in patients dying following surgery and being able to relate these to the cause of death allows the formulation of a hypothesis for the treatment of high risk surgical patients based on reversal and prevention of the deleterious physiological changes by maintaining blood volume and blood flow and preventing tissue hypoperfusion (see Chapter 5: An hypothesis for the management of high risk surgical patients). This can be done by maintaining cardiac output and oxygen delivery, and by maximizing cardiac function by fluid therapy to maximize stroke volume (SV).

There are, however, a number of practical aspects to the manipulation of cardiac output and oxygen delivery during the perioperative period (reviewed in Chapter 6:...
Practical aspects to manipulating oxygen delivery in the perioperative patient). These concern the calculation of oxygen transport parameters and the required measurements (reviewed in Chapter 6.4: Cardiac Output, and incorporating reference to Paper 9), and the techniques for increasing cardiac output (Chapter 6.4.3 and 6.4.4: Increasing Cardiac Output: Fluid therapy, and Increasing Cardiac Output: Pharmacological agents) particularly inotropic agents (Chapter 6.4.4.2: Inotropes with particular reference to dopexamine hydrochloride, incorporates Papers 1 and 3) and anaesthetic agents (Chapter 6.4.4.3: Other drugs with specific reference to anaesthetic agents, incorporates Paper 10).

Because oxygen delivery and cardiac output relate to the whole body, and it is likely that some regions of the body are more susceptible to the consequences of poor perfusion than other regions, a number of techniques have been suggested to try to refine attempts to increase cardiac output by specifically targeting susceptible regions (reviewed in Chapter 7: Other physiological treatment goals in the perioperative period). The two most commonly mentioned techniques are those effecting manipulations of VO$_2$I (Chapter 7.2 below: Oxygen consumption, incorporating Papers 6 and 7) and those concerning measurements of intramucosal pH (pHi) (Chapter 7.3.1 below: Intramucosal pH measurement, incorporating Paper 8).

There are now a number of published studies that have tested the hypothesis that preventing tissue hypoperfusion may result in improved outcome (Chapter 8 below: Trials with specific goal of increasing cardiac output and oxygen delivery). These have targeted treatment to cardiorespiratory values obtained from the PA catheter or the oesophageal Doppler monitor. Studies in surgical patients are reviewed in Chapter 8.3: Randomised studies in surgical patients which incorporates references to Papers 2 and 4. Other investigators have used the same approach in patients with other conditions, reviewed in Chapter 8.4 below Studies in patients with other conditions. A number of systematic reviews have been conducted and these are discussed in Chapter 8.6 below: Systematic reviews, which incorporates Paper 5.
The critical assessment of the current state of knowledge is preceded in Chapter 2 by a summary of the submitted works describing their scope and content, and contribution to advance in the subject. This summary has also been submitted separately as part of the regulations for submission of an MD thesis.
2. Summary of scope and contribution of the submitted works

2.1 Introduction

As the demands of the population for access to healthcare rises, and medical and technological advances allow previously unthought-of procedures to be undertaken, increasingly complex surgery is being offered to an increasingly elderly population. Many of the procedures which were pioneered in young, fit subjects are now virtually routine in higher risk, elderly patients with various concurrent disease states. While the risks of these procedures for the younger or highly selected patients may be acceptable, and are those most frequently quoted, the risk of death is very much greater for the unselected population. Although some of the patients who do not survive will die from a direct, anatomical result of the procedure undertaken, most will die from MODS. The insidious onset and complicated pathology of MODS is often not recognised on the general ward and many of the patients who die will be considered to have died from a single cause, such as bronchopneumonia or heart failure, while the complicated multi-organ pathology of MODS is missed. Furthermore, the prognosis even for correctly diagnosed MODS has altered little over 20 years.

A prevalent view is that a high perioperative mortality is the inevitable consequence of performing complicated surgery on these high risk patients and that the patients "have been given a chance" by undergoing surgery. This view, however, must be questioned as there is increasing evidence that the mortality and morbidity associated with surgery may be reduced by suitable therapeutic intervention instituted in the perioperative period. This body of published work is concerned with investigation of the therapeutic implications of maintaining tissue perfusion, by treatment targeted to goals for cardiac index (CI), oxygen delivery (DO$_2$I) and stroke volume (SV), as part of the treatment regime in the perioperative care of high risk surgical patients. The emphasis on treatment targeted to attain perfusion related variables has become known as "goal-
directed therapy”. Two lines of inquiry have dictated the actual goals to be used. The first arises from the observation that higher risk patients who survive surgery have high levels of CI and DO$_2$I than they non-survivors; the actual goals for therapy were pragmatically taken to be the median value demonstrated by the survivors. The second type of goal aims to maximise cardiac function, this is usually undertaken by maximizing SV measured by a Doppler technique; in this situation a specific numerical target is not set.

At the time that this body of work was being conceived there were only two published randomised trials of surgical patients in which attempts had been made to adjust cardiovascular and other physiological parameters towards preconceived goals. The first trial was published in 1985 [7] and only came to light during extensive reviews of the literature in the 1990's, this trial concerned patients with fractured neck of femur. But the main trial that stimulated further research was undertaken by Shoemaker and colleagues and published in 1988 [8]. Shoemaker's trial investigated general high-risk surgical patients and produced an extremely positive response in terms of improved outcome, reduced complications, and reduced cost. However a number of questions came to light and it became clear that further investigation was needed in an attempt to address these. Specifically there were questions concerning the identification of patients in the trial, the protocols used in the trial, the method of randomising and selecting patients, the confusing cocktail of drugs in the trial, and the specific endpoints of treatment.

This body of work was conceived to investigate the question of whether specific cardiovascular treatment targeted to pre identified goals of therapy improved outcome in high risk surgical patients. Additional questions arose during the trial and these were investigated and are also presented as part of this body of published work. Initially a pilot study was performed to review the feasibility of using a single drug therapy and a carefully defined protocol to treat high-risk surgical patients in the British Intensive Care Unit setting (Paper 1: Boyd O, Grounds RM, Bennett ED. The use of dopexamine hydrochloride to increase oxygen delivery peri-operatively. Anesth

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Analg 1993; 76: 372-376). This was followed by a large randomised study which built on the lessons learned in the pilot study (Paper 2: Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 1993; 270: 2699-2707). A study concerning the cost analysis of treatment of this type was published separately (Paper 4: Guest JF, Boyd O, Hart WM, Grounds RM, Bennett ED. A cost analysis of a treatment policy of a deliberate perioperative increase in oxygen delivery in high risk surgical patients. Int Care Med 1997; 23: 85-90). Paper 3 is a study comparing different pharmacological agents that could be used to increase cardiac output in high-risk surgical patients, this study was conducted to investigate this place of dopexamine is this treatment regimen (Paper 3: Boyd O, Lamb G, Mackay CJ, Grounds RM, Bennett ED. A comparison of the efficacy of dopexamine and dobutamine for increasing oxygen delivery in high risk surgical patients. Anaest Int Care 1995; 23: 478-484). This section of the published work is concluded by the first systematic analysis of trials published to 1995 concerning goal-directed therapy (Paper 5: Boyd O, Bennett ED. Enhancement of perioperative tissue perfusion as a therapeutic strategy for major surgery. In: Shoemaker WC, Belzberg H, Gutierrez G, Taylor DE, Brown SD (ed) New Horizons: Recent advances in invasive and non-invasive monitoring, Society of Critical Care Medicine, Anaheim, Ca 1996; 4: 453-465). This publication performed the first tentative combined analyses of data from published trials and informed subsequent work by separating trials undertaken in patients with established organ failure from those trials undertaken in patients in the perioperative period prior to the onset of organ failure.


This paper reports the results of a pilot study in 8 patients which was designed to investigate the practicality of using dopexamine hydrochloride to increase CI and DO₂I
in high risk, perioperative patients. In addition the study reviewed whether the modifications of Shoemaker’s initial higher risk of criteria could identify patients who appeared to be at high risk in a British setting, and tested out the feasibility of using a reproducible treatment protocol in high-risk surgical patients. This pilot study was therefore testing many of the criteria and protocols that were planned in a larger randomised study. To address some of the problems with Shoemaker’s study [8] it was decided early on to use only one pharmacological agent to increase CI and DO$_2$I and this has been followed by most subsequent studies. Dopexamine hydrochloride is a $\beta_2$ and dopamine-1 receptor agonist, which had previously been shown to increase cardiac output with minimal increase in heart rate, arterial pressure or myocardial oxygen consumption.

Patients, mean age 71, were identified pre-operatively by a modification of the Shoemaker entry criteria, which was designed to increase objectivity and simplify the entry criteria at the same time. The patients were admitted to the Intensive Care Unit (ICU) 12 to 24 hours prior to their operation and an arterial line and pulmonary artery (PA) catheter were inserted. All patients were subjected to treatment that was subsequently designated to the protocol group of the randomised trial, and followed a careful and reproducible regime. Colloid infusions were given to achieve a PAOP of 12 to 15 mmHg and DO$_2$I ($CI, L \min^{-1} m^{-2} \times \text{haemoglobin concentration, g dL}^{-1} \times \text{arterial oxygen saturation, } \% \times 0.134$) was calculated. If the DO$_2$I had not reached a target value of 600 mL min$^{-1}$ m$^{-2}$ a dopexamine infusion was started at 0.5 mcg kg$^{-1}$ min$^{-1}$ and increased by 0.5 mcg kg$^{-1}$ min$^{-1}$ each 30 minutes until the target DO$_2$I was achieved or heart rate rose to greater than 20% above baseline. The limits on increase in heart rate was a new part of an optimization protocol and was included to limit the possibility of myocardial ischaemia during drug infusion, this was also followed by most subsequent studies. Dopexamine infusion was continued throughout the operation and was discontinued post-operatively when the arterial lactate level had fallen below 1.5 mmol L$^{-1}$. It had always been unclear what endpoints for treatment had been used in the trial of Shoemaker and colleagues and an endpoint of the normal lactate level was included to respond to this question.
The results of the pilot study showed that it was possible to treat patients to follow the proposed regimen, and that dopexamine would be a suitable agent to increase CI and $DO_2I$ in these patients; at a mean pre-operative dose of 1.7 mcg kg$^{-1}$min$^{-1}$ there was a 46% increase in CI and a 44% increase in $DO_2I$ ($P<0.05$), pulse rate increased by only 2% ($P>0.05$) and there were no significant changes in rate-pressure product. Five of the patients achieved $DO_2I$ of $>600$ mL min$^{-1}$m$^{-2}$. Post-operatively, cardiac output and $DO_2I$ could be maintained at elevated levels. The pilot study also showed that it would be possible to identify patients that met the proposed study entry criteria, and that it would be feasible to admit them to the ICU pre-operatively for necessary treatment.

2.1.2 Paper 2 Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 1993; 270: 2699-2707

This paper presents the results of a randomised, controlled clinical trial of the effect of a deliberate increase in $DO_2I$ in the perioperative period. This was the fifth paper published investigating this phenomenon and was the largest to that date. Other studies had enrolled patients with fractured neck of femur [7], high risk surgical patients [8], vascular surgery patients [9], and trauma patients [10]. One hundred and seven patients, mean age 70.1 years, who were assessed as being at high risk of post-operative mortality by previously identified criteria, a modified version of the “Shoemaker” criteria, were enrolled in the study in an 18 month period. Patients were randomised to a control group ($n=54$) or a protocol group ($n=53$). An important aspect of this research was that all patients enrolled in the study had investigations of CI and $DO_2I$, and treatment regimes for control and protocol patients were managed by predefined treatment algorithms. This allowed a robust comparison between the groups to be performed as the treatment of the control patients was specified. It is disappointing that subsequent studies have not all followed this approach.
All patients had insertion of arterial lines and PA catheters and were admitted to the ICU prior to operation (n=81) or immediately after surgery (n=26), no treatment that would normally have been given to any patient was withheld. In the control group haemodynamic management was given to attain the following goals: mean arterial pressure 80 - 110 mmHg, pulmonary artery occlusion pressure 12 - 14 mmHg, arterial oxygen saturation >94%, haemoglobin concentration >12 g dL⁻¹, urine output > 0.5 mL kg⁻¹hr⁻¹. In addition, patients randomised to the protocol group had infusion of dopexamine hydrochloride, using the same regimen as in the pilot study, in an attempt to attain a DO₂I of >600 mL min⁻¹m⁻² by increasing cardiac output. Results were analysed on an 'intention to treat' basis. There were no differences in demographics, admission criteria, operation type or admission haemodynamic variables between the groups. During the study period there were again no differences in haemodynamic variables between the groups except those that had been specifically targeted by the study; both CI and DO₂I were significantly higher in patients in the protocol group. The main output measures of the study were post-operative complications and 28 day mortality. Using a check-list for the presence of standard complications, it was shown that the mean number of complications per patient were halved from a mean of 1.35 to 0.68 in the protocol group (P=0.008). Furthermore, 28 day mortality was significantly lower in the protocol group, 5.7% compared to 22.2% (P=0.015). We concluded that perioperative increase in DO₂I towards a target value of 600mL min⁻¹m⁻² using dopexamine hydrochloride significantly reduced post-operative mortality and morbidity in high risk surgical patients. The publication of this study gave a significant impact to further work on care of the high risk surgical patient with regard to treatment targets for cardiac output and oxygen to delivery. Since the publication of this study a further 16 works have been published.

In the study presented above, dopexamine hydrochloride was used to increase Cl and DO$_2$I. Many would consider dobutamine hydrochloride or combinations of agents as more usual therapy, and indeed other investigators have used dobutamine. This paper presents the results of a study comparing the efficacy of dopexamine compared to dobutamine in increasing perioperative DO$_2$I using the same regimens as above (papers 1 and 2). Sixteen perioperative patients were randomly allocated to receive dopexamine or dobutamine as the inotropic agent. Results showed that using this regimen, Cl and DO$_2$I could be significantly increased in the dopexamine group, but not the dobutamine group due to side-effects. Five patients in the dopexamine group and 3 patients in the dobutamine group reached target DO$_2$I, other patients were limited by increase in heart rate. Three dobutamine patients had angina or dysrhythmias. It was concluded that, using our titration regimen, dopexamine allowed greater increases in Cl and DO$_2$I than dobutamine, the titration of dobutamine being limited by cardiac side-effects or increase in heart rate >20% above baseline. Since the publication of this trial and the work presented in paper 2 other investigators have also used dopexamine as a single inotropic agent in perioperative patients, but only one other comparison between agents has been made [11].


As developed nations spend more of their gross domestic product on health care, new treatment strategies must be placed in context by considering their impact on use of resources. This paper presents data collected retrospectively on the cost implications of the study presented in Paper 2. Purchasing records and business managers were consulted to obtain the unit cost of resources used. Each patient record, both hospital records and study data, was then reviewed to isolate the use of resources by each patient. Results showed that the cost of treating a protocol patient was lower than the cost of treating a control patient (£6525 vs. £7784), this reduction was due to the significantly decreased cost of treating complications (£213 vs. £668), and reduced ICU
and hospital stays. The cost of obtaining a survivor showed a 31% reduction in patients in the protocol group. We concluded that a treatment policy aimed at deliberately increasing DO$_2$I in the perioperative period in high risk surgical patients resulted in reduced hospital costs. These results confirmed the findings of Shoemaker and colleagues [8] but in the earlier study accurate methodology to assess the robustness of the costing analysis was not provided. We pointed out that findings such as these have important implications for the funding of Intensive Care. Since the publication of this paper one further detailed cost analysis has been performed by another group and this also showed significant cost savings could be achieved by a policy of goal-directed therapy in the perioperative phase [12].


This paper is a review of clinical trials in which there have been deliberate attempts to enhance tissue perfusion in the critically ill; patients with myocardial infarction, sepsis, general critical illness and perioperative patients were included. The paper was invited by the Society of Critical Care Medicine as part of its New Horizons series, and it is one of the first review articles in this field presenting the rationale behind the techniques of increasing CI and DO$_2$I in critically ill patients. The review also was the first to attempt a systematic compilation of the literature, and was the first to generate the hypothesis that different patient types might respond differently to techniques designed to raise tissue perfusion; to do this we divided the reviewed studies into two groups; the first group concerned patients with established organ failure, the second concerned patients prior to the onset of organ failure, frequently in the perioperative phase. Paper 2 was the largest trial on perioperative patients published to 1996.
The scientific basis behind these trials is that tissue hypoxia can be one of the triggers for the onset of MODS, and it is known that most critically ill patients who die will do so from MODS. There appears to be a particular theoretical link between tissue hypoperfusion and MODS in perioperative patients. The combined odds ratio (OR) for randomised controlled studies in which treatment was targeted towards improvement of tissue perfusion was calculated. Studies which intervened early in the course of a patient's illness, with studies on pre-operative patients having the earliest intervention, generally showed an improvement in outcome; OR 0.34 (Confidence Interval 0.23 - 0.49). In contrast, studies that intervened late did not shown improvement; OR 1.05 (Confidence Interval 0.82 - 1.34).

The review also presented new data on the identification of high risk surgical patients. In a retrospective analysis of data from our clinical trial (Paper 2) we showed that the greatest influence of increasing DO$_2$I on improvement in outcome might be on patients with lowest baseline DO$_2$I and greater numbers of high risk criteria. In subsequent work by others these findings were frequently ignored, with many trials being performed on much lower risk patients. This review concluded that there was good evidence that improving tissue perfusion in perioperative patients reduced mortality, but if intervention was left too late there was no improvement in outcome.

2.2 Additional studies

During the course of the work presented above it became clear that a number of additional issues needed to be addressed. Of specific interests to investigators in the field were questions concerning the appropriate targets of therapy. The initial work [13] had included VO$_2$I as the target. However it became apparent that one major influence on VO$_2$I around the time of surgery was the sedation level of the patient. This was investigated by the study presented in paper six (Paper 6: Boyd O, Grounds RM, Bennett ED. The dependency of oxygen consumption on oxygen delivery in critically ill postoperative patients is mimicked by variations in sedation. Chest; 1992: 101: 1619-1624), which concluded that in perioperative patients VO$_2$I would be
an inappropriate target for therapy. This work was extended in paper 7 where other influences on VO$_2$I were reviewed to see if it was logical to use VO$_2$I as a treatment target in critically ill patients (Paper 7: Boyd O, Bennett ED. Is oxygen consumption an important clinical target? In: Vincent J-L (ed) Yearbook in Intensive Care and Emergency Medicine 1992, Springer-Verlag, Berlin 1992, 310-322). Another target that became controversial at the time that these studies were being performed was gastric tonometry calculated intramucosal (pH$_i$). Paper 8 (Paper 8: Boyd O, Mackay CJ, Lamb G, Bland JM, Grounds RM, Bennett ED. Comparison of the information gained from routine blood gas analysis and from gastric tonometry for intramural pH. Lancet 1993; 341: 142-146) investigated the relationship between pH$_i$ and other measures of acidosis in a general population of critically ill patients to see if pH$_i$ might be a suitable target in perioperative patients in the future.


2.2.1 Paper 6 Boyd O, Grounds RM, Bennett ED. The dependency of oxygen consumption on oxygen delivery in critically ill postoperative patients is mimicked by variations in sedation. Chest; 1992: 101: 1619-1624

In original targets for treatment proposed by Shoemaker and colleagues, VO$_2$I had been included as one of the cardiorespiratory targets [13]. However observations during the
planning stages of the randomised study suggested that other influences on VO\(_2\)I might make it an unsuitable target for treatment in the perioperative phase as changing sedation levels also seemed to affect VO\(_2\)I.

This paper reports the results of a study of the influence of changing sedation levels and temperature on the apparent relationship between DO\(_2\)I and VO\(_2\)I. In healthy individuals at normal or high DO\(_2\)I, VO\(_2\)I is relatively constant, this is a supply independent pattern; however, as DO\(_2\)I decreases a critical point is reached after which VO\(_2\)I also falls, this is a supply dependent pattern and is a normal physiological finding. However in a wide range of critical illness investigations had shown that there is a dependence of VO\(_2\)I on DO\(_2\)I to a much greater level of DO\(_2\)I. This was termed ‘supply dependence’ and many authors have suggested that this represented an unmet demand for oxygen at the tissue level and if demonstrated clinically should prompt further increases in DO\(_2\)I until VO\(_2\)I reaches a plateau. Moreover, it was suggested that observed increase of VO\(_2\)I was a suitable marker of the effectiveness of increasing DO\(_2\)I as it demonstrated improved tissue perfusion.

It had been noted however, that VO\(_2\)I could be influenced by medical and nursing intervention, particularly changes in sedation. To investigate the possible importance of this, 13 perioperative patients were studied. Sedation score and core body temperature were measured and recorded each time CI, DO\(_2\)I and VO\(_2\)I were calculated. Results showed that change in sedation levels, but not change in temperature, was significantly correlated with change in VO\(_2\)I (r=0.77, P<0.01). There was also a significant correlation between DO\(_2\)I and VO\(_2\)I, but if the VO\(_2\)I was mathematically standardised for changes in sedation level there was no positive relationship between DO\(_2\)I and VO\(_2\)I. We concluded that the apparent supply dependence exhibited by the patients studied in the postoperative phase of care was a result of changing sedation levels. Because many critically ill patients, particularly those in the perioperative period, are sedated, and the sedation level is varied, the results suggested that therapy designed to achieve raised VO\(_2\)I by raising DO\(_2\)I may not be appropriate as it would be impossible to necessarily relate the changes in VO\(_2\)I to changes in oxygen delivery. In clinical
studies we did not included VO$_2$I as a target for treatment due to the results of this publication. This was an important study course it was one of the first to question the use of VO$_2$I as a clinical target in a more general sense, and after the publication of this paper only 3 of 16 subsequent studies included VO$_2$I as part of their treatment protocols.


Following our findings in Paper 6 it became timely to review the literature looking at the relationship between DO$_2$I and VO$_2$I. This invited paper critically reviewed published studies in terms of methodology and data analysis, and the influence other factors may have had on VO$_2$I which may have affected the results of the studies. The review concluded that VO$_2$I could be changed by so many factors, such as sedation and inotropic use, that it had little use as a therapeutic endpoint when it came to increasing DO$_2$I, and, in common with others, the review questioned some of the methodology in studies which had originally defined the supply dependent pattern of VO$_2$I on DO$_2$I. Of particular relevance to the use of perioperative goal-directed therapy, in which the use of inotropes is an integral part of the treatment protocol, the review noted that in normal individuals, who would not be expected to have a supply dependent relationship between DO$_2$I and VO$_2$I, the use of inotropic medication to increase DO$_2$I also increased VO$_2$I. Since inotropic medication is the mainstay of therapy to increase DO$_2$I in critically ill patients the review concluded that it was illogical to target VO$_2$I with these medications, and that work demonstrating a supply dependent pattern of DO$_2$I and VO$_2$I by using inotropes might be flawed. The detailed review of the literature that was presented in this paper, combined with the results of paper 6 further confirmed the impression that VO$_2$I should not be included as a target in perioperative care.
A goal of Intensive Care research has been to identify poor organ perfusion. As discussed above, increasing VO$_2$I had been suggested as one method of showing the benefits of increased perfusion; the gastric tonometer was presented as another method to specifically identify poor splanchnic perfusion by a reduction in calculated intramucosal pH (pH$_j$) [14]. This study compared the information gained by using gastric tonometry to that obtained by routine blood gas analysis in critically ill patients.

Twenty consecutive patients were studied with a mean of 8 datasets obtained for each patient. There was good correlation between calculated base deficit and pH$_j$ (r=0.63, P<0.001), and blood base deficit of -4.65 or less could estimate pH$_j$ below 7.32 (lower limit of "normal" range) with sensitivity of at least 77% and specificity of at least 96%. The results suggested that in the patients studied, either systemic acidosis was influenced largely by splanchnic acidosis, or that the calculation of pH$_j$ was influenced by systemic acidosis. It was concluded that the information obtained by gastric tonometry could be obtained more easily from measurement of base deficit in blood. In subsequent work on goal-directed therapy in perioperative patients no studies have used pH$_j$ as a target for treatment although a number of studies have used base deficit and lactate measurements.

During the pre-operative work up of the patient, using the regimen described in Papers 1 and 2, it is necessary to perform repeated cardiac output measurement at the same time as fluid infusion for volume loading of the circulation. It was noted that injectate,
used for thermodilution measurement of cardiac output, occasionally returned up the sidearm of the introducer sheath of the thermodilution catheter, and that during fluid infusion using the sidearm of the introducer sheath there was frequently some instability in the measurement of cardiac output by thermodilution.

This paper reports the results of a study of the effects of combinations of fluid infusion and varying depths of insertion of the thermodilution catheter into the introducer sheath on cardiac output measurements. Findings were that the more open the infusion arm and the more proximal the injection port of the thermodilution catheter the higher was the measured cardiac output, the greatest variation being more than 23%. The study concluded that the infusion sidearm must be closed during measurement of cardiac output by thermodilution, and consequently fluid infusions, using the same line, could not be given at the same as cardiac output was being measured. The results of this study added to the literature on methodological problems in using the thermodilution technique to measure cardiac output. It also emphasised the need for very strict protocols and techniques when using cardiac output results obtained by this technique as a basis for the calculation of DO$_2$I and the titration of treatment in both clinical and investigative settings.

2.2.5 Paper 10 Boyd O, Murdoch LJ, Mackay CJ, Bennett ED, Grounds RM. The cardiovascular changes associated with equipotent anaesthesia with either propofol or isoflurane, with particular emphasis on right ventricular function. Acta Scand Anaesthesiol 1994; 38: 357-362

Anaesthetic agents are known to have negatively inotropic effects on cardiac function, and this may be important when choosing an anaesthetic technique in elderly patients or those with significant co-morbidity. By a cross-over design this study compared the effects of propofol and isoflurane on cardiac, specifically right ventricular, function. Ten patients were anaesthetised with equivalent minimal alveolar concentration of isoflurane or minimal infusion rate of propofol during surgery for peripheral vascular reconstructive procedures. Cardiac function was assessed using a PA catheter with a
fast response thermistor allowing measurement of right ventricular ejection fraction and calculation of right ventricular end-diastolic and end-systolic volumes. There were no differences in heart rate or blood pressure between the two agents suggesting that equivalent anaesthetic doses had been given. However there were significantly (P<0.05) higher cardiac output (4.0 to 4.5 l min⁻¹), right ventricular ejection fraction (35.1 to 39.4 %), SV (35.4 to 39.6 mL) and right ventricular end-diastolic volume index (102 to 110 mL m⁻²) with propofol compared to isoflurane. The study concluded that anaesthesia with propofol resulted in improved right ventricular performance compared to isoflurane. It also suggest that propofol may be a more suitable agent than isoflurane for anaesthesia in patients who may already have impaired right ventricular function and in whom maintaining high cardiac output may be beneficial.
3. Physiological changes in the perioperative period.

It has been known for some time that there are changes in a number of the parameters of oxygen transport at the time of life threatening illness. As early as 1931 20% to 25% increases in basal oxygen consumption were seen in patients who sustained orthopaedic injuries and operations [15]. Some years later, patients who had sustained multiple fractures were classified by their cardiac output into three groups, no shock, mild shock, and severe shock; with the more severe groups having lower cardiac output and the higher peripheral resistance [16]. In the majority of cases induction of general anaesthesia was found to lead to an immediate reduction in cardiac output, and postoperatively there was a rise in cardiac output above the control level [17]. Also trauma patients not undergoing surgery showed an increase in cardiac output if significant haemorrhage was not present [18] and when blood volumes were maintained in the normal range [19]. These findings started to suggest that an appropriate response to a physiological insult, for example surgery or trauma, might be increased cardiac output, but that this failed if haemorrhage or dehydration were present.

Correlating these changes to the outcome of the patient proved difficult. It was shown, however, that in patients undergoing thoracotomy, low Cl and arterial hypoxia were indicators of non-survival [20]. Similarly, survivors and non-survivors of closed head injury could be classified in terms of their cardiac output [21], and the same has more recently been demonstrated in patients with blunt chest trauma [22]. Using the model of major surgery for the study of shock and critical illness it was possible to make observations of the temporal patterns of various haemodynamic and oxygen transport parameters before and after the surgical insult. This task became much easier with the development of the balloon tipped flow directed PA catheter [23]. It was shown that patients who survived major surgery had higher CI, lower systemic vascular resistance (SVR), and higher VO$_2$I than non-survivors [5, 24]. These changes were initially related to the perceived stage of the patient in their illness and recovery, and later were shown to be valid as a temporal pattern of the changes seen [13].
Further analysis of data from critically ill patients showed good sensitivity and specificity for predicting survival [25]. In this study each of 35 variables could be given a predictive coefficient based on their ability to predict survival, the predictive coefficient being taken as a measure of the usefulness of each variable [26]. It was found that the commonly monitored vital signs: heart rate (HR), temperature, central venous pressure (CVP) and haemoglobin were the poorest predictors while perfusion related variables, such as DO$_2$I and VO$_2$I and CI which express the interrelationship between oxygen transport and red cell volume and flow, were the best [26]. Other groups confirmed that preoperative haemodynamic monitoring using normally measured parameters was no help in predicting mortality or morbidity in a separate group of 41 surgical patients [27]. Shoemaker's group subsequently stratified patients in different age ranges and while confirming that high risk survivors of surgery have increased cardiac output and oxygen delivery compared to those that die also show that the changes that occur vary depending on age, sex and associated medical conditions [28].

The importance of oxygen transport values has further indirect evidence to support it. It has been shown that oxygen transport values change before the more commonly monitored variables in cases of surgery [13, 24, 29] and septic shock [30], and that VO$_2$I [31] and arterial venous oxygen content difference [32] are negatively correlated with mortality. Moreover, vital signs usually remain in the normal range until the terminal event in non-survivors, while oxygen transport variables had started to change some hours previously in surgical cases [13], and young trauma patients [33]. This has been recently confirmed in patients undergoing oesophagectomy [34]. In this study DO$_2$I at 6 hours was significantly lower in patients who subsequently died, developed an anastomotic leak or postoperative pneumonia compared to uncomplicated survivors. The differences in DO$_2$I that indicated a poorer postoperative outcome were only short-lived, because after day 1 no differences in DO$_2$I were seen between patients with a complicated postoperative course and uncomplicated survivors.
It has been hypothesised that a rise in oxygen transport requirements after surgery may be necessary to pay back an oxygen debt that has accumulated during the surgical procedure because patients undergoing longer procedures had longer periods of increased VO$_2$I post-operatively [35]. Furthermore, if the cumulative tissue oxygen debt is calculated during the period of operation it is found that patients who survive have the smallest oxygen debt and patients who fail to survive have the biggest; patients with organ failure who survive have intermediate oxygen debts [36].
4. Pathological changes in the perioperative period

4.1 Introduction

Since the first operation which had a 200% survival rate [37], it has been recognised that surgery does in fact carry a measurable risk of death. There are surprisingly few publications which review or publish figures for surgical mortality and even fewer that link postoperative mortality to features of the patient such as coexisting diseases. The picture is complicated by publication bias, only good results being published, and publications mainly from tertiary or quaternary referral centres which may have quite a marked bias in the selection of patients at outset due to bias in both referral and acceptance.

4.2 Surgical mortality and morbidity

Overall surgical mortality is considered acceptable at about 2% on a worldwide basis. This figure includes, however, a large number of low risk procedures in low risk patients that have a very low mortality rate. The National Veterans Surgical Risk Study in the USA has shown that in a two year period 83958 operations were performed, patients had a mean age of 60 years and the mortality rate overall was 3.1% at 30 days, but 17% of patients had one or more major complication [38]. Assessing mortality rates in higher risk patients is more difficult, however many of the higher risk surgical candidates will be admitted to the ICU postoperatively, and mortality rates for surgical patients on the ICU are indeed much higher. The Acute Physiology and Chronic Health Evaluation (APACHE) database gives a 10.5% mortality for patients admitted directly to Intensive Care from the operating theatre, and this has changed little between the APACHE II [39] and APACHE III (10.3%) databases [40]. In the South West Thames ICU database mortality was higher (9.4% for elective surgery and 28.7% for emergency surgery in 1993-1994) [41], and this possibly represents differences in admission policy.
or patient demographics. Furthermore, these figures may under-represent true surgical mortality because they will ignore postoperative patients admitted from wards rather than directly from the operating theatre, and whose mortality is likely to be higher.

The National Confidential Enquiry into Peri-Operative Deaths in England and Wales 1992-1993 showed that there were 19861 deaths post-operatively in the year in question, with the median day of death being day 6 [42]. Post-operative mortality is increased in patients with pre-existing disease [43], and this has recently been highlighted by the Society of Cardiothoracic Surgeons of Great Britain and Ireland [44], who show in their large database of almost 60000 patients that postoperative mortality is related to age, co-existing disease and severity of surgery. The mortality and morbidity seen in elderly patients has recently been reviewed [45]. The impact of the aging population is very important for healthcare planning as numbers are increasing and although approximately 12% of those 45 to 60 years of age have surgery each year, over 21% of the elderly present for surgery each year.

Despite the finding of an age-related increase in post-operative mortality, age itself does not seem to be a predictor, and coexisting disease plays a larger role. When age and severity of illness are compared, the number of coexisting diseases outweighed the effect of age [46]. Bufalari et al. [47] studied patients age 80 and older in the 1990s, and found the American Society of Anesthesiologists physical status (ASA grade), presence of two associated diseases, and type of surgery to be better predictors of mortality than age alone. Studies have also shown that thoracic and abdominal procedures have higher mortality and complication rates [48-50], and in elderly patients undergoing non-cardiac surgery mortality is more related to factors such as a history of cardiac disease and signs of low CI around the time of surgery than factors such as the type of operation performed [51]. This is probably related to physiological reserve. For example age is known to affect the hepatic acute phase response and despite normal baseline function, on day 1 and 2 postoperatively elderly patients after abdominal surgery had evidence of reduced hepatic perfusion [52]. In general, patients with non-elective admissions (mortality rate 30% vs. 5% for elective admissions), ASA grade 3+ (mortality rate 27%
vs. 8% for ASA <3), age over 75 (mortality rate 20% vs. 11% for patients aged 65 to 74) and major surgery (mortality rate 25% vs. 10% for non-major surgery) are associated with much higher mortality [53-56].

The data presented above show that a patient most likely to die in the post-operative period is an emergency, presenting with coexisting cardiovascular, renal or hepatic impairment and is usually old, these factors are more important than the type of surgery [57].

4.3 Multiple organ dysfunction syndrome and the surgical patient

A syndrome in which there was multiple failure of a number of organ systems was first described in the 1970’s in a group of surgical patients who developed pulmonary and renal failure culminating in death following repair of ruptured abdominal aortic aneurysms [58, 59]. This was initially termed multiple organ failure syndrome (MOF), but recently the terminology has been standardised and it is now called multiple organ dysfunction syndrome (MODS) this is preceded by an initial inflammatory response, the systemic inflammatory response syndrome (SIRS) [60-62]. Although the definitions of SIRS and MODS are wide and lack specificity [63], they remain a useful pathological concept. When first described, MOF was thought to be the end result of an uncontrolled infective process, and indeed its occurrence is frequently linked to sepsis or septic shock, but the pathophysiology of MODS is now known to be far more complex [64]. MODS carries a high mortality which increases as the number of organ systems fail [65]. The incidence of MODS in surgical ICU patients can be as high as 44.3%, and is associated with prolonged illness, death and increased cost [66]. Similarly, the antecedent of MODS, SIRS, occurs in as many as 93% of an ICU population [67]. It is currently estimated that MODS accounts for up to 80% of all surgical ICU deaths and this is confirmed by a recent Scottish survey showed the mortality of patients with renal and respiratory failure was 64% [68]. Disappointingly there appears to have been little improvement in prognosis of established MODS over the last 20 years [69].
There are a number of factors which acting independently or in combination trigger the onset of MODS [70] but the final common pathway is that of cytokine activation; first a local production of cytokines in response to an injury or infection which is a physiological response, then a release of a small amount of cytokines into the body's circulation, and finally a massive systemic reaction where cytokines turn destructive by compromising the integrity of the capillary walls and flooding end organs [71]. Experimental evidence considering other causes of the syndromes of SIRS and MODS, such as sepsis and septic shock, implicate a large number of inflammatory mediators, particularly the cytokines, in the development of the syndromes. Some of this work has been undertaken on patients having cardiac surgery, looking specifically at the implications of cardio-pulmonary bypass; this thesis is concerned more with general surgery, and will therefore concentrate primarily on studies on non-cardiac surgery patients. The release of the cytokines and other inflammatory mediators is part of the normal response to injury, and as well as inflammatory pathways other cascades involving coagulation and fibrinolysis are also activated. These cytokines are also stimulated as part of the normal inflammatory response to surgery. When the normal response to injury becomes unregulated, abnormal activation of multiple cascades leads to diffuse inflammation, endothelial cell injury, and thrombosis with resultant organ hypoperfusion, leading to end-organ dysfunction and syndrome of multiple organ dysfunction. The triggers that lead from a normal response to an unregulated pathological response probably involve genetic factors and the priming of the inflammatory system by other stimulants. One can imagine in the surgical situation multiple stimulants to the inflammatory pathways been present in any one individual; these could include trauma, ischaemia, reperfusion injury, and infective and chemical insults. Despite the fact that there is no categorical scientific evidence showing a relationship between surgery and tissue hypoperfusion and the onset of SIRS and MODS, there is considerable circumstantial evidence to show that all of these stimulants are likely to be exaggerated in the presence of general tissue hypoperfusion occurring as a result of limited physiological reserve.
One of the factors initiating cytokine activation appears to be alterations in microcirculatory flow [72], and others are related to tissue damage and the stimulation of inflammatory mediators. It is the importance of alterations in perfusion and microcirculatory flow that form a central part of this thesis. It is known that circulatory shock and tissue hypoxia are related to the development of MODS [61, 62], and there is also evidence of microvascular injury in patients dying of MODS [73]. Inadequate DO$_2$I to the tissues may lead directly to tissue death and the ischaemia reperfusion syndrome may cause continuation and amplification of the tissue damage [74]. The link between failure of the normal post-operative responses of increased CI and DO$_2$I maintaining flow and perfusion, and the development of MODS and death has been reported by Shoemaker and colleagues [75]. They retrospectively divided 253 surgical patients into three groups, those that survived, those that survived with complications or organ failure and those that died with organ failure. The group that survived developed the expected post-operative increase in CI and DO$_2$I, while the group that died showed no increase in these parameters. The group that survived but had complications or organ failure showed an intermediate or variable increase in CI and DO$_2$I.

In animal models it is well established that ischaemia and reperfusion injury is associated with the release of pro-inflammatory cytokines [76, 77] probably as a result of the activation of nuclear factor (NF)-κB [78, 79]. But demonstrating the same in humans undergoing surgery and then relating this to the pathogenic processes of MODS and patient outcome has been more complicated. The most frequently studied human situation has been around the time of aortic aneurysm repair. Thoracic-abdominal aortic aneurysm repair results in the increased plasma appearance of tumour necrosis factor α (TNF-α), interleukin-6 (IL-6), IL-8, IL-10, and shed TNF receptors. The frequency and magnitude of postoperative organ dysfunction after thoraco-abdominal aneurysm repair is associated with an increased concentration of the cytokines TNF-α, and IL-6, and this is related to extended visceral ischaemia times [80]. The same is true for abdominal aneurysm repair [81, 82], and most patients develop postoperative SIRS: 89% in an elective group, 92% in an emergency non-ruptured (urgent) group, and 100% in a ruptured group [83]. Other investigators have shown that a profound inflammatory
response, consisting of increased IL-6, IL-10 and monocyte chemoattractant protein-1, after abdominal aneurysm repair can persist for up to one week post-operatively [84]. In trauma patients there is evidence of a similar pathological process [85], which is also seen in abdominal compartment syndrome and results in increased cytokines and oxygen free radical production [86]. In major abdominal and thoraco-abdominal surgery issue hypoperfusion, as a manifested by an increase to plasma lactate, has been shown to be related to an altered nitrite/nitrate ratio used as a marker of increased nitric oxide production [87]. In summary, pathophysiological evidence shows a direct link between surgery and trauma and the development of SIRS and MODS in some patients, there is also an implication that the degree of surgery makes this chain of events more likely.

4.4 Risk assessment in surgical patients

There are a number of tests that can be used pre-operatively to identify patients at risk of post-operative organ dysfunction. This is an essential step if viable techniques are to be developed to proactively treat such patients. Risk assessment tools have concentrated on general risk assessment or organ specific, particularly cardiac, risk assessment. These assessment tools are discussed here to show that while such tools exist and are commonly used they are poorly refined for preoperative identification of higher risk surgical patients. This becomes important when considering the patient groups, and the identification of these, that have been studied as part of a goal-directed perioperative therapeutic approach.

4.4.1 General preoperative risk stratification

A widely used perioperative risk tool is the Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM) [88]. This is generally accepted to be a good scoring system for routine use [89], and is better than the Acute Physiology and Chronic Health Evaluation (APACHE) system for general surgical patients [90]. However, POSSUM scoring may not be universally applicable. In
ruptured abdominal aortic aneurysms POSSUM scoring was not a good predictor of outcome and APACHE scoring was better [91]. However even the APACHE score, while being better for the group of patients, was not good at discrimination between those that survived and those that died [91]. Other variations of POSSUM scoring have been suggested which may work better in gastrointestinal surgery [92] and vascular surgery [93]. In one study POSSUM scoring has been used as part of a risk stratification analysis to identify patients who might benefit from post-surgical high dependency care or ICU care [94]. However the score was used retrospectively and neither POSSUM nor APACHE scoring, by the nature or the required data collection, can be used to preoperatively identify patients at higher risk.

A slightly different approach has been taken by Older and colleagues who performed preoperative cardio-pulmonary testing to define an anaerobic threshold [95, 96]. If the anaerobic threshold was less than 11 mL min⁻¹Kg⁻¹ patients had a mortality rate of 18%, but if it was greater mortality rate was only 0.8%. Other groups have identified patients at risk by using a check-list of preoperative disease factors known to put patients at greater risk of postoperative morbidity or mortality, such systems were used by Shoemaker and Boyd [8, 97]. Another technique is to identify patients by the type of operative procedure they are to undergo, such as abdominal surgery or aortic aneurysm repair; these procedures are more complex and have a higher risk of postoperative complications, and this is another way to identify the higher risk surgical patient.

4.4.2 Preoperative risk stratification for myocardial events

There are many methods to investigate cardiac function and coronary artery perfusion, and it is hardly surprising that many have been investigated for their ability to stratify risk in surgical patients. It is disappointing that while many of these can clearly identify different risks, there is very little information that outcome is improved by knowing the risk.
Two cardiac risk indices are well known. The Goldman Index gives scores for a number of cardiac conditions, the higher the overall score the greater the risk of cardiac events [98], and a second score was developed by Detsky and colleagues with similar results [99]. However intra- and post-operative factors also influence the outcome of surgical procedures [100], and therefore no pre-operative system will be completely accurate. Even-so the established cardiac risk indexes are better than chance with odds ratios of 0.642 (CI, 0.588 to 0.695) for the Goldman index, 0.601 (CI, 0.544 to 0.657) for the modified Detsky index, and 0.654 (0.601 to 0.708) for the Canadian Cardiovascular Society index [101].

Exercise stress testing can be a useful method of risk stratification in non-cardiac surgery patients [102], and a combination of clinical variables and exercise electrocardiography improved preoperative risk stratification. Other studies have used echocardiography and stress echocardiography to risk stratify surgical patients [103]. However adding echocardiographic information to established predictive models may not increase predictive values in any clinically important way [104]. In contrast dobutamine stress echocardiography has predictive value for perioperative cardiac events [105] that has incremental value over clinical, electrocardiographic and rest echocardiographic variables [106]. However the link between testing and reducing mortality remains complicated, as shown in one centre where the number of patients undergoing preoperative stress testing was reduced, cardiac morbidity and mortality remained the same [107].
5. An hypothesis for the management of high risk surgical patients

The previous sections of this thesis set out the observational and scientific background of mortality in high risk surgical patients. This shows in summary that there is high mortality in sub-groups of surgical patients and their death is frequently caused by MODS. Many causes of MODS exist in surgical patients particularly circulatory failure which occurs in high ask surgical patients, particularly those that die. In addition there are straightforward but basic scores to aid in the identification of higher risk patients.

Sometime before all these theoretical links had been put in place, Shoemaker and his colleagues had proposed a pragmatic treatment approach to the high-risk surgical patient [6]. This approach was based on their earlier physiological studies comparing physiological patterns in survivors and non-survivors surgery (see Chapter 3: Physiological changes in the perioperative period.). They had shown that the most significant differences were found in perfusion related variables, most easily obtained at the bedside by measuring CI, VO$_2$I and DO$_2$I. They therefore proposed that all patients should be treated to targets CI, VO$_2$I and DO$_2$I as defined by the values seen in the survivors; the value chase and, again on a pragmatic basis, was the median value for these parameters demonstrated by the survivors of surgery [6].

This hypothesis fits elegantly into the current scientific context described above. By preemptively influencing one of the major potential factors causing and stimulating cytokine release and the resultant syndromes of SIRS and MODS, that of tissue hypoperfusion, this approach would be expected to limit the degree of inflammatory activation and reduce the incidence and severity of SIRS and MODS. It is also likely, on a theoretical basis, that preemptive treatment to increase tissue perfusion would be more successful in preventing the onset of SIRS and MODS rather than treating the established syndromes. Although it is conjecture it is likely that the hyperdynamic
circulatory responses observed by Shoemaker and colleagues [24] in their survivors of surgery may have reduced the inflammatory response in these patients to those of the normal and healthy physiological response to injury.

The goals proposed by Shoemaker and colleagues [6] were for a CI > 4.5 L min⁻¹, VO₂ > 170 mL min⁻¹ m⁻² and DO₂ > 600 mL min⁻¹ m⁻². Significantly the goals suggested were above the previously determined normal level. This was a hugely important idea combining, as it did, invasive monitoring technology, raised expectations for surgical intervention, a new confidence in fluid therapy and inotropic medication, and a preventative approach to medical care. The terms 'supra-normal goal-directed therapy' and simply 'goal-directed therapy' and 'optimization' have arisen from this hypothesis, and are used almost synonymously. In 1978 when this was first suggested it was just a hypothesis, but it has spawned a huge body of literature and considerable controversy, which remains to this day [108].

Although Shoemaker and colleagues laid down a very proscribed approach in their first descriptions of the goal-directed therapeutic approach using a PA catheter. The evolution of new technologies and a deeper understanding of the subject have meant that this thesis needs to take a broader approach. This thesis has employed the term 'goal-directed therapy' to describe the treatment approach whereby specific physiological goals for treatment are set, these goals being specifically related to aspects of tissue perfusion, and therapy is then given to the patient with the aim of attaining these goals of treatment. As will be seen studies have generally used either the PA catheter or the oesophageal Doppler monitor to assess the goals for treatment, and have used combinations of fluid and inotropic therapy to attain these goals (see Chapter 8.3: Randomised studies in surgical patients). Before describing clinical studies to test the validity of this hypothesis, this thesis will describe practical aspects to attaining the defined goals and alternative investigative and treatment strategies could also be employed in high-risk surgical patients.
6. Practical aspects to manipulating oxygen delivery in the perioperative patient

6.1 Introduction

Oxygen flux around the tissues is referred to as oxygen transport. There are theoretically a number of methods to alter aspects of oxygen transport in the clinical setting, and a number of incidental factors that can affect oxygen transport. Papers 3 and 10 are clinical studies investigating these two points. There are also a number of possible errors in the calculation of oxygen transport parameters, and Paper 9 investigates the possible importance of a new error when CI is measured frequently during fluid infusions.

6.2 The calculation of oxygen transport parameters

The oxygen transport of a patient is defined in terms of the total oxygen delivered to the tissues, the total amount of oxygen that is consumed by the tissues and the ratio between the two: the extraction ratio. The oxygen delivered (DO₂, mL min⁻¹) is the product of the amount of oxygen carried by the blood on the arterial side, the arterial oxygen content, expressed as the number of millilitres of oxygen dissolved in a litre of blood (CaO₂, mL L⁻¹), and the cardiac output (CO, 1 min⁻¹):

\[ DO_2 = CO \times CaO_2 \]

To compare different patients this is indexed to the body surface area (BSA, m²) to give the oxygen delivery index (DO₂I, mL min⁻¹ m⁻²):

39
The oxygen consumption index (\(VO_2I\), mL min\(^{-1}\) m\(^{-2}\)) is the difference between the arterial oxygen content (\(CaO_2\), mL L\(^{-1}\)) and the venous oxygen content (\(CvO_2\), mL L\(^{-1}\)) multiplied by the cardiac output (\(CO\), L min\(^{-1}\)); it too is usually indexed to body surface area (BSA, m\(^2\)):

\[
VO_2I = \frac{CO \times (CaO_2 - CvO_2)}{BSA}
\]

The arterial oxygen content is usually derived from the arterial oxygen saturation (\(SaO_2\), %) the haemoglobin concentration (\(Hb\), g dL\(^{-1}\)) and 0.134 \([109]\) the number of mL of oxygen carried per gram of haemoglobin per 100 mL of blood:

\[
\frac{CaO_2}{100\text{ml}} = SaO_2 \times Hb \times 0.134
\]

So that:

\[
VO_2I = \frac{CO \times (SaO_2 - SvO_2) \times Hb \times 0.134}{BSA}
\]

### 6.3 Blood Oxygen Content

The standard method for measuring blood oxygen content is the Van Slyke-Neill manometric vacuum extraction technique \([110]\) but this is difficult, tedious and clinically impractical. Arterial oxygen content is calculated using the equation:

\[
CaO_2 = (Hb \times S_aO_2 \times 0.134) + (PaO_2 \times 0.003)
\]
Where Hb is the haemoglobin concentration (g dL⁻¹), \(S_\text{a}O_2\) is the percent oxygen saturation of haemoglobin (%), 0.134 is the mL of oxygen per dL of haemoglobin (mL dL⁻¹), \(P_\text{a}O_2\) is the partial pressure of oxygen (kPa) and 0.003 is the oxygen solubility coefficient when the partial pressure of oxygen is measured in kPa. Oxygen saturation can be measured directly by using an oximeter, or it can be calculated using the oxyhaemoglobin dissociation curve. The position of the oxyhaemoglobin curve is influenced by a number of factors [111], many of which occur in surgical patients and inaccuracy can be quite high [112, 113]. Oxygen saturation should therefore be measured directly, particularly if the value is to be used for further calculations [114].

The oxygen combining capacity of haemoglobin is usually taken as 1.34 mL g⁻¹ in the clinical setting, a value derived from comparisons of haemoglobin concentration and oxygen capacity [109], which is lower than the theoretically derived maximum of 1.39 mL g⁻¹ [115]. Use of different coefficients can give a 3.7% variation in the final calculated value for oxygen delivery. Inclusion of the dissolved oxygen in the calculation is important under hyperbaric conditions but otherwise represents less than 1% of the total oxygen content.

6.3.1 Increasing oxygen saturation

The \(S_\text{a}O_2\) appears to be the most obvious factor to change when considering increasing \(D_\text{O}_2\)I. In the well, spontaneously breathing patient there is no problem with achieving oxygen saturations of 96% to 99%. In the ventilated, perioperative patient an adequate \(S_\text{a}O_2\) may be more difficult to maintain. Changes in minute volume, oxygen transfer, functional residual capacity and pulmonary shunting have varying effects in different patients. \(S_\text{a}O_2\) must therefore be measured at each calculation of the oxygen transport.

In most high-risk surgical patients mechanical ventilation is used and this may have a paradoxical effect on \(D_\text{O}_2\)I, while \(S_\text{a}O_2\) may increased, cardiac output might fall [116, 117]. Factors such as left ventricular preload [118] and right ventricular function [119] play a part in determining when and to what extent this decrease occurs. Furthermore, it
has been shown that positive pressure ventilation and the addition of peak end-expiratory pressure (PEEP) induces changes in the distribution of blood flow which may further compromise delivery of oxygen to certain tissues [120, 121]. These complicated inter-plays emphasise the importance of continuously monitoring the values contributing to $\text{DO}_2\text{I}$ in surgical patients.

### 6.4 Cardiac Output

The measurement of cardiac output is fundamental to the assessment of $\text{DO}_2\text{I}$. Cardiac output describes the measurement of the output of the left ventricle in L min$^{-1}$. This is usually interpreted as being equivalent to a measure of tissue perfusion; however this need not necessarily be the case due to variations in regional blood flow and blood flow within separate organs. While various efforts are being made to find more accurately the adequacy of organ and regional blood flow (See Chapter 7.3 below: Other indicators of inadequate tissue oxygenation), the most reliable evidence based information comes from the global assessments of CI, $\text{DO}_2\text{I}$ made by PA catheter, and SV made by oesophageal Doppler.

#### 6.4.1 Measuring Cardiac Output: The pulmonary artery catheter

The most common method of cardiac output measurement is a variation of the indicator-dilution technique using cold fluid or warmed blood as the indicator [122], the change in temperature being inversely proportional to the cardiac output [123, 124]. The thermodilution technique is simple but there are a number of disadvantages. A major disadvantage is the need to catheterise the PA and recently there has been considerable debate as to the role, importance and safety of PA catheterisation (See below). Also, at low cardiac output, thermodilution may progressively overestimate cardiac output [125], ventilation may effect measurements due cyclical changes in venous return and right ventricular after-load [126-129], and injectate volume and temperature need to be accurately controlled [130, 131]. Usually the PA catheter is
placed into an appropriate central vein using a sheath down which the catheter is
inserted this is frequently fitted with an infusion arm, changes in the use of the side arm
may lead to variations in the measured cardiac output due to induced blood or injectate
temperature changes [132]. During the perioperative workup of a surgical patient who
may be dehydrated, and in whom multiple cardiac output estimations are being made,
fluids are often given down the sidearm at the same time as thermodilution
measurements are being made. Paper 9 investigated the importance of this and showed
that differences of up to 23% could occur in the measurement of cardiac output
depending on the conditions of use of the sidearm.

The use of the PA catheter has itself generated much controversy since its first
description as a bedside technique in man [23]. In the mid 1980’s there were cautionary
words concerning its use [133], and calls for a moratorium on the use of the PA
catheter, due to the lack of evidence concerning improved outcome [134]. However
these arguments were supercilious because as an invasive monitor the PA catheter
could only ever be shown to be harmful. It is the use of the information gained from the
monitoring tool that may or may not prove to be useful in treating the patient.
Furthermore, although the expectation of good patient management is an improvement
in outcome; a monitoring tool can be useful in patient management in other ways, for
example by allowing patients to be treated more easily or, by avoiding other
investigations, more cheaply.

The correct indications for placement of a PA catheter have been the subject of debate
[135], and no formal indications are widely accepted. It is also known that the true
potential of the monitor is unlikely to be reached in current circumstances as physicians
knowledge of the PA catheter was inadequate 1990 [136], and has not changed in 7 year
[137]. Recently a questionnaire sent to board-certified intensivists, who were members
of the American College of Chest Physicians or Society of Critical Care Medicine,
showed a significant heterogeneity in selecting an intervention based on PA catheter
data [138]. This study also suggested that any randomised trial evaluating efficacy of
PA catheters would have to have strict treatment protocols. This is particularly
important when considering the debate concerning the use of the PA catheter, and also when considering details of the treatment regimes for protocol and control patients in studies of perioperative goal-directed therapy.

The debate concerning the use of the PA catheter has been rejoined after the publication of the findings of the SUPPORT investigators that the appeared to be an excess mortality in the cohort of patients who had placement of a PA catheter [139]. Although the methodology of this study has been questioned [140] it cast serious doubt over the continued use of the technique [141, 142]. Further questions were asked when a study of 10217 patient showed that the PA catheter independently predicted admission to a surgical ICU [143], and a study of 4059 patients undergoing elective non-cardiac surgery reported that patients who received a PA catheter had a three-fold increase in major cardiac events [144]. These three studies were all retrospective data analyses and this thesis has been unable to find any randomised trial evidence that confirms these conclusions, although the study by Sandham and colleagues did suggest a higher incidence of pulmonary embolism in the PA catheter group of a goal-directed therapy study, there was no difference in overall mortality [145]. In contrast a meta-analysis of trials using PA catheters using a total of 1,610 patients from 12 trials showed a reduction in morbidity in the PA catheter group (relative risk ratio of 0.78, 95% confidence interval of 0.64-0.94) [146], this followed a similar meta-analysis by the same group that had demonstrated a non-significant trend to reduced morbidity in a PA catheter group [147].

Recently Richard and colleagues performed a randomised study of the PA catheter in patients with shock or adult respiratory distress syndrome [148]. The investigators found no difference between the PA catheter and no PA catheter groups for organ dysfunction, duration of mechanical ventilation, ICU stay, hospital stay or mortality. It is important in interpretation of this study to realise that no specific treatment strategies were required, therapy being left up to individual physicians and, although this a pragmatic approach, it is very difficult to generalise the study's findings to other times, places or patient populations [108]. Other groups have however found similar findings.
In a study of 751 medical ICU patients a retrospective analysis could not detect an association between PA catheter use and mortality [149], and two studies from the UK show similar results both in a retrospective analysis [150], and a randomised study [151].

6.4.2 Measuring Cardiac Output: Doppler Flow Measurement

The PA catheter has always been regarded as an invasive investigation, and the discussion above emphasises both the confusion about what could be expected from the placement of a PA catheter and also the current controversy regarding its safety. As well as safety concerns, the PA catheter also requires technical skill and experience and takes over 45 minutes to obtain information after the decision to place the catheter has been made [152]. Investigators have therefore attempted to find a less invasive and quicker method for monitoring cardiac output in patients; one such method is the oesophageal Doppler.

The oesophageal Doppler monitor, described in the early 1970's [153] and subsequently refined by Singer [154, 155], provides a safe and minimally invasive means of continuously monitoring the circulation. The oesophageal Doppler monitor provides measurement of aortic blood flow described in terms of flow velocity and flow time, flow time can be corrected to the heart rate giving corrected flow time (FTc); normograms based on the subjects height and weight allow these measurements to be used to calculate SV and cardiac output. Various investigations have found good correlation between cardiac output measured by oesophageal Doppler and that measured by PA catheter thermodilution during cardiac surgery [156, 157], vascular surgery [158], and in non-surgical situations such as pre-eclampsia [159] and general critical care [160].

Monitoring haemodynamic status by use of the oesophageal Doppler allows indirect calculation of CI but does not measure any of the pressure parameters used for the titration of fluid therapy, such as CVP or PAOP. Fluid therapy is instead titrated to
increase FTc and SV, and studies using the goal-directed therapy and the oesophageal Doppler have taken this approach in patients with fractured neck of femur [161, 162], cardiac patients [163] and patients having abdominal surgery [164].

It is still too early to be able to define the risk profile of monitoring with the oesophageal Doppler. Despite the fact that this is usually described as a non-invasive technique a number of risks, such as trauma, can be associated with it, although there is no published wide experience giving descriptions of the technique and its complications. Similarly, the use of the oesophageal Doppler monitoring is frequently accompanied by the placement of a central venous cannula, both to aid monitoring of volume state and to provide a central venous point of access for drug and fluid infusions. This association with the oesophageal Doppler monitoring and the placement of a central venous cannula will encompass many of the risks associated with placement of a PA catheter. There are also problems with placement of the device in awake patients, although new devices are much thinner and are said to be suitable for such patients.

6.4.3 Increasing Cardiac Output: Fluid therapy

Fluid loading will increase CI and hence DO₂I by driving the CI up the Starling curve, by increasing venous return and left and right ventricular filling pressure. However, not all patients will respond to fluid loading with an increase in cardiac output, presumably due to left ventricular compliance defects [165], and this shows how important is the documentation of any response. As well as increasing the CI, fluid loading will be expected to increase the circulating volume and may allow better distribution of blood flow to and within organs, by opening up previously underperfused vascular channels.

There is an ongoing debate concerning the appropriate fluid management for surgical patients [166], too little fluid may limit tissue perfusion and too much may result in pulmonary and peripheral oedema. Some studies have shown that increased fluid administration, guided by the results of oesophageal Doppler monitoring, may reduce
hospital stay after repair of fractured neck of femur [161] and complications after cardiac surgery [163], and indeed the same may be true of much more simple surgery also [167]. Other studies have suggested that too much fluid can be given and a treatment policy where some limitation is made on the fluid given might result in reduction in hospital length of stay [168]. This has been recently confirmed in patients having elective colonic resection where positive salt and water balance to a 3 kg weight gain resulted in prolonged hospital stay [169]. Similarly, in patients having radical head and neck surgery excessive fluid administration may lead to oedema and increased bleeding and a randomised study has shown that relative fluid restriction to a mean 426 mL hr⁻¹ (compared to 1018 mL hr⁻¹), while resulting in mild intraoperative oliguria, does not result in a detrimental renal outcome [170].

6.4.4 Increasing Cardiac Output: Pharmacological agents

6.4.4.1 Vasodilators

Another method for increasing CI is to decrease the afterload of the heart with vasodilator therapy, many vasodilators will act through dilation of capacitance vessels to reduce preload as well. The rationale for improving cardiac function with vasodilators is well proven in cases of cardiac failure, showing benefit in both symptoms and longevity in the chronic situation and improved cardiac function in the acute situation [171, 172]. However, vasodilators may have negative side-effects on the delivery of oxygen to tissues, diverting blood from the vital areas to those of less importance, the ‘steal phenomenon’ [173, 174], or decreasing SaO₂ by increasing intrapulmonary shunting [175, 176].

Compared with the situation with the treatment of heart failure there is little evidence that vasodilators improve the outcome in the surgical patient; and one early non-randomised study showed an increased mortality rate when patients were treated primarily with vasodilators [177]. A number of the randomised goal-directed studies
have included vasodilator therapy as part of the therapeutic treatment to attain the specific haemodynamic goals of the study [7, 8, 145] (see Chapter 8.3: Randomised studies in surgical patients). In these studies it is however not possible to ascertain exactly how the vasodilators were used. It has to be concluded that vasodilators might be a suitable therapeutic agent as part of a goal-directed therapy approach, but that it might be most suitable to use them as part of a more global treatment policy involving fluid loading and inotropes as well.

6.4.4.2 Inotropes with particular reference to dopexamine hydrochloride

As suggested above the most straightforward method to increase CI, tissue perfusion and DO₂I are a combination of fluid therapy and inotropic medication. A number of different pharmacological products are available and the randomised perioperative studies have used various agents (reviewed in Chapter 8.3: Randomised studies in surgical patients). Some studies have specifically used dobutamine with or without additional vasodilators [8, 10, 178-182], other studies have used dopexamine usually as a single inotrope [11, 183-185], however in a number of studies the inotropic medication is either not stated or can be selected from a cocktail of drugs [7, 9, 145, 186, 187].

The use of inotropic agents in surgical patients is a controversial topic with concerns being focused primarily on the risk of inducing myocardial ischaemia [188]. An increase in myocardial oxygen consumption occurs to some extent with all inotropes due to a combination of changes in heart rate, left ventricular contractility and left ventricular wall tension; and generally the choice of inotrope suffers from the lack of standardisation. In a recent survey in France [189] dopamine was selected in a clinical setting requiring an optimisation of regional blood flow, as with high-risk surgical patients; dopexamine was used as a second or third choice agent to improve regional blood flow and cardiac output. It was suggested that particularly for improvement of regional circulation and management of high-risk surgical patients guidelines that define the place of each catecholamine in these settings would improve the quality of
care. This is a difficult topic as there are only two comparisons of inotropes used in the pre-operative setting; one which has shown that dopexamine could be used more easily than dobutamine for pre-operative increases of CI and DO2I due to reduced tachycardia and other complications (Paper 4), and the other has shown that outcome may be better if dopexamine is used instead of adrenaline [11].

In the studies of Boyd and colleagues dopexamine was used as the inotropic medication. Dopexamine is a derivative of dopamine with both vasodilatory and mild inotropic actions. The main features of dopexamine are dopamine1 and dopamine2 receptor agonism with marked β2 stimulation. There is no effect on α receptors, although uptake-1 is inhibited. In addition, dopexamine has no activity at cholinergic, histamine or 5-hydroxytryptamine [190]. Dopexamine results in decrease in SVR and increase in HR. SV and CI rise due to both vasodilatation and a mild inotropic effect. The effects on blood pressure are more variable and depend probably on fluid status [191] [192] [193].

We showed in an early study that dopexamine could be used successfully to increase CI and DO2I preoperatively, Paper 1. We also performed a comparison with dobutamine and showed that dopexamine was superior, Paper 4. Following this work a number of other studies have used dopexamine as the inotrope of choice in their protocols to increase DO2I pre-operatively [11, 183-185]. Other investigators have studied dopexamine in surgical patients looking at specific aspects such as renal protection, splanchnic effects and anti-inflammatory effects. This has stimulated more interest with regard to dopexamine and will be discussed below.

Vasoactive medication can also be expected to have effects on gas exchange and pulmonary blood flow. Pulmonary circulatory tone is controlled by α- and β2-receptors under normal physiological conditions with α-receptors being more important, and both dopamine, and to a lesser extent dobutamine, have been shown to impair oxygenation in animal models [194]. Berendes et al. [195], looking at coronary artery bypass graft patients with a left ventricular ejection fraction >50% showed that dopexamine caused a
significant decrease in pulmonary vascular resistance, and others have found a decrease in \( \text{SaO}_2 \) (Boyd, unpublished observations). The extent of this decrease is only limited and the overall effect of dopexamine is usually an increase in \( \text{DO}_2I \) as a result of an increase in CI. Other side-effects are also possible, for example dopexamine and higher doses of dopamine induce at least partial hypopituitarism, which may possibly affect postoperative morbidity in men undergoing abdominal surgical procedures [196].

Early work suggested a role for dopexamine in increasing renal blood flow [197], and this has prompted investigation into the renal effects of dopexamine as a 'reno-protective' agent. In healthy volunteers given equipotent doses of dopamine, dopexamine and dobutamine, renal plasma flow was higher with dopamine, slightly increased with dopexamine, and unchanged by dobutamine. However, only dopexamine increased glommerular filtration rate [198]. Other studies have shown that creatinine clearance is increased even at low doses of dopexamine [195], and there are increases in renal blood flow [199, 200], although this may be a systemic effect [201]. In the clinical context there are few studies investigating this. Dopexamine has been shown to protect renal function during aortic surgery [202], but in more general studies no such effect has been demonstrated [203].

Of more interest than the renal effects is the possibility of dopexamine having specific effects on splanchnic and hepatic perfusion, and the inflammatory pathway. It is hypothesised that relative gut ischaemia may lead to the translocation of endotoxin and bacteria into the portal system [204], and that improving the splanchnic blood supply may help prevent this. Consequently, selective splanchnic vasodilators have been keenly sought, with dopexamine being proposed as one such agent [205]. In animal models dopexamine has been shown to positively influence gut serosal, liver and skeletal muscle oxygenation in sepsis [206, 207]. Dopexamine also appears to preserve hepatic ultrastructure in septic pigs [208] and to improve oxygenation [209]. In humans, investigation has concentrated on changes in gastric intramucosal pH (pH\(_i\)) (See Chapter 7.3.1 below: Intramucosal pH measurement) and direct measurement of splanchnic flow and mucosal and serosal flows in the intestine. This area has been
recently reviewed [205, 210].

In clinical practice techniques for measuring splanchnic flow are not yet fully established. The most commonly used method is the measurement of pHj. The effect of dopexamine on pHj is variable. Some studies have shown an increase in pHj in patients with critical illness and septic shock [211, 212], and others have shown that an increase in pHj in patients following abdominal surgery who have been given dopexamine is associated with reduced multiple organ failure score and MODS [213]. Other studies, however, show no change in pHj as a result of dopexamine infusion in general critically ill patients [214] or after surgery [195, 215, 216].

However, gastric mucosal ischaemia may occur independently of adequate splanchnic supply due to redistribution of villous flow or altered cellular metabolic function under a variety of clinical states including sepsis and surgery. While low dose dopexamine improved tissue oxygenation (P\textsubscript{t}O\textsubscript{2}) at the serosal side of the gut in the small bowel level, it did not improve gastric mucosal PCO\textsubscript{2} [217]. Other studies have confirmed the possibility that dopexamine, while increasing mesenteric blood flow, also diverts blood away from the jejunal mucosa [218]. Their however seems to be a fairly consistent finding that dopexamine increases colonic blood flow in sepsis [219], and in surgical patients [220]. On a more functional level, gut permeability in post bypass patients was reduced by dopexamine but not dopamine [221], and this appeared to be related to increased DO\textsubscript{2}I in the dopexamine group. However, in a larger group of 102 critically ill patients predicted to require organ support for more than four days no effect on gastrointestinal absorption or permeability was found [203].

Another important possible role for dopexamine is as an anti-inflammatory one via its \beta\textsubscript{2} sympathomimetic properties. Although it is not yet clear whether changes in inflammatory mediators relate to clinical correlates of improvement in outcome [222], dopexamine has been studied before, during and after cardiac surgery for its anti-inflammatory properties. IL-6 levels rose to a maximum after 6-8 hours and were significantly lower following dopexamine infusion; serum amyloid A and C-reactive
protein levels were also lower in the dopexamine group at 24 hours [195]. In an experimental study, dopexamine decreased leukocyte adherence and macromolecular leakage in the post-capillary venules of endotoxin treated rat mesentery [223]. Furthermore a specific $\beta_2$ receptor affect has been implicated in improving survival from oxygen free radical infusion from 20% to 70% in a similar rat experimental model [224]. In the clinical situation 30 patients undergoing Whipple’s procedure showed significantly elevated endothelin-1 and vasopressin levels in control patients, an effect that was abolished by dopexamine infusion [225]. Not all clinical studies however have found improvement in inflammatory responses as a result of dopexamine infusion [226], and while dopexamine seems to have a favorable haemodynamic profile it is not yet possible to claim any other specific benefits of dopexamine use in surgical patients over any other agents.

6.4.4.3 Other drugs with specific reference to anaesthetic agents

A number of other drugs given around the time of operation are likely to have effects on haemodynamic variables. This may be important if the perioperative care of the patient is following a goal-directed therapy approach. The most widespread drugs will of course be the anaesthetic agents, it is surprising therefore that there is little work on the effect of anaesthetic agents on DO$_2$I, CI or regional blood flow during the period of anaesthesia and surgery. Much of the work on anaesthetic agents has been concerned with the period of induction of anaesthesia or has been concerned with specific cardiac effects of drugs at the time of cardiac surgery.

It has been understood for some time that the various anaesthetic agents have different cardiovascular depressant effects for example propofol is more depressant of blood pressure than thiopentone [227] at the time of induction of anaesthesia. In a more complicated study using supra-ternal Doppler, thiopentone had little effect on either CI or SVR, propofol increased CI and decreased SVR while etomidate decreased CI and increased SVR [228]. Other variations are seen at the time of the liver reperfusion
following liver transplant surgery where both isoflurane and propofol maintain CI, isoflurane by increasing SV and propofol by increasing HR [229].

In a study on vascular surgery patients, Boyd and colleagues showed that propofol maintained CI and right ventricular performance better than isoflurane Paper 10. In complete contrast a second study showed that propofol caused a greater decrease in CI and right ventricular ejection fraction than isoflurane [230].

For interpretation of work later in this thesis (reviewed in Chapter 8.3: Randomised studies in surgical patients) it is relevant to note that there has been no investigation of the influence of anaesthetic technique, although some of the studies have instituted a standardised anaesthetic technique for patients in protocol and control groups. The influence of different techniques on the outcome of these studies is a question that is open for further investigation. Moreover, some of the studies allowed epidural analgesia to be given as part of the anaesthetic protocol, the influence of this in conjunction with other therapeutic techniques to increase CI and DO$_2$I is not known.

6.5 Haemoglobin

The amount of oxygen carried by the blood is proportional to the haemoglobin (Hb) concentration and it might appear that manipulation of the oxygen carrying capacity of the blood is the most promising way to affect DO$_2$I. Following transfusion maximum VO$_2$I and muscle performance in exercising man is enhanced [231] leading to the successful practise of 'blood doping' to improve athletic performance [232]. However increasing the red cell concentration increases blood viscosity and may impair cardiac output and limit the potential for rise in DO$_2$I. In experimental animals the cardiac output is inversely related to the haematocrit in the range <24% and >64% [233], and a maximum DO$_2$I is seen at haematocrit values lower than normal [234, 235]. Furthermore, stored blood has a relative left shift of the oxyhaemoglobin due to low 2,3-diphosphoglycerate [236], and although this affect may be reversible after 24 hours [237] and may have a negligible affect during normal oxygenation [238], it will limit
oxygen availability at the tissues while increasing calculated oxygen delivery (see also Paper 7).
7. Other physiological treatment goals in the perioperative period

7.1 Introduction

As described earlier the hypothesis generated by Shoemaker and colleagues set targets for CI, DO$_2$I and VO$_2$I [6]. Prior to discussion of studies that have investigated this hypothesis, including studies that have used oesophageal Doppler, this chapter questions the validity of these targets, specifically VO$_2$I, and also reviews the possible application of new technology to provide new targets for therapy and monitor the success of therapy in the future.

Although a goal-directed therapy approach is practical in the perioperative patient it appears likely that some patients are inadequately treated, while others are may be excessively treated. Inadequate treatment does not offer the patient the anticipated improvement in outcome for the intervention undertaken and excessive treatment might expose the patient to unnecessary side-effects. Some studies have attempted to avoid the possibility of side-effects by introducing surrogate physiological markers of over treatment, for example Paper 2 used a rise in heart rate of greater than 20% as an indication that further increase in the dopexamine infusion rate should not be performed. Other studies have used slightly different limits on their treatment. A different, but related problem in the studies described has been the indication for stopping the deliberate increase of CI, DO$_2$I and SV. Some studies have used a general physiological indicator such as a normal lactate value (Paper 2), while others have used a predefined time interval.

It would appear a more logical approach to titrate the initial therapy to an endpoint that might be more related to the suspected ‘at-risk’ organs. Treatment could then be discontinued when these organs were able to function again normally, without risk of subsequent deterioration. However, there are only a limited number of bedside
techniques that might be suitable. The finding of a supply dependent state of VO$_2$I in critically ill patients prompted the suggestion that DO$_2$I should only be increased if VO$_2$I rose, this was taken as an indication that there was an unmet oxygen demand. **Paper 6** investigates the possible use of oxygen consumption as an endpoint for perioperative cardiac output manipulation, with particular emphasis on the effects of changing sedation levels. **Paper 7** reviews the literature and highlights problems in the use of oxygen consumption as a therapeutic target. Considering a separate endpoint for resuscitation, **Paper 8** compares the information obtained from pH$_i$ data and data concerning metabolic acidosis.

### 7.2 Oxygen consumption

In a normal subject sufficient oxygen can be extracted, on a whole body basis, until the oxygen supply falls below approximately 8 - 10 mL min$^{-1}$Kg$^{-1}$, below this point there is supply dependency, a situation where there is a linear relationship between oxygen supply and consumption [239, 240]. However in patients with Adult Respiratory Distress Syndrome supply does not become independent until the delivery is 2.5 times above normal [117, 241-244]. In septic shock a similar supply dependant pattern is seen [245-247]. In fact a mathematical analysis of data from a series of patients with different acute illnesses has shown a linear relationship between uptake and delivery over the entire range of delivery observed [248].

It therefore appears that critically ill patients have a significant impairment in oxygen extraction [249], and it was therefore suggested that VO$_2$I should become a target for treatment in its own right [6, 250]. **Paper 7** explores the evidence that might make VO$_2$I an inappropriate target in perioperative patients and reviews much of the literature in this area, which will not be redescribed here. The influence of therapeutic manoeuvres, drugs, intra-operative events, methodology, and changes in oxygen demand all effect VO$_2$I. Of particular importance are changes in sedation and paralysis which occur in most high risk surgical patients and which can also change oxygen
demand, indeed variations in DO$_2$I and VO$_2$I that occurred during variations in sedation level in critically ill post-operative patients mimicked 'supply dependence' (see Paper 6).

Changing VO$_2$I therefore seems to be an inappropriate target for treatment, particularly in perioperative patients.

### 7.3 Other indicators of inadequate tissue oxygenation

#### 7.3.1 Intramucosal pH measurement

Hollow viscus tonometry has had a resurgence of interest in the last 20 years as a method of measuring perfusion in end-organs, specifically the gastrointestinal tract [251, 252]. There are several important reasons why attention has focused on the gastrointestinal tract: first splanchnic organs suffer vasoconstriction in response to hypovolaemia [253]; second, the critical level of oxygen delivery in the gastrointestinal tract is higher than in other organs systems [254]; and thirdly, gastrointestinal tract hypoxemia may increase endotoxin and micro-organism translocation fuelling the inflammatory reaction [255]. The information from hollow viscus tonometry has traditionally been used for the calculation of intramucosal pH (pH$_i$) [256, 257], but this calculation requires the use of arterial bicarbonate which is unlikely to be a true representation of mucosal bicarbonate [258, 259]. Despite this early studies using this calculation showed that a decrease in gastrointestinal tract blood flow was reflected in a decreased pH$_i$ [260, 261].

Our perioperative targeted treatment studies were being conducted at the height of this interest in pH$_i$ measurement and there was considerable peer pressure to add pH$_i$ as a target of our work. This was increased by the publication of a trial [262] in which a protocol group of critically ill patients had been treated with a combination of fluid infusions and dobutamine to try to maintain or attain a normal pH$_i$ (pH$_i$ >7.35), compared to a control group who had routine care. This treatment was given to the
protocol patients in the expectation that systemic DO$_2$I would be increased. Retrospectively the patients were divided into those that had a normal pH$_i$ at the initial measurement, and in whom treatment was to maintain this value, and those patients who had a low pH$_i$ at the initial measurement, in whom treatment was to try to increase pH$_i$. Data analysis showed that in the low pH$_i$ group there was no difference between the protocol (mortality 63%) and the control groups (mortality 64%); but in the group that had a normal pH$_i$ at the outset of the study, and in whom it could be inferred that tissue perfusion was adequate and organ failure had not yet commenced, the mortality in the protocol group (42%) was significantly lower than the mortality in the control group (58%).

We therefore investigated the additional information that pH$_i$ measurement could add to information already available from routine blood gas analysis of systemic acidosis and showed that either systemic acidosis was influenced largely by splanchnic acidosis, or that the calculation of pH$_i$ was influenced by systemic acidosis, see Paper 8. As a result of this study we did not add pH$_i$ as a target of perioperative treatment. Further analysis of critically ill patients by Bennett's group continues to show in a study of 148 patients that base excess and lactate, or the combination of the two, can be used to predict outcome in patients admitted to the intensive care unit [263].

More recently arterial pCO2 has been referenced to gastric mucosal pCO2 to calculate a pCO2 gap (pgCO2) and this has been proposed as a better marker of gastrointestinal tract ischaemia [264]. Some even suggest that pgCO2 monitoring might the method of choice to identify end-organ hypoperfusion and provide treatment targets in the perioperative patient [265]. It is also possible to automate the process and it might be possible to measure gap by using end-tidal pCO2 [266]. We reanalysed our original data from Paper 8 to calculate pgCO2 and showed that pgCO2 correlated with pH$_i$ ($r=-0.71$, $p<0.0001$) but there was no correlation between the pgCO2 and acid/base data derived from routine blood gas analysis, or any of the haemodynamic parameters measured. This is in contrast to the pH$_b$, which is strongly correlated with acid/base measurements. We concluded that pgCO2 was clearly measuring something pertinent to
the splanchnic beds, but that it remained to be confirmed whether it gave an indication of the effectiveness of the mesenteric circulation, or whether treatment can both reduce the gap and improve patient survival [267]. Other studies have shown that a reduced pgCO2 is associated with an increase in splanchnic blood flow [268], but in contrast some animal studies have shown that the pgCO2 might not detect mesenteric ischaemia [269].

A number of studies have noted a relationship between low pHj and morbidity and mortality in surgical patients [213, 270], possibly related to altered hepato-splanchnic blood flow and the release of inflammatory mediators from the splanchnic circulation [271]. Although in other studies the routine use of pHj in the management of critically ill patients could not be supported, and it was suggested that pHj was simply a marker of disease rather than a factor in the pathogenesis of multiple organ failure [272, 273].

In a group of cardiac surgery patients there were increases in gut permeability but these preceded gut mucosal ischaemia [274]. Other studies have not even confirmed the predictive value of pHj measurements in compromised patients following cardiac surgery [275], but in contrast Lebuffe et al. reported that automated air tonometry might be able to identify patients at risk of circulatory failure after cardiac surgery better than conventional haemodynamic variables [276]. These variations in findings may be because, gastric mucosal pH does not necessarily reflect changes in splanchnic blood flow after cardiac surgery [277].

There is also some doubt as to the correct drugs and approach to correct an abnormal pHj. Some studies have shown increases in pHj following various drug infusions and some, in apparently similar groups of patients, have not shown any change. During and after cardiac surgery neither low dose dopexamine or low dose dopamine had any influence on pHj [215], and some studies have shown that during abdominal aortic surgery, dopexamine infusion might avoid the decrease in pHj following removal of the cross clamp [278], and dopexamine can reverse a low pHj in high-risk surgical patients who had a low pHj in the pre-operative period [213]. Again in patients undergoing
major surgery, it has been shown that fluid volume resuscitation with hydroxyethyl starch solutions, compared to crystalloid, may prevent falls in pH, suggesting that microvascular flow is better maintained, but there were no differences in clinical outcome measures between the groups [279]. Similarly, a study of patients having elective repair of infra-renal abdominal aortic aneurysms confirmed that low pH values (< 7.32) and their persistence were predictors of major complications, however treatment to elevate low pH values did not improve postoperative outcome [280].

In trauma patients pHi and pCO\textsubscript{2} have been suggested as an alternative method to the PA catheter to guide resuscitation [262, 281-283]. One small, observational study found no correlation between pHi and systemic oxygen transport variables and, in addition, logistic regression analysis showed that only pHi, base deficit and SvO\textsubscript{2} were significantly associated with mortality during the study period [284]. As the patients in this observational study were all treated using an oxygen transport approach, the authors conclude that the measurement of gastric tonometry may give supplemental information [284]. Other studies have also shown poor agreement with oxygen transport data and pHi data [281]. One trial has compared the efficacy of a global oxygen transport approach versus a pHi guided approach in 57 trauma patients randomised into two groups. One group had normalization and maintenance of pHi at or above 7.3 and the second group had treatment to maintain DO\textsubscript{2}I > 600 mL min\textsuperscript{-1} m\textsuperscript{-2} or VO\textsubscript{2}I > 150 mL min\textsuperscript{-1} m\textsuperscript{-2}. The groups had statistically similar injury severity scores, lactate levels, and base deficits, and there was no difference in the mortality of the two groups. However, a persistently low pHi was associated with complications and mortality, and was the first finding in all the non-survivors at least 48 to 72 hours before death [285].

Despite the possible usefulness of pHi to provide a monitor of the adequate nature of resuscitation, it does not fit well with a goal-directed therapeutic approach to surgical patients. The values of pHi fall either within the normal range or an abnormally low range, and do not allow the possibility of a preemptive treatment approach. For example, if using only pHi as the monitoring tool no specific additional therapy would be indicated if results showed a normal value. Conversely, if the pHi value was low it
would suggest that significant hypoperfusion was already taking place and this would be counter to philosophical approach of goal-directed therapy where treatment is given preemptively to prevent hypoperfusion occurring in the first place. It seems unlikely that any monitoring tool that is designed to support to identify the state of hypoperfusion could be used in a goal-directed therapeutic strategy.

### 7.3.2 Indicators of metabolic acidosis: lactate and base deficit

Lactate concentration is a variable that is commonly used to assess the severity of shock [286]. With trauma, increased lactate concentration is assumed to be the result of anaerobic glycolysis, but increased lactate concentration can result from other causes and frequently correlates with base deficit [287]. Increased lactate concentration that persists after 12 hours of ongoing resuscitation is probably indicative of defective mitochondrial function in peripheral tissues because of prolonged hypoperfusion, hypoxemia, and acidemia and these patients are at high risk of developing MODS and dying [288]. It is often difficult to interpret a raised lactate concentration as it can be elevated due to hypoperfusion and hypoxia, and also as a result of direct failures in the Krebs cycle. This results in a build-up of intracellular pyruvate that is converted to lactate, this exits the cell for transport back to the liver to be converted into glucose in the Cori cycle [289, 290]. Furthermore lactate levels are altered by adrenergic agonists and antagonists [291], both types of medication are frequently given during shock resuscitation and therefore the rationale for using lactate as a resuscitation endpoint is weakened. Despite this some studies investigating goal-directed therapy in the perioperative period, including that presented in Paper 2, have used normal lactate as a marker of final successful resuscitation.

Base deficit is often mentioned anecdotally as a resuscitation target in perioperative and shock management. There is little evidence that it is either useful or appropriate in the perioperative situation, but Davis and colleagues showed base deficit to have strong association with blood loss, crystalloid fluid infusion, need for operative intervention, and mortality after trauma [292-296]. As a result, base deficit has become a standard
method of assessing the severity of shock in the emergency department, and serial base deficit determinations can be used as an index of adequacy of resuscitation. We showed it was equivalent to pH in predicting outcome in critically ill patients on the ICU (Paper 8) and continued work has emphasised its importance in general [263]. Again despite the lack of definite supporting evidence some studies investigating goal-directed therapy in the perioperative period have used normal base deficit as a marker of final successful resuscitation.

7.3.3 Mixed Venous Oxygen Saturation

Mixed venous oxygen saturation (SvO\textsubscript{2}) might be an appropriate goal for therapy in the perioperative phase as it appears to represent a balance between oxygen supply and demand. However, concentration on this one calculated parameter emphasises the importance of oxygen flux and ignores other possible benefits of a goal-directed therapeutic approach, such as a more general maintenance of tissue perfusion. Furthermore, changes in SvO\textsubscript{2}, while representing changes in oxygen supply or demand, do not identify appropriate points for intervention, such as replacing a falling haemoglobin concentration, without other appropriate investigations. Two of the studies investigating goal-directed therapy in the perioperative period (See Randomised studies in surgical patients) have used SvO\textsubscript{2} as a target for treatment [179, 182], and one study investigating early goal-directed therapy in patients with septic shock used central venous saturation (ScvO\textsubscript{2}) [297]. A further study of 40 patients with multiple injuries randomised them to a group in whom DO\textsubscript{2}I was routinely maintained above normal levels by use of fluids or dobutamine, and a second group in whom DO\textsubscript{2}I was only increased if SvO\textsubscript{2} decreased or the ‘dobutamine test’ was positive [298]. In the second group there was significantly greater survival and reduced incidence of organ failures however in this complicated analysis all patients in the study did achieve high levels of DO\textsubscript{2}I.
In a separate development fiberoptic oximetry technology can be added to a central venous catheter to monitor ScvO₂. Although ScvO₂ is not the same as mixed venous oxygen saturation measured by a PA catheter, the principle that these variables reflect the balance between DO₂I and VO₂I is familiar to most clinicians. This technology is known to provide an accurate, stable measurement and a recent randomised controlled trial in which ScvO₂ was used as the endpoint for resuscitation of septic shock starting very early in the accident and emergency department, demonstrated improved survival compared with routine care [297]. However this thesis could not identify any randomised study looking at ScvO₂ as an endpoint for treatment in the perioperative patient.

SvO₂ and ScvO₂ could be useful monitoring tools in perioperative patients, and it would undoubtedly be possible to use these tools in many patients. However, once again, no preemptive targets for venous oxygen saturation measurements have been defined and using such measurements to identify an abnormally low value, for which treatment can then be given, implies that tissue hypoperfusion might already be occurring.

7.3.4 Less invasive monitors of tissue oxygenation

Most of the monitoring that has been discussed in this paper relies on invasive techniques. These have been have been criticised due to the risk of side-effects and difficulty in placing the monitoring equipment in terms of location, equipment and expertise. Apart from oesophageal Doppler monitoring and pH or pgCO₂ monitoring, which have been discussed above, there is little published literature on the usefulness of more non-invasive techniques in surgical patients, most of the data comes from emergency and trauma patients.

Some time ago it was demonstrated that transcutaneous PO₂ (PtcO₂) and PCO₂ (PtcCO₂) monitoring is accurate and useful in shock resuscitation [299]. In a recent study 48 consecutive trauma patients were studied in the emergency room with measurements of
PtcO₂ and PtcCO₂ tensions, which directly measure skin oxygenation and CO₂ retention with the objective of evaluating skin oxygenation and perfusion in emergency patients. The survivors had higher PtcO₂ and lower PtcCO₂ than the group who died, and it was concluded that monitoring continuously to evaluate tissue perfusion may serve as early warning in critically injured patients [300]. Furthermore, when early noninvasive monitoring in the emergency department showed reduced tissue perfusion there was an increased incidence of adult respiratory distress syndrome (ARDS), and the patterns were further pronounced in the ARDS patients who died [301]. Other studies have shown that placement of extremely small probes with PO₂, PCO₂, and pH sensors directly in skeletal muscle can also successfully monitor resuscitation responses [302], and sublingual PCO₂ measurement can also be used [303]. Using a combination of these techniques survival can also be predicted by models based on the quantitative assessment of the net cumulative deficits of CI, arterial hypoxemia, and tissue perfusion, [304].

Additionally, Shoemaker’s group have demonstrated the utility of transthoracic electrical bioimpedance (TEB) to monitor CI and to detect myocardial dysfunction in the emergency room [305] and the operating theatre [306, 307]. When used in a combination assessment of the adequacy of resuscitation TEB, with pulse oximetry to reflect pulmonary function, PtcCO₂ to reflect tissue perfusion, and blood pressure to reflect the overall circulatory status, noninvasive monitoring systems could provide continuous displays of data for early recognition of circulatory dysfunction in emergency conditions [304].

Another technology that might be useful in the future is near infrared spectroscopy (NIRS) which monitors haemoglobin O₂ saturation in skeletal muscle and subcutaneous tissue oxygenation. In a recent study, NIRS was used to monitor subcutaneous tissue oxygenation in the deltoid region during shock resuscitation and was found to be correlated with DO₂I [308]. NIRS also has the potential to monitor the aa₃ redox state, which reflects mitochondrial oxygen consumption [288]. NIRS appears to potentially be a very useful tool to guide perioperative care but despite
that fact that it has been investigated in animal models [309] and critically ill patients with compartment syndrome [310], it has not been investigated in perioperative surgical patients.

Although the less-invasive monitors of tissue oxygenation described above could all theoretically be used in the perioperative patient, this thesis has not been able to identify any randomised controlled trials. As with the other technologies described in this chapter the use of tissue oxygen measurements has been to identify abnormally low ranges and then to provide treatment with the aim of restoring adequate oxygenation, this is not in keeping with the philosophical approach of a preemptive treatment described in the context of goal-directed therapy.

### 7.4 Alternative approaches in the perioperative period

There are number of studies that have investigated alternative treatment strategies to goal-directed therapy with the aim of reducing perioperative mortality and morbidity. This thesis considers these alternative strategies to help give a context for the understanding of the goal-directed therapy approach to treatment; and so that the results of trials investigating goal-directed therapy can be compared in terms of numbers of studies, numbers of patients studied and outcome to studies investigating various alternative strategies.

#### 7.4.1 Fluids without monitoring

Some studies have taken the approach of just giving additional fluids without the invasive monitoring. Garrison and colleagues gave a 2L infusion of normal saline over 2 hours to 306 patients undergoing non-cardiac surgery, and found that there was an improvement in intraoperative cardiovascular stability (57% saline vs. 38% control), a reduction in the need for pharmacologic support of blood pressure (19% saline vs. 30% control), and reduction in the amount of intraoperative fluid administration (hydration
Furthermore, in patients undergoing aortic reconstructive procedures, there was a reduction in the incidence of postoperative complications (52% to 28%) primarily attributed to a reduction in pulmonary complications [311]. Another study compared colloid, with crystalloid administration in patients having major non-cardiac surgery. The colloid group had significantly less nausea and vomiting, use of rescue anti-emetics, severe pain, peri-orbital edema, and double vision, but also received less fluid overall; it was concluded that colloid infusion was associated with an improvement in the quality of postoperative recovery [312]. However there may be a detrimental side to unmonitored fluid infusion as it has been recently shown in patients having elective colonic resection that positive salt and water balance to a 3 kg weight gain resulted in prolonged hospital stay [169].

7.4.2 β-blockers

A number of investigators have realised that many perioperative events are associated with myocardial ischaemia, and have attempted to reduce this risk by perioperative β-blockade. The conflict between the approach of increasing CI and DO$_2$I and one in which heart rate, and possibly CI, are limited has been described as a tortoise vs. hare conflict [188]! However this conflict has probably been exaggerated, as most of the studies involving increasing CI and DO$_2$I offer strict limits on any increases in heart rate that can be induced by the therapy. Furthermore, precise attention to fluid therapy and volume status of the patient will limit tachycardia and improve coronary perfusion, as well as perfusion in other organ systems.

Initial interest in β-blockade came from a randomised, double blind study of 200 patients at risk of coronary artery disease undergoing non-cardiac surgery. Atenolol was give intravenously at the time of surgery and orally until hospital discharge. Low hospital mortality was unchanged at 3%, but following discharge at six months, one and two years there were significant reductions in mortality, principally from cardiac causes [313]. In a separate study, Poldermans and colleagues used perioperative bisoprolol in a randomised trial of 59 vascular surgery patients identified by positive dobutamine
echocardiography as being at high risk of postoperative myocardial infarct, and showed a reduction in deaths from cardiac causes [314]. A follow-up study confirmed these results [315]. Despite the small size of the earlier trial the American College of Cardiology formally recommended that β-blockade should be used in surgical patients at risk of ischaemic events in 1996 [316]. This author considers the recommendation to be premature as there appear to be many outstanding issues not addressed and the sized of the trials are only small. Others have come to the same conclusion particularly in patients at low or intermediate risk, in emergency surgery, and in patients having epidural anaesthesia for post-operative pain relief [317]. Even at a theoretical level the presumed link between perioperative tachycardia, ischaemia and post-operative myocardial infarction is not clear [318, 319]. Moreover there are a number of questions regarding safety and the use of perioperative use of β-blockade as a number of other studies using β-blockers, albeit in differing contexts [320], had a much higher incidence of side-effects than the studies of Mangano [313] and Poldermans [314]. Furthermore, β-blockade is know to have effects on platelet function [321] and immune function [322], which may have been harmful in many surgical patients.

A further complicating issue is the finding in Mangano’s paper of only a delayed reduction in mortality at 6 months [313]. Fleisher [318] has pointed out that the placebo group in Mangano’s study [313] had a higher incidence of coronary artery disease than the treatment group and a significantly lower incidence of pre-operative β-blocker therapy, which once started was continued in the post-operative period. It could therefore be suggested that the survival benefit could be the already well recognised benefit of long term β-blockade in patients with established coronary artery disease. It is clear that while β-blockade in the perioperative period might be of importance in reducing surgical mortality, it is not the whole story and much further work needs to be undertaken.
8. Trials with specific goal of increasing cardiac output and oxygen delivery

8.1 Introduction

There are a number of published studies investigating the role of goal-directed therapy in high risk perioperative patients and other patient groups. These studies followed a preemptive approach where targets for treatment are set with a specific goal of increasing tissue perfusion. These studies have used the monitoring tool of the PA catheter to provide treatment targets for increasing cardiac output and oxygen delivery, or have used the oesophageal Doppler monitor to provide treatment targets for increasing SV. In addition a number of studies have used S\textsubscript{\text{O}}\textsubscript{2} as the target for treatment. The initial studies were observational non-controlled studies and these have been followed by randomised, controlled studies in the perioperative patient.

For completeness this thesis also discusses the results of trials in non-surgical patient groups. These have included patients with general critical illness, sepsis, burns and trauma, and the studies have been discussed here to allow a comparison to be made with the studies investigating treatment effects in high risk surgical patients.

8.2 Non-randomised studies in surgical patients

Although in the 1980’s it was becoming widespread practice to invasively monitor perioperative patients with PA catheters and titrate fluid therapy to the left and right ventricular filling pressures, very few studies, or patient series, were actually published. Notable exceptions were the publications by Babu and colleagues [323], Whitmore \textit{et al.} [324], Grindlinger \textit{et al.} [177] and Rao \textit{et al.} [325]. Some of this work was included in the review in \textbf{Paper 5}. 

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Babu and colleagues [323] showed that in patients undergoing elective vascular reconstructions while 33% had normal left ventricular function, 67% had impaired left ventricular function responding to volume load (27%), after-load reduction (13%), inotropic support (17%), or combination therapy (9%). Furthermore, they showed that in the patients who had therapeutic intervention outcome was improved compared to similar groups in that institution that had no such intervention. At the same time Whittmore and colleagues investigated the use of PA catheters for control of fluid management in patients undergoing elective abdominal aortic aneurysm repair [324]. Fluid was titrated to raise the PAOP to a point at which the cardiac output peaked, or to a maximum of 12 - 14 mmHg if the CI was already greater than 2.5 L min\(^{-1}\)m\(^{-2}\). The authors concluded that the sophisticated fluid management in their patients played an important role in a reduction of mortality rate from 6% to 0.9%. Showing contrasting results, Grindlinger et al. also studied patients undergoing abdominal aortic aneurysm repair, but in addition to careful titration of fluid in the pre-operative period, they gave vasodilators to 1 of 3 groups in the intra-operative period [177]. This intervention resulted in a fall in cardiac output in these patients, and they had a higher incidence of myocardial infarction than the other two groups (P<0.03).

Rao and colleagues, analysed the effect that a change in practice had on mortality in patients who had previously suffered a myocardial infarction and were now undergoing non-cardiac surgery [325]. Retrospectively data collected from 1973-1976 showed a perioperative re-infarction rate of 7.7%. Data from a second group was collected prospectively from 1977-1982. In this prospective group a change in policy towards invasive haemodynamic monitoring had been undertaken: PA catheters were inserted pre-operatively and fluids, vasodilators and inotropes were given to optimise the patient’s cardiac status, although it is not clear what cardiovascular targets were used during the perioperative period. The intervention was successful because in the second prospective group there was a significant reduction in re-infarction rate to 1.9% (P<0.005).
At the same time Shoemaker's group were trying specific cardiovascular targets [6], in high risk perioperative patients [8, 29, 326]. 252 patients undergoing 276 operations were studied and the ongoing results published [8, 29, 326]. Patients were allocated to a control group, having normal cardio-respiratory goals, or a protocol group having higher goals for oxygen transport. The patient mix in each group was comparable, but patients were allocated to the groups by pre-determined temporal schedule, not by randomisation. Routine parameters such as blood pressure (>120/80 mmHg), heart rate (60-120 bpm) and urine output (>30 mL hr⁻¹) were the same for both groups, but goals for CI (2.8 - 3.5 L min⁻¹ m⁻² for control patients and >4.5 L min⁻¹ m⁻² for protocol patients) and DO₂I (400 - 550 mL min⁻¹ m⁻² for control patients and >600 mL min⁻¹ m⁻² for protocol patients) were greater in the protocol patients. The mortality in the control group was 48% (1982) [326], 35% (1983) [29] and 38% (1988) [8] as the study developed. In the protocol group the mortality rates were consistently lower than those in the control group, 13% (p<0.03) in 1982 [326], 12.5% (p<0.02) in 1983 [29] and 21% (p<0.05) in 1988 [8]. Furthermore, the number of complications per-patient were reduced from 1.54 in the control group to 0.97 in the protocol group (p<0.01) [8].

More recently Older and colleagues have used exercise testing to determine the anaerobic threshold [95] of patients prior to major intra-abdominal surgery, this allowed the identification of high-risk patients and the appropriate selection of perioperative management [96]. Twenty-eight percent of the patients were admitted to the ICU preoperatively, allowing baseline monitoring with a PA catheter and optimisation of fluid status and haemodynamics of these patients [327]. Twenty-one percent of patients went to a high dependency unit post-operatively for ECG, CVP and arterial pressure monitoring. All other patients were sent to the general ward after surgery. Overall mortality was 21 of 548 patients (3.9%). Of these 21 deaths, 11 deaths (52%) occurred in patients with poor cardiopulmonary function detected preoperatively, although no randomisation of patients was conducted it was felt by the investigators that the care of these patients had been optimal.
8.3 Randomised studies in surgical patients

After the non-randomised studies and anecdotal observations discussed above, there was an urgent need for randomised studies [328, 329]. This review has identified 21 randomised, controlled studies on patients undergoing surgery. The earlier ones are described in Paper 5 and will only be briefly mentioned in this text (the studies are summarised in Appendix 10.1, Table 1 Randomised, controlled studies of perioperative goal-directed therapy).

The earliest trial, of 70 patients undergoing operative repair of hip fracture was published in 1985 [7]. Protocol patients, monitored with insertion of a PA catheter, were given fluids, inotropes and vasodilators to correct CI and other physiological parameters and mortality was significantly reduced to 2.9% compared to a mortality of 29% in the non-monitored group. Shoemaker's non-randomised studies, described above [8, 29, 326], were followed in 1988 by the report of a randomised study of 58 high risk surgical patients using identical entry criteria and treatment goals that the same group had employed in their non-randomised studies [8]. This study showed a significant reduction in the number of complications per patient, 0.39 in the protocol group compared with 1.3 in the control group (P<0.05), and mortality, 4% in the protocol group compared with 33% in the control group (P<0.01).

In a different group of patients undergoing limb-salvage arterial surgery [9], treatment endpoints were PAOP of 8 - 15 mmHg, CI of > 2.8 L min⁻¹ m⁻² and SVR of <1100 dyne-sec cm⁻⁵. This resulted in fewer adverse intra-operative events (P<0.05), less post-operative cardiac morbidity (P<0.05) and less early graft thrombosis (P<0.05) than the control group. The group that had a PA catheter also had a lower mortality (P=0.08). In 1993 Boyd and colleagues (Paper 2) reported the results of a randomised trial in which high risk surgical patients had a deliberate increase of DO₂I towards 600mL min⁻¹ m⁻² and showed a significant reduction in postoperative complications and mortality was significantly reduced from 22.2% to 5.7%. More recently in only 34 patients undergoing surgery for resection of hepato-
cellular carcinoma, a significant reduction in liver failure and hyperbilirubinaemia was found postoperatively in patients treated to raise CI to >4.5 L min⁻¹ and DO₂I to >600 mL min⁻¹m⁻² [180]. In this small study other morbidity rates and mortality rates were not different between the two groups.

Stimulated by the study of Berlauk et al. [9] further work has been undertaken on vascular surgery patients. Valentine and colleagues, studied patients undergoing abdominal aortic aneurysm repair but in this lower risk group no significant reductions in adverse postoperative events or mortality was seen [330]. Another study on patients undergoing elective vascular surgery again noted no differences between patients managed to optimise cardiac output to >2.8 L min⁻¹ and a control group [186]. The same year a similar group of 72 patients having elective aortic reconstruction or lower limb salvage procedures, failed to show any difference in mortality rate (9% in the protocol group and 5% in the control group) or morbidity (25% vs. 27% respectively) when a protocol group was treated with fluids, red blood cell transfusions, inotropes and vasodilators to a target of a SSV₂ of >65% [179]. However, these patients also had a low overall mortality rate of 7%. These 3 studies with low mortality rates are likely to be under-powered, and have a considerable cross-over effect it is therefore not surprising that no statistically significant differences were found between protocol and control groups [331].

There are also three trials that have investigated the influence of increased oxygen delivery in trauma patients (See also Trauma patients). Many of these patients underwent surgical procedures, but it is unclear how formally the DO₂I targets were applied around the time of surgery, as opposed to during the resuscitation phase in the emergency room. In a study of major trauma patients a significant reduction in morbidity and a reduction in mortality from 44% to 24% did not reach statistical significance [10]. However, in a follow-up study, conducted by the same group, a significant reduction both mortality and morbidity was found [178]. In contrast a
study on a much lower risk group of patients, with control group mortality of 10% failed to show any improvement in either mortality or morbidity [187].

Further studies in surgical patients have utilised oesophageal Doppler to measure cardiac output, SV and corrected flow time (FTc) (See also Doppler flow measurement). A study of the effect of plasma volume expansion with 6% hydroxyethyl starch infused to maximum SV on outcome in elective cardiac surgical patients with ejection fraction >50% was carried out by Mythen and Webb [163]. The protocol group received more crystalloid and colloid infusion than the control group and had significantly higher SV. They also had a significantly reduced number of postoperative complications and shorter hospital stay, although mortality was low and not a primary endpoint and was not significantly reduced. The same group [161] reported the results of a randomised study of 40 patients undergoing repair of proximal femoral fracture. Again the patients were treated with intravenous fluid boluses to maximise SV, and the protocol group had significantly reduced hospital stay (identified in this study as time fit for hospital discharge, 10 days vs. 15 days), with the implication that they also had less postoperative complications, but once again mortality was low, not a primary endpoint and was not significantly reduced by the intervention. A second study on patients undergoing surgery for fractured neck of femur was undertaken by Venn and colleagues [162]. Ninety patients were randomised to three groups one having conventional intraoperative fluid management and two groups receiving additional repeated colloid fluid challenges guided either by central venous pressure or oesophageal Doppler ultrasonography. Patients in the two invasively monitoring groups received more intraoperative fluids compared to the routinely treated group, but no differences were seen between the three groups for major morbidity and mortality. However patients in both the invasive intraoperative haemodynamic monitoring had shortened time to being medically fit for discharge. These were very similar results to those of Sinclair et al. [161], but suggested that the oesophageal Doppler may not have been the only method to optimise fluid therapy.
Polonen and colleagues conducted a second study on cardiac surgery patients [182], testing whether increasing $\text{DO}_2\text{I}$ immediately after cardiac surgery would shorten hospital and ICU stay in a randomised study of 403 elective cardiac surgical patients. Goals of the protocol group were to maintain $S_{\text{O}_2} > 70\%$ and plasma lactate concentration $\leq 2.0 \text{ mmol L}^{-1}$ from admission to the ICU and up to 8h thereafter. Dobutamine infusion up to $15 \text{ mcg kg}^{-1}\text{min}^{-1}$ was started to increase CI to achieve this goal. The control group was treatment by standard care which included volume expansion ($\text{PAOP} 12-18 \text{ mmHg}$), and if CI was less than $2.5 \text{ L min}^{-1}\text{m}^{-2}$ despite this a dobutamine infusion was started. The median hospital stay was shorter in the protocol group (6 vs. 7 days, $P < 0.05$), and morbidity at hospital discharge was also reduced in the protocol group (1.1% vs. 6.1%, $P < 0.01$).

Wilson and colleagues published a randomised study of 138 elective general surgical patients investigating whether outcome was improved by optimisation of $\text{DO}_2\text{I}$ [11]. A control group receiving standard ward care was compared with an optimisation group admitted preoperatively to the ICU. The optimization group was further divided to a group receiving dopexamine hydrochloride and a group receiving adrenaline as the therapy used to increase CI. Groups were well matched, and the two optimisation groups had preoperative fluids and inotropes administered although it is not known how the control group was treated during 'standard care' [332]. The results of the study showed a significant reduction in mortality in both optimised groups to 3% compared with a control mortality of 17% ($P=0.007$). Morbidity was reduced in the dopexamine group, who also had reduced length of stay in hospital. This group recently reported the results of a second randomised study of 100 patients undergoing major abdominal surgery [185]. This study was designed to investigate whether adding an infusion of dopexamine hydrochloride to patients already having optimal fluid therapy had an effect on postoperative mortality and morbidity. Patients were given fluid infusions guided by the results of SV measured by an oesophageal Doppler monitor. Patients were then randomised to receive dopexamine hydrochloride infusion ($0.25 \text{ mcg kg}^{-1}\text{min}^{-1}$) or placebo. Comparison of the protocol and control groups showed that the dopexamine group
had more pre-existing disease and overall no significant differences were found in postoperative complications, length of stay or mortality. It is interesting to note that in a number of instances second studies from the same group have failed to show significant differences, one reason may of course be there that are in fact no significant differences between the treatment groups or that any differences were small and the studies were underpowered; but an alternative explanation could be that in groups with an established practice of preoperative optimisation many of the control patients may reach optimisation targets with fluid therapy alone, resulting in a large, but unknown, crossover effect when statistical analysis is undertaken.

One study of general surgical procedures concentrated on fluid therapy, guided by the oesophageal Doppler monitor to maintain maximal SV, without the addition of inotropic medication [164]. All patents in the study had oesophageal Doppler monitoring, but in the control group the anaesthetic team were blinded to the results. A detailed fluid regimen was given for the control group and the anaesthesiologists could administer additional fluid if deemed clinically indicated. Despite this the protocol group were given significantly more fluids and had a significantly higher SV and CI at the end of surgery compared with the control group. Outcome data showed that patients in the protocol group had a shorter duration of hospital stay compared with the control group: 5 ± 3 vs. 7 ± 3 days (mean ± SD), with a median of 6 vs. 7 days, respectively ($P = 0.03$). These patients also tolerated oral intake of solid food earlier than the control group: 3 ± 0.5 vs. 4.7 ± 0.5 days (mean ± SD), with a median of 3 vs. 5 days, respectively ($P = 0.01$). Appropriately mortality was not a primary outcome measure for this study.

Returning to the use of the PA catheter, Lobo et al. [181] studied the effects of maximizing the DO$_2$I on morbidity and mortality in patients 60 yrs of age and/or with chronic diseases of vital organs who underwent major elective surgery. Difference in the 60 day mortality rate caused the study to be stopped early by the local ethics committee after the enrolment of just 37 patients. Therapy in both groups consisted of volume expansion and, when necessary, dobutamine to reach
target values of DO$_2$I $>600$ mL min$^{-1}$m$^{-2}$ in the protocol group and $>520$ mL min$^{-1}$m$^{-2}$ in the control group. The mortality rate in the control group was not significantly different from the protocol group at 28 days (33% vs. 15.7%, relative risk 0.47, 95% confidence intervals 0.139-1.616), but at 60 days follow-up it was significantly higher (50% vs. 15.7%, relative risk 0.32, confidence intervals 0.101-0.984). This study is slightly difficult for a number of reasons firstly the mortality in the control group is much higher than that found in studies enrolling apparently similar patients, and secondly the follow-up arrangements are unclear as it is unusual to follow-up patients for up to 60 days post-operatively and it is not clear that this was an original intention of the study.

As the complexity of studies in this area has increased two multi-centre studies have been conducted to test the hypothesis that increasing DO$_2$I might improve outcome in surgical patients. The first was conducted at 13 institutions in Europe recruiting 412 patients [184]. Patients undergoing mainly elective major surgery were identified as being at high risk using the criteria first developed by Shoemaker et al. [8] and modified by Boyd et al. Paper 2. All patients had PA and arterial catheters and fluid was administered to a PAOP of up to 12 mm Hg and haemoglobin concentration of 10 g dL$^{-1}$. The patients were randomised into one of three groups. In a control group, infusion of placebo was commenced and continued throughout the length of the study period. In the first protocol group, dopexamine hydrochloride at a dosage of up to 0.5 mcg kg$^{-1}$min$^{-1}$ was administered intravenously in the pre- and intraoperative periods and was maintained postoperatively for up to 12 hrs. In the second protocol group, dopexamine was administered similarly but at a dosage of up to 2.0 mcg kg$^{-1}$min$^{-1}$. In the protocol groups no specific targeting of DO$_2$I or CI was undertaken and it is questionable whether this study should be included with the others were goal-directed therapy is given. This thesis has however included this study due to its size and the belief of the investigators that it was a goal-directed therapy study [333]. Similarly the study is included in the systematic analysis performed for this thesis (see Chapter 8.6; Systematic reviews of the effects of goal-directed therapy). Despite the lack of targeted treatment limits on the infusion were
determined by tachycardia, arrhythmias, or evidence of myocardial ischaemia, patients were otherwise treated conventionally until the time of discharge or death. The primary outcome variables were 28-day mortality and morbidity, the latter being identified from a predetermined list of complications. The three patient groups were well matched demographically, with a large majority being elective cases undergoing surgery for cancer. The results of the study showed no difference in mortality or morbidity in the groups: there was an overall mortality rate in the placebo group of 13%, which was not significantly different from the 7% mortality rate in the low-dose dopexamine group or the 15% mortality rate in the high-dose group. Furthermore, there were no significant differences between the groups in complication rates.

Recently the largest study of perioperative flow directed therapy has been published by the Canadian Critical Care Trials Group [145]. This study from 19 centres in Canada enrolled 1994 patients aged over 60 years who were graded as ASA III or IV, and were scheduled for emergency or elective abdominal, thoracic, vascular or hip fracture surgery. The main results for the study show no difference between the standard care group and the group the received a PA catheter. Mortality rate in the PA catheter group was 7.8% and in the non PA catheter group was 7.7%. Median length of hospital stay was similar in the two groups (10 days) and complications were also similar between the two groups except that the rate of pulmonary embolism was higher on in the PA catheter group. However there are a number of potential points of confusion in the original paper. Primarily, the goals for treatment in the protocol group, and the methods for achieving these goals, are poorly defined. Goals of treatment were given a priority order: \( \text{DO}_{2}I \ 550 - 600 \ \text{mL min}^{-1} \text{m}^{-2} \), \( \text{CI} \ 3.5 - 4.5 \ \text{L min}^{-1} \), mean arterial pressure 70 mmHg, PAOP 18 mmHg, HR <120 bpm and haematocrit > 27%. In addition a priority list for treatment included fluid loading, inotropic therapy, vasodilator therapy, vasopressors and blood transfusion. Furthermore, while treatment targets were met on average in the catheter group, less than half (48.9%) of them received perioperative inotropic therapy, only 8.5% received vasodilators and only 54.8% received colloid fluid therapy. This is a significantly higher degree of
intervention than the control group, but still suggests that half the catheter group achieved targets without treatment, resulting in a huge possible crossover phenomenon [334]. The study is further confused by the high degree of intervention given to the control group of patients. As noted above, 48.5% of the patients in the catheter (treatment) group received inotropes, but 32.8% of the control group also received inotropic therapy, and 47.7% received colloid infusion compared to 54.8% in the treatment group. CI and DO₂I measurements were not performed in the control patients, but with this degree of therapy it would be surprising if many of the control patients did not also obtain targets of treatment for the catheter group, again adding to the crossover phenomenon. There is also a surprisingly low recruitment rate into the study. 3803 patients were identified as fitting the study entry criteria (age over 60 years, ASA III or IV, and abdominal, thoracic, vascular or hip fracture operations) over a 113 month period in 19 centres. This produces the surprisingly low figure of 1.7 such patients in each centre per month (only 0.9 patients for each centre each month were actually recruited into the study).

8.4 Studies in patients with other conditions

The same approach of increasing DO₂I and CI has been extended to other patient groups, specifically patients with burns and trauma, and patients with established critical illness including sepsis. These will be briefly discussed.

8.4.1 Burns patients

Traditionally burns patients have been fluid resuscitated with fluid protocols based on the burn area, but when these resuscitation attempts were monitored more carefully using a PA catheter unsustained or inadequate response to hyperdynamic resuscitation was associated with non-survival [335-337]. Furthermore, survivors of burn injury have increased levels of VO₂I, DO₂I and Interleukin-6 (IL-6) [338], with a supply
dependency pattern of DO$_2$I and VO$_2$I [339], and burn patients are responsive to therapy aimed at increasing DO$_2$I [340]. In an uncontrolled study 30 adult patients with a burn area greater than 42%, already resuscitated using the Parkland formula for fluid administration, further fluids and inotropes were given as determined by oxygen transport values. Compared to historical controls, and despite having a higher burn area, there were reductions in MODS and a fall in mortality from 49% to 10% [341]. In another study historical controls had a mortality rate 48%, while a protocol group who were resuscitated to hyperdynamic endpoints had mortality rate of only 10% [342].

There are however no randomised studies of treatment aimed at increasing CI and DO$_2$I in patients with burns.

8.4.2 Trauma patients

It has also been suggested that a treatment approach targeting DO$_2$I and CI should be used on patients suffering severe traumatic injuries, as they display very similar physiological responses to surgical patients. This strategy is in contrast to the traditional approach of searching for abnormal physiologic and clinical chemistry measurements, then intervening if possible to normalise these variables. Once again the original proposal was to resuscitate the patients to DO$_2$I >600 mL min$^{-1}$m$^{-2}$, as had been suggested with the surgical patients, although the exact endpoints are still controversial [343]. Researchers in this field have tended to emphasise treatment of elderly patients as they have a particularly low DO$_2$I suggesting that they might respond best to targeted treatment [344-346].

The published literature includes prospective randomised trials and observational studies, but interpretation of this literature is complicated, particularly in a review that is concentrating on the treatment of the surgical patients, as the studies have included patients undergoing surgery following trauma and this thesis includes the
studies of Fleming et al. [10], Bishop et al. [178] and Durham et al. [187] in the data analyses above (see Chapter 8.3; Randomised studies in surgical patients).

Fleming et al. showed in a study of trauma patients with estimated blood loss more than 2000mL, or pelvic or two long bone fractures with requirement for blood transfusion, that mortality was reduced from 44% to 24% and there was a significant reduction in morbidity [10]. A follow-up study by Bishop et al. conducted to increase the statistical power enrolled 115 patients, and showed significant falls in mortality and morbidity [178]. However, in the control group there was a longer time taken to reach the operating room (86±14 vs. 56±10 minutes) and more prolonged periods of systolic hypotension (82±15 vs. 59±10). Moreover, the control group received only half the volume of colloid and blood products administered to the protocol group, suggesting that the worse than predicted outcome may have been due to an under treatment of the control patients. In contrast in a much lower risk group of patients, with control group mortality of 10%, Durham et al. failed to show any improvement in either mortality or morbidity in trauma patients with massive blood loss, sepsis, hypotension, or respiratory failure [187]. But in this study there was no significant difference between the groups with respect to the mean haemodynamic and oxygen transport parameters after twenty four hours of resuscitation.

In a large study from Gattinoni and colleagues a subgroup of patients, approximately 100 out of a total of 762, was trauma patients, and outcome information is given on these patients [347]. Admission criteria included 48 hours of critical illness prior to patient enrollment consequently treatment was started very late compared to other studies, and results showed no improvement in outcome in trauma patients treated to targets for CI or S$_{O_2}$ compared to control. In the most recent randomised study from Shoemaker and colleagues [348], trauma patients
who achieved supranormal goals, spontaneously or through intervention, had improved survival rate (100 vs. 70%), less organ failure (29 vs. 70%), and less sepsis (64 vs. 31%) compared with those patients who did not. However, in contrast with their previous trials, the intention to treat to DO$_2$I greater than 600 mL min$^{-1}$m$^{-2}$ was not associated with increased survival (85 vs. 89%), or decreased organ failure (38 vs. 57%). This may have been due to the fact that the protocol and control resuscitated patients were managed by a trauma team with an established practice pattern of supranormal resuscitation. There was also no difference in the average volume of fluid (14 vs. 13 L) or blood (11 vs. 11 units) given to either group, effectively implying that both groups were treated to supranormal goals. The only apparent difference was the fraction of patients in each group to receive inotropic support during the first 24 hours after hospital admission (32 vs. 17%), but the use of inotropic of medication in the control group is surprisingly high.

Supranormal resuscitation compared with normal resuscitation is associated with more fluid infusion and there have been ongoing concerns that this might have negative consequences for trauma patients particularly in terms of raised intracranial pressure and abdominal compartment syndrome. With regard to intracranial pressure, a randomised trial to assess the effects of goal-directed therapy on intracranial pressure, showed that despite the significantly greater volume of fluids given to the goal-directed group there was no difference in neurological recovery [349]. Goal-directed therapy has been shown in other studies of patients specifically at risk of abdominal compartment syndrome to result in decreased intestinal perfusion, by demonstration of a higher pgCO2 and an increased incidence of intra-abdominal hypertension, abdominal compartment syndrome (16% vs. 8%), multiple organ failure (22% vs. 9%), and death (27% vs. 11%) [350]. The same group showed that changing resuscitation targets from 600 mL kg$^{-1}$min$^{-1}$ to 500 mL kg$^{-1}$min$^{-1}$ was indistinguishable, but resulted in less volume loading being required to attain and maintain DO$_2$I greater than or equal 500 mL kg$^{-1}$min$^{-1}$ than 600 mL kg$^{-1}$min$^{-1}$ using computerised protocol technology to standardise resuscitation during the first 24 ICU hours [351].
The differences in the results of these studies may be explained by a number of confounding variables, the most important being (1) different inclusion criteria, (2) variable timing of resuscitation, and (3) different interventions.

8.4.3 Critically ill patients including those with sepsis

Following Shoemaker's early work which demonstrated an impressive reduction in mortality in a group of high risk surgical patients using 'goal-directed therapy' [8, 326] there was much interest from other groups in extending the protocol to include other critically ill patients. Initial outcome results from a study involving patients with septic shock appeared promising [352]; however this study was limited by its uncontrolled and retrospective nature. In comparison a later prospective, randomised, controlled study of the effects of increasing CI and hence $DO_2I$ in septic shock demonstrated no difference in outcome between an 'optimal' (CI $> 6$L $\min^{-1}m^2$) and a 'normal' (CI $> 3$L $\min^{-1}m^2$) treatment group using an intention to treat analysis, although there appeared to be a trend towards a lower mortality in the 'optimal' treatment group [353]. However a retrospective subgroup analysis, conducted in an attempt to rule out the statistical cross-over effect, compared patients in the 'optimal' treatment group with a CI $> 4.5$L $\min^{-1}m^2$ with patients in the 'normal' treatment group who only achieved a CI $< 4.5$ L $\min^{-1}m^2$, and this found that there was a significant reduction in mortality in the 'optimal' treatment group who achieved a high CI.

In a heterogeneous group of 109 critically ill patients treated following admission to intensive care using an aggressive protocol to try and achieve supernormal levels of CI ($> 4.5$L $\min^{-1}m^2$), $DO_2I$ ($> 600$mL $\min^{-1}m^2$) and $VO_2I$ ($> 170$mL $\min^{-1}m^2$) [250], mortality was surprisingly significantly higher in the protocol group than in the control
group. In this study, patients were only randomised if they did not achieve the supranormal goals after standard fluid resuscitation. Those who did achieve the goals with fluids alone or with fluids and low dose dobutamine had a good outcome, moreover when all patients were grouped together there was an inverse relationship between DO$_2$I and mortality. The question arises as to whether the increased mortality in the protocol group may have been secondary to the larger doses of dobutamine administered. It would therefore be of interest to see if smaller doses of dobutamine or other drugs which improve DO$_2$I by other mechanisms, may have a more beneficial effect.

Yu et al. have also investigated the effects of maximising DO$_2$I in a heterogeneous group of critically ill patients, and showed no difference in mortality between control and protocol groups [354]. As with the study above, subgroup analysis demonstrated that mortality was significantly lower in patients in whom DO$_2$I exceeded 600 mL min$^{-1}$m$^{-2}$, regardless of whether this was achieved spontaneously or in response to treatment, as compared to those in whom DO$_2$I remained below this level. The same group have also published a further trial investigating the responses of patients of different ages [355]. Consecutive patients aged >50 yrs with systemic inflammatory response syndrome, and sepsis with or without shock were studied. In the patients aged 50-75 yrs mortality was significantly reduced from 52% to 21% in the protocol group, whereas patients aged >75 yrs showed no improvement in mortality.

A large multicentre study of 762 critically ill patients demonstrated no difference in morbidity or mortality when three different treatment groups were compared (CI > 4.5L min$^{-1}$m$^{-2}$, $S_{a}O_2$ > 70% or Control) [347]. However, in this very late intervention study, those patients with a higher DO$_2$I did have a better outcome. This trend to improved outcome with the ability to achieve goals was also found in the study of Alia et al. [356]. Sixty-three patients classified according to predetermined criteria as having severe sepsis or septic shock were randomly assigned to a control group (n = 32) who received conventional therapy with a normal targeted value of DO$_2$I, and a treatment group (n = 31) who received therapy with a targeted DO$_2$I value of > 600 mL min$^{-1}$m$^{-2}$. 

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Other therapy was similar in both groups. The two groups were similar at baseline, except that there was a significantly higher rate of positive blood cultures in the control group, respectively: 34 vs. 13% (p = 0.04). Despite the average CI being significantly higher in the treatment group than in the control group (3.96 vs. 3.05 L min⁻¹ m⁻², P = 0.01). DO₂I was surprisingly not significantly different, casting some doubt on the attention to the protocol in this study. Furthermore only nine of the 31 treatment group patients reached an average DO₂I value of > 600 mL min⁻¹ m⁻². Mortality to ICU discharge was 66% in the control group and 74% in the treatment group (P = 0.46). Moreover the number of organ dysfunctions per patient was similar in the control and treatment groups (2.1+/−1.1 vs. 2.6+/−1.2, P = 0.12).

Despite the disappointing results from these studies based on the statistical analysis of major outcome measures undertaken on an intention-to-treat basis, the studies generally show that mortality rates are lower in patients who achieve higher levels of DO₂I, whether in response to more aggressive resuscitation or spontaneously. This was specifically tested by Tuchschmidt [353].

It is possible that a patient's underlying physiology is important and can be augmented by therapy. Vallet et al. demonstrated, in a group of patients with the sepsis syndrome, that survivors responded to a short term infusion of dobutamine by significantly increasing DO₂I and VO₂I, whereas in non-survivors there was little or no increase in DO₂I and VO₂I [357]. In a similar study by Bennett's group, responders to a dobutamine stress test had a hospital mortality of 14%, whereas non-responders had a mortality of 91% (p<0.01). The responders were also significantly younger, had higher APACHE III scores, and had a greater requirement for inotropic support [358]. The ability to achieve higher values of DO₂I and VO₂I in response to resuscitation therefore seems to be indicative of greater physiological reserve, a less severe illness and consequently a better prognosis. Many studies have now demonstrated that survival is associated with a hyperdynamic response [24, 359-363], however attempts to drive patients to achieve this with pharmacological agents, have not translated to an improved outcome. This type of therapy may therefore serve only to identify those patients who have the ability
to attain survivor values if they need to, although in some patients it might push them into a survivor group.

Given the controversy that now surrounds the existence of supply dependency, plus the observation that the critical level of DO\textsubscript{2}I may be lower than expected and not altered by sepsis [364], it would appear unnecessary to aim for excessively high levels of oxygen transport in all critically ill patients. Hayes et al. even demonstrated that outcome was worse when aggressive treatment with inotropes was used to try and attain supranormal levels of DO\textsubscript{2}I and VO\textsubscript{2}I [250]. This resulted in the European Consensus Conference concluding that continued aggressive attempts to increase oxygen transport in all patients are unwarranted, although they did point out that timely resuscitation and achievement of normal haemodynamics is essential [365].

More recently however the debate about the usefulness of goal-directed therapy in patients with sepsis has been reopened by a study investigating treatment given in the emergency room [297]. This study was designed to evaluate the efficacy of early goal-directed therapy in the first six hours of hospitalisation and before admission to the intensive care unit 263 patients were enrolled to receive a modified central venous catheter in the emergency room. The catheter was adapted to monitor central venous oxygen saturation (ScvO\textsubscript{2}) by a fibre-optic technique, and a resuscitation target of saturation greater than 70% was set; this was to be achieved by optimizing arterial saturation to greater than 93%, raising haematocrit to greater than 30%, increasing CI with dobutamine infusion and reducing VO\textsubscript{2}I by sedation and ventilation. One hundred and thirty patients were randomly assigned to early goal-directed therapy and 133 to standard therapy; there were no significant differences between the groups with respect to base-line characteristics. In the early treatment phase, the patients assigned to early goal-directed therapy had a significantly higher mean ScvO\textsubscript{2} (70.4+/-.10.7% vs. 65.3+/-.11.4%, P<0.05) showing that targets had been reached. They also had a lower lactate concentration (3.0+/-.4.4 vs. 3.9+/-.4.4 mmol L\textsuperscript{-1}, P<0.05), a lower base deficit (2.0+/-.6.6 vs. 5.1+/-.6.7 mmol L\textsuperscript{-1}, P<0.05), and a higher pH (7.40+/-.0.12 vs. 7.36+/-.0.12, P<0.05) than the patients assigned to standard therapy. Mortality to hospital discharge was 30.5
% in the group assigned to early goal-directed therapy, as compared with 46.5 % in the
group assigned to standard therapy (P = 0.009).

8.5 Economic considerations

Healthcare economies are becoming increasingly financially constrained and it is
essential to identify the cost-effectiveness of all new treatments [366]. This can be
difficult as many potential cost savings only occur some time after a therapy has been
undertaken and it may be difficult to relate the therapy under question to the cost
savings [367]. Three of the studies undertaken on goal-directed therapy have performed
a cost analysis, all of these are concerned with pre-operative care.

As part of his original trial Shoemaker and colleagues considered the costs of treatment
basing these on hospital charges. Costs were $27665 for patients treated in the protocol
group and $37335 for patients treated in the control group with $31438 for patients that
were not randomised and $30748 for patients treated with a CVP line only [8]. This
analysis could be criticised because the relationship between charges and costs is not
always straightforward [367].

We therefore repeated a retrospective cost effectiveness analysis of our data from our
randomised trial Paper 5. This analysis showed total costs to be £6525 in the protocol
patients and £7784 in the control patients. When analysed on a cost for a survivor basis,
costs were £6916 for a survivor in the protocol group and £10008 for a survivor in the
control group.

A similar retrospective cost-effectiveness analysis was undertaken by the York group
following their original randomised controlled trial [11]. This trial of 138 patients
undergoing major elective surgery had three treatment arms with pre-operative
optimisation employing either adrenaline or dopexamine (assigned randomly), and a
control group receiving routine perioperative care. Differential health service costs were
based on trial data on the number and cause of hospital in-patient days and the utilisation of health care resources and were undertaken in association with the Centre for Health Economics, University of York. The mean total costs were €11,310 in the protocol groups and €16,965 in the standard care group. Life-years were 1.68 in the protocol groups and 1.46 in the standard care group. Due to the high probability that pre-operative optimisation was less costly than standard care (98%) and the probability that it dominated standard care (93%), the investigators concluded that pre-operative targeting of DO$_2$I and CI was cost effective when compared to standard care [12].

8.6 Systematic reviews of the effects of goal-directed therapy

There have been a number of publications systematically reviewing the studies described in this thesis. However not all of the reviews have primarily addressed issues concerning optimisation of tissue perfusion, and treatment aimed at increasing DO$_2$I and CI or SV, concentrating instead on possible effectiveness of right heart catheterisation [147, 368]. Others have included studies enrolling patients at a later stage of their illness [334, 369] although separating those in the perioperative period for the purposes of analysis [369]. This is the approach that we used in Paper 5 when we published one of the first attempts to combine the various studies that had used goal-directed therapy. As part of the review we identified 13 studies presenting 14 data analyses of patient groups. We divided the studies and calculated odds ratios and confidence intervals for the combined data of the studies that had undertaken goal-directed therapy early and those that had undertaken such therapy late. For patients that had undergone goal-directed therapy early (7 studies) 647 patients had been studied and the odds ratio for an improvement in mortality was 0.34 (95% confidence intervals 0.23 - 0.49). For studies that had enrolled patients with established critical illness, 1031 patients had been studied and the odds ratio for improvement was 1.05 (95% confidence intervals 0.82 - 1.34). This systematic review included two papers [262, 370] which have not been included in subsequent systematic reviews. The first study [262] is not usually included because no specific measurement of CI, DO$_2$I or blood flow were made, treatment was given purely in the expectation that systemic oxygen
delivery would be increased, furthermore details of the treatment protocol are rather vague (see also Chapter 7.3.1; Intramucosal pH measurement for results of this trial). The second study [370] used prostaglandin E1 as a vasodilator in patients with adult respiratory distress syndrome and although the study showed an increase in cardiac output in the protocol group there was a marked reduction in SVR and blood pressure and it was the intention of the investigators to cause a pulmonary vasodilatation rather than to increase blood flow and DO₂I. Inclusion of these trials in current systematic reviews does not affect the odds ratios, but due to increased patient numbers reduces the confidence intervals slightly.

A recent systematic analysis has also divided patient groups [371]. The investigators found 21 randomised clinical trials described in 20 articles, and they divided the studies into groups based on the time that goals of treatment were implemented (i.e., "early," 8 to 12 hrs postoperatively or before organ failure, vs. "late," or after onset of organ failure. They further subdivided the studies based on the severity of illness, determined by the control group mortality as greater than 20% (12 studies) or less than 15% (nine studies). Results showed that in severely ill patients (control mortalities group greater than 20%), the combined data from six studies demonstrated that mortality was reduced by 23% (P <.05) between the control and protocol groups with early optimization. This contrasted with the six studies in which patients were treated after the development of organ failure, when mortality was not significantly improved. Moreover, outcome was not significantly improved in less severely ill patients with control mortalities less than 15%.

When considering specifically perioperative patients Ivanov and colleagues [147] gave a combined OR for the studies that they analysed of 0.58 (95% Confidence Intervals 0.36-0.94) for improved outcome following early goal-directed therapy, and Heyland and colleagues [334] gave a combined OR of 0.20 (95% Confidence Intervals 0.07-0.55), both reviews including slightly different studies. In a review by Leibowitz and colleagues [368] no figures were given but they concluded that the right heart catheter did not reduce risk in patients already at low risk, but, based only on the results of one
study [9], probably did reduce risk in patients at higher risk particularly high risk vascular surgery patients. A recent review, specifically concerning implications for vascular surgery [372], found four papers to be adequate randomised prospective studies with similar exclusions, therapeutic endpoints, and interpretable complication and mortality rates. These studies showed that the use of a PA catheter did not prevent morbidity or mortality, although a statistically significantly greater amount of fluid was given to patients who underwent PA catheterization. Meta-analysis indicated that in moderate-risk vascular surgery patients routine preoperative PA catheterization was not associated with improved outcomes [372].

Matuschuck investigated the role of supranormal oxygen delivery in critical illness [373], but only identified 2 trials in surgical patients [8, 183]. Despite the positive nature of these trials the author was not able to suggest that outcome might be improved and called for more studies in surgical patients. Additionally Matuschuck identified 8 trials in patients that were defined as already having sustained SIRS and found that there was no consistent direction in the results of these trials. Interestingly 3 of these trials [10, 178, 187] involved intervention very early in the patients under study and have been included in this thesis in the group of early intervention studies, all three studies individually show no significant improvement in outcome.

One systematic review has specifically addressed the issue of a possible reduction in complications, rather than mortality, following therapeutic alterations guided by information for a PA catheter [146]. Twelve trials, including patients in the perioperative period as well as those with general critical illness, defined major morbidity as organ failures; these studies enrolled a total of 1,610 patients. Morbidity events showed a statistically significant reduction using PA catheter guided strategies, 62.8% of the PA catheter treatment group displayed organ failure morbidity, and 74.3% of the control group (relative risk ratio 0.78, 95% confidence interval 0.65-0.94, P<0.02).
In earlier reviews, we in 1999 [369] analysed studies that had used $\text{DO}_2\text{I}$ and CI targets for treatment. Studies at that time on perioperative patients had enrolled a total of 994 patients and showed a combined OR of 0.35 (95% Confidence interval 0.23 – 0.53). Of the studies individually, 4 showed significant improvement in mortality, 5 showed trends to improvement and an OR of less than 0.5, and the remaining 3 show no difference in outcome. We also recalculated the ORs using an arbitrary division taken at the median of the mortality rates of the studies. The six studies with mortality rates greater than 10% had a combined 451 patients and OR of 0.25 (95% Confidence interval 0.15-0.43). Conversely the seven studies with mortality rates less than 10% included 543 patients and gave an OR of 0.88 (95% Confidence interval 0.39-2.00). In that publication we also analysed patients who had targets of $\text{DO}_2\text{I}$ and CI treated after the onset of their critical illness. In this patient group 917 patients had been studied, and the OR for improvement with the treatment was 0.91 (95% Confidence interval 0.70 - 1.18).

A recent analysis using Cochrane methodology, identified 12 published and peer-reviewed papers, which used goal-directed perioperative targeting of global flow values: $\text{DO}_2\text{I}$ and $\text{VO}_2\text{I}$, SV, lactate and $\text{Sv}_\text{O}_2$. The studies include 1252 patients with an overall mortality of 6.2%. The mortality in the control group was 56/587 (9.5%) versus 21/665 (3.2%) in the protocol group, and the Peto odds ratio (CI 95%) was 0.3(0.19 - 0.49) for a reduction in mortality [374].

A similar analysis for this thesis shows that there are a total of 30 randomised studies, 8 studies treat patients late in the course of their illness once organ failure has occurred, and 1 study by Rivers et al. [297] is difficult to categorise as it intervenes early in patients with sepsis. The late intervention studies have enrolled a total of 980 patients; overall the mortality rate of patients in the protocol group is 48.4%, and mortality in the control group is 46.7% (odds ratio 1.63, 95% Confidence intervals 0.74 - 3.59). If the study of Rivers and colleagues [297] is included in this classification, i.e. as one taking place after organ failure has occurred, the combined figures show a total of 1243
patients with a protocol group is 43.3%, and mortality in the control group is 48.0% (odds ratio 0.83, 95% Confidence intervals 0.66 - 1.03).

In contrast to the late intervention studies this thesis identifies perioperative studies enrolling 4258 patients in 21 studies, overall the mortality of the protocol patients is 7.06% and of the control patients is 10.25% (OR 0.67 95% Confidence intervals 0.54 - 0.83). The studies can be further subdivided based on the severity of illness as defined by the control group mortality. Studies with a control group mortality ≤10% include 11 studies enrolling 3130 patients, the mortality of the protocol patients is 6.01% and the mortality of the control patients is 6.26% (OR 0.96, 95% Confidence intervals 0.71 - 1.28). Studies with control group mortality >10% include 10 studies enrolling 1128 patients, the protocol mortality is 9.7% and the control mortality is 22.6% (OR 0.37, 95% Confidence intervals 0.26 - 0.52). As mentioned earlier the study by Rivers et al. [297] is difficult to place, if it is included as an early intervention study the combined results show a total of 1391 patients with a protocol group mortality of 13.19%, and mortality in the control group is 27.65% (OR 0.40, 95% Confidence intervals 0.26 - 0.52).
9. Conclusions

The thesis integrates the body of published work presented by Dr Owen Boyd for consideration of the Degree of Doctor of Medicine. This thesis has provided a critical review of the current state of play in the area of therapeutic interventions designed to attain particular cardiorespiratory parameters concentrating on targets for cardiac output and oxygen delivery and stroke volume. The review of scientific and clinical work in the area of the pathophysiology of MODS has demonstrated that there is a theoretical link between poor tissue perfusion and tissue hypoxia and the onset of MODS. The thesis has discussed how it has been hypothesised that the prevention of poor tissue perfusion and hypoxia might prevent the onset of MODS. The scientific understanding of MODS suggests that once the syndrome has started there are no therapeutic interventions currently available that can attenuate the inflammatory cascade in a consistent fashion. Therefore the scientific background would suggest that if treatment specifically designed to maintain tissue perfusion is to be used to effectively improve mortality and morbidity in patients at risk of developing MODS it must be started very early. This early intervention can be undertaken in surgical patients to increase and subsequently maintain tissue perfusion prior to the onset of the stimulus, which, if left unchecked, might lead to the development of MODS and its associated high mortality rate. This to some extent remains conjecture and a fruitful area for further research would be to study the effects of treatment designed to maintain tissue perfusion on markers of the inflammatory cascade.

The review has shown that there is a high mortality rate in some groups of surgical patients, particularly those who are elderly with coexisting to the states. Considering the complex nature of these cases and their requirement for increased length of hospital stay and critical care resources, as well as their increased morbidity and mortality rate, it is surprising that more accurate methods for their identification are not available. Outcome studies on high-risk surgical patients have been limited by the lack of
objectivity in this area. Studies have therefore used slightly subjective lists of patient related criteria, specific operation types, or disease types (such as trauma) that have tended to inhibit more general applicability of the results. More subjective assessment methods are available but these have not been used in outcome studies and techniques such as cardiorespiratory exercise testing [96] could not be used in emergency or urgent cases. There it is therefore an urgent need for more accurate, subjective, and widely applicable methods of assessing the risk in a patient about to undergo surgery.

Despite these limitations in patient selection, randomised studies in higher risk groups of surgical patients have shown improved outcome in terms of both mortality and morbidity post-operatively. This has been shown both in individual studies conducted on the highest risk group of patients, and in all the systematic analyses that have been performed over the last eight years. Although there are potential problems with systematic analyses, this thesis shows an odds ratio of 0.67 (95% Confidence Intervals 0.54 - 0.83) for a reduction in mortality in a combined analysis of 21 studies enrolling 4015 patients. It is particularly disappointing that some of the studies, including some recent studies, can be criticised in terms of patient selection, statistical analysis and numbers included in the study, and the vague nature of the treatment regimes.

The number of surgical studies is adequate to allow some separate conclusions for different risk bands to be made. All the studies that individually reach statistical significance come from the group of studies that that have a mortality rate of greater than 10% in the control group. This suggests that these studies were investigating the sickest patients and that this patient group might be the one that benefits most from targeted increases in DO₂I and CI and tissue perfusion. The systematic reviews undertaken for this thesis and by others [371] confirm the finding that in the lower risk group of perioperative patients there is no reduction in mortality following, early goal-directed therapy. However, morbidity is reduced in studies that have used morbidity or surrogates of morbidity, for example length of stay, as primary endpoints even in the lower risk group of patients.
These conclusions need to be seen in the light of several problems that can be identified in the clinical studies; these include patient randomisation, treatment of the control subjects, blinding, study design and the statistical analysis. Valid interpretation of patient-based studies relies not only on randomisation at recruitment but also on the integrity of the treatment protocols designated to different groups within the study. Firstly, the treatment and management of patients in the protocol groups may be unclear, and it may be unclear how tightly the treatment of these patients conformed to the original protocol, this is particularly true when only 'suggested' treatment guidelines have been given for patients in the protocol group [145, 184]. Secondly, the management of patients in the control group may not be adequately describe by the description of the study or designated in the original methodology. For example a number of studies state that treatment of the control patients is in accordance with routine practice, but do not describe this further [7, 11, 145, 163, 182, 330], and other studies have monitored patients with PA catheters [9, 179, 186, 187] or oesophageal Doppler [161, 164] but have not changed treatment as a result of the findings. In contrast some studies have specified treatment targets for control patients using either PA catheters [180, 181, 183] or oesophageal Doppler [185]. It is obvious that 'routine practice' may well vary between institutions and between treatment for different types of patients and it may therefore be difficult to generalise the findings to different areas. Thirdly, there may be inadequate information to understand the haemodynamic consequences of treatment in the control group. In some studies it appears very likely that this has occurred, for example the study of Sandham et al. treated up to 33% of control patients with inotropic medication [145].

A further potential weakness of the studies on goal-directed therapy discussed in this thesis is the lack of blinding. In all the studies mentioned above it has been made clear whether they are observational, compare data to historical controls or are randomised. However in these patient-based interventional studies it has proved very difficult to blind the studies and this is weakness of many of the study designs. Some studies do claim to have been adequately double blinded [164, 184], but it is difficult to see how this could in fact have been rigorously achieved. It is difficult, for example, to see how
the administration of additional fluid boluses could have been missed by the anaesthetists looking after a surgical case. Moreover, most of the inotropic medication that has been used in the studies causes a very consistent tachycardia, again something that would be difficult to miss during careful observation of the patients. Other studies blinded certain parts, for example the decision to discharge patients is frequently not made by the study team [97, 161], but how far this solves the problem of blinding is unclear, and probably depends on the type of institution and the cross pollination between different care teams.

The designs of the studies are inevitably different and this causes further difficulties when trying to draw conclusions from a combined analysis. Most of the studies discussed above are undertaken in single centres and therefore tend to be quite small as regards patient numbers. This reduces the power of the studies, particularly when the incidence of the primary outcome variable is low. For example, low anticipated mortality rates in some of the studies associated with the small patient numbers means that the power of the study for finding any significant differences between treatment groups will also be low [179, 185, 186, 330]. Indeed the power of the studies is likely to have been so low that no valid conclusions can be drawn from them. On a positive note, it is likely that the personal supervision of the studies is likely to be extremely good and therefore data quality and compliance with protocols is likely to be extremely high.

These problems are not necessarily solved by larger multi-centre studies and recently two have been presented [145, 184]. These studies have, as anticipated, recruited higher patient numbers and therefore some of the problems with statistical power are alleviated, but the multi-centre study itself may have a number of other intrinsic problems. The low recruitment rate for the study of Sandham et al. has been described above. Under the circumstances it could be suggested that familiarity with the study regime may be lost, or that some patients who may have fitted the study entrance criteria may have been missed. Moreover the value of
multi-centred studies in the complicated environment of the intensive care unit may have its own particular difficulties. Differences in admission and discharge criteria, staffing levels, available facilities, and the historical precedent may dilute the findings of an important difference in outcomes. Furthermore, the ability to control protocol adherence and to provide individual responsibility at individual unit level may be reduced.

As with study design, the statistical analyses performed in each of the studies is also different. This occurs with different major outcome parameters for the various studies and the statistical tests that are being used, but also has more fundamental problems. In the early studies mortality was emphasised as the only relevant endpoint for treatment. Some of the early studies therefore had mortality as a primary endpoint in small studies that did not have an adequate anticipated mortality to start with. The three early studies concerned with vascular surgery patients fall into this group, the mortality rates were 5% in a study of 72 patients [179], 2% in a study of 104 patients [186] and 1% in a study of 120 patients [330]. The authors concluded that the routine use of DO₂I and CI targeting was not of benefit, but in fact the studies were not adequately powered to make this conclusion.

A further complicating factor is that some patients will achieve the goals of therapy spontaneously; indeed this is how Shoemaker and colleagues chose their targets for treatment as the median values of the survivors [6]. This phenomenon will be occurring in both the treatment groups of the trial and the control groups. Based on Shoemaker's data 50% of patients in the control groups are likely to have achieved 'optimisation targets' in all the studies conducted. This gives rise to a 'cross-over' phenomenon [334] and weakens the power of a study to detect any treatment effect. A statistical approach to this is extremely complicated and most of the studies, which undertook data analysis on an intention-to-treat basis, provide insufficient information to be able to analyse their data to exclude so called 'spontaneous achievers' from the data analysis. However, some studies in patients with established critical illness attempted to
overcome this problem by only randomising patients after targeted fluid resuscitation [250] or analyzing patients based on their final DO$_2$I regardless of how this was achieved [375]. While modern evidence based medicine accepts intention-to-treat as a standard analysis which allows a particular treatment to be given to a group of patients with the anticipation of an improved outcome, a one size fits all approach; modern critical care medicine may be able to offer something more sophisticated. The individual monitoring and treatment that can be given to individual patients requires development of statistical techniques and study designs to allow the utility of this individual approach to be tested.

The potential importance of the 'spontaneous achiever' phenomenon is illustrated by the study of Sandham and colleagues [145] discussed earlier. Their data show that while treatment targets were met on average in the protocol group, only half required any therapy to achieve these targets: only 48.9% received perioperative inotropic therapy, only 8.5% received vasodilators and only 54.8% received colloid fluid therapy, the three therapies that were advocated to treat the patients. While this is a statistically higher degree of intervention than the control group, it suggests that half of the patients randomised to the protocol group achieved targets without treatment. Furthermore, as the study was randomised it could be concluded that the same proportion of patients achieved these targets in the control group as well, although this was not measured. Similarly out of 72 patients enrolled in another study only 34 were found to have S$_0$O$_2$ low enough to be treated by the protocol [179]. This level of required intervention is much lower than other studies, such as that published by Boyd et al. [183] in which, for example, 85% of treatment group patients received inotropes.

Most of the systematic reviews have used a meta-analysis to combine the studies and draw conclusions. There has been much discussion about the value and pitfalls of using meta-analyses in this way. In the context of this thesis any combination analysis will combine all the problems with the studies that have been discussed above. While the intention behind a meta-analysis is that sample size is increased by combining data from small studies, and to some extent the problems in individual
studies is diluted, this is by no means certain to occur. The combination of flawed studies might provide a vicarious validity for all of them, and combining studies that investigate very different situations might hide important data concerning the value of treatment in one or two instances.

In distinction to the studies on perioperative patients, studies in patients groups other than those undergoing surgery have not shown positive results. Whether this is due to a fundamental problem with the treatment being applied to different disease categories or whether it is because treatment to increase and maintain tissue perfusion has been instituted too late is open to question. Intriguingly one study specifically designed to intervene very early in patients with septic shock has shown an improved outcome [297] and further investigation needs to be undertaken on this last point.

It is slightly difficult to know whether further investigations on high-risk patients undergoing surgery would be worthwhile. For such a study to add robustly to the previous literature it would require a very precise and objective methods of patient enrollment, a requirement that may not currently be possible, a large number of patients, and a very precisely defined treatment regime for both protocol and control groups of patients, with the possibility to analyse the spontaneous achiever separately. Furthermore the study should be blinded for investigators interpreting the nature of the outcome measures.

By comparison of the studies that have been undertaken in high-risk surgical patients, and other patient groups, it should be possible to form some conclusions on the merits of different monitoring techniques, different drugs, and different targets for treatment. However, due to the diminishing numbers of patients when studies are broken down and compared in this way few firm conclusions can be reached. When considering the techniques for monitoring cardiac function in high-risk surgical patients both the PA catheter and the oesophageal Doppler monitor have been used in clinical studies. Both techniques appear to be safe and to provide informative results, and while most of the studies reporting a positive effect have used PA catheters as opposed to oesophageal
Doppler, the Doppler technique has tended to be used on the lower risk patients in whom mortality was not necessarily a primary outcome measure. It is therefore not possible at this time to conclude that there is a favoured technique. It is likely that the most important feature resulting in a good outcome is the close attention to targeted treatment that comes from the use of such monitors, rather than the monitoring technique itself.

It is also difficult to make valid conclusions concerning the pharmacological techniques that should be used to increase cardiac output. Studies have used mixtures of inotropic and vasodilator agents or single agents, such as dopexamine, and each method has had positive and negative studies for improvement in patient outcome. There is not enough evidence to suggest one method is superior to the others and once again it is probably the close attention to a treatment regime that is of fundamental importance.

Some of the studies have not used pharmacological agents at all and have concentrated on careful fluid titration alone. The studies have usually being undertaken in the lower risk patient groups so it is not possible to address the question of whether pharmacological agents need to be included in a goal-directed therapy regime or whether very accurate fluid titrations will suffice. This is similar to the situation of drawing implications as to the superior monitoring technique. However it is likely that the pharmacological agents are not of added benefit if targets are met by fluid titration alone, but it is not possible to absolutely conclude that this is correct. In the work on high-risk surgical patients all of the studies have used targets of treatment involving parameters concerned with cardiac performance and blood flow such as Cl, \(\dot{Q}_\text{O}_2\) and SV. It is therefore not possible to know the effects of targeting other parameters such as those related directly to tissue perfusion. It is tempting to suggest that this would be a superior and far less invasive method. However it would not follow the philosophical track concerning the preemptive nature of goal-directed therapy, as therapeutic intervention would only be possible once a change in tissue perfusion measured by whatever technique had occurred. Based on the scientific evidence presented in this thesis such intervention might be expected to occur too late and therefore be ineffective.
Lastly it is interesting to discuss what is necessary for treatment in high risk surgical patients and patients with other critical illness to be accepted as a standard guideline. Three studies, referred to in this thesis, have been adopted into the guidelines published by national bodies into the care of high-risk surgical patients. The studies of Mangano et al. [313] and Poldermans et al. [314] into the use of perioperative β-blockade have been adopted by the American College of Cardiology and the American Heart Association into standard guidelines for care of surgical patients [316]. As discussed in the text the studies are themselves controversial and open to differing interpretations and enrolled only 312 patients. Recently, the study by Rivers and colleagues [297] has been adopted by the Surviving Sepsis Campaign [4]. This is only one positive study enrolling only 263 patients, and calculations for this thesis show the OR for this single study to be 0.49 (95% Confidence Interval 0.30 - 0.81), compared to the 8 other studies which have enrolled patients with general critical illness and sepsis and have included 980 patients and did not show any improvement in outcome, odds ratio 0.93 (95% Confidence Interval 0.73 - 1.20). The degree of difficulty in changing practice was recently demonstrated by a questionnaire sent to 170 intensive care and high dependency units in Britain in order to quantify the number of units practising pre-operative optimisation. There was a 91% response rate. Of the respondents familiar with the evidence advocating pre-operative optimisation, 91% believe pre-operative optimisation improved outcome but only 62% admitted patients for such preparation. Moreover, only eight units (6%) admitted more than 25% of eligible patients. The reasons given for not admitting such patients pre-operatively were a lack of manpower, beds or both [376].

In the context of this thesis these important and influential recommendations concerning perioperative β-blockade and early goal-directed therapy in sepsis must be seen in comparison with the 21 individual studies and 4015 patients that have been involved in investigations into the targeted increase of CI, DO₂I and tissue perfusion in high risk surgical cases, and as result of which no influential recommendations have
been forthcoming. Furthermore, all systematic reviews of these studies have shown improved morbidity and mortality. It becomes a point of philosophical discussion to speculate why those caring for patients at high risk of mortality seem more able to adopt positive findings from smaller studies than positive findings from a group of studies. At least part of the reason may be the very fact that interpreting an understanding of the message from a larger body of literature is a more complex undertaking. Differences between the exact methodology employed in the different studies can sidetrack the debate about their outcome and general message into a debate undertaken largely between academic clinicians about the influence of the methodology on the results. In addition the complexity of influencing change in treatment on a large number of patients that may not traditionally be viewed as representing a group in whom such treatment should be employed cannot be overemphasised. Changes in attitude, care pathways and organizational structures would all need to be undertaken if treatment to specific tissue perfusion targets was to be offered to all at risk patients. While this may appear a daunting task the goal of cutting mortality by a third and reducing morbidity in these patients should not be ignored.
10. Appendices

10.1 Table 1 Randomised, controlled studies of perioperative goal-directed therapy
Table 1.

Randomised, controlled studies of perioperative goal-directed therapy.

PA = pulmonary artery, PAOP = pulmonary artery occlusion pressure, DO$_2$I = oxygen delivery index, VO$_2$I = oxygen consumption index, CI = cardiac index, SVR = systemic vascular resistance, CVP = central venous pressure, SBP = systolic blood pressure, HR = heart rate, UO = urine output, SV = stroke volume, S$_v$O$_2$ = mixed venous oxygen saturation, MAP = mean arterial pressure.

<table>
<thead>
<tr>
<th>Study First author and reference</th>
<th>Criteria for study admission</th>
<th>N</th>
<th>Target for treatment in all patients</th>
<th>Target for treatment in the 'protocol' group</th>
<th>Odds ratio for reduction in mortality (95% Confidence Interval)</th>
<th>Other significant differences in outcome between treatment and control groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schultz</td>
<td>Fractured neck of femur</td>
<td>70</td>
<td>Routine care</td>
<td>General 'optimised' physiological profile. Fluid. Vasodilators and inotropes used</td>
<td>0.07 (0.01-0.61)</td>
<td>None.</td>
</tr>
<tr>
<td>Shoemaker</td>
<td>List of high risk criteria for general surgical patients</td>
<td>58</td>
<td>PA catheter used. PAOP 4-12 mmHg and DO$_2$I 400-550 mL min$^{-1}$m$^{-2}$ using fluids, vasodilators and inotropes</td>
<td>CI &gt; 4.5 L min$^{-1}$m$^{-2}$ DO$_2$I &gt; 600 mL min$^{-1}$m$^{-2}$ VO$_2$I &gt; 170 mL min$^{-1}$m$^{-2}$ using fluids, vasodilators and inotropes</td>
<td>0.07 (0.01-0.63)</td>
<td>A significant reduction of complications, duration of ICU stay, hospitalization, mechanical ventilation and costs in the treatment group.</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Criteria</td>
<td>Failure</td>
<td>OR (95% CI)</td>
<td>Results</td>
<td></td>
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<tr>
<td>Berlau</td>
<td>Limb salvage arterial surgery</td>
<td>Routine care as directed by the anaesthesiologist, PA catheter only in some patients</td>
<td>CI &gt; 2.8 L min⁻¹ m⁻² PAOP 8-15 SVR &lt; 1100 dyne.sec cm⁻⁵ Analysis is based on treatment groups combined vs. control</td>
<td>0.14 (0.01-1.65)</td>
<td>Reduced intraoperative events, less post-operative cardiac morbidity, less than the graft thrombosis in the protocol group.</td>
<td></td>
</tr>
<tr>
<td>Fleming</td>
<td>Trauma specific diagnostic criteria</td>
<td>Conventional resuscitation criteria using CVP 8-12 mmHg or PAOP 8-12 mmHg</td>
<td>DO₂I &gt; 670 mL min⁻¹ m⁻² Vo₂I &gt; 166 mL min⁻¹ m⁻² using fluid infusion and dobutamine if targets not met</td>
<td>0.41 (0.14-1.15)</td>
<td>Protocol patients had fewer organ failures, shorter hospital stay, and reduced requirement for ventilation.</td>
<td></td>
</tr>
<tr>
<td>Boyd</td>
<td>List of high risk criteria for general surgical patients</td>
<td>All patients had PA catheter</td>
<td>DO₂I &gt; 600 mL min⁻¹ m⁻² using dopexamine</td>
<td>0.21 (0.06-0.79)</td>
<td>A significant reduction of complications in the treatment group.</td>
<td></td>
</tr>
<tr>
<td>Bishop</td>
<td>Trauma specific diagnostic criteria</td>
<td>SBP &gt; 120, HR &lt;110, UO 30-50 mL/hr, If measured CVP 8-12 mmHg, PAOP 8-12 mmHg</td>
<td>CI &gt; 4.5 L min⁻¹ m⁻² DO₂I &gt; 600 mL min⁻¹ m⁻² Vo₂I &gt; 170 mL min⁻¹ m⁻²</td>
<td>0.38 (0.16-0.90)</td>
<td>Reduced organ failures in the treatment group.</td>
<td></td>
</tr>
<tr>
<td>Mythen</td>
<td>Elective cardiac surgery</td>
<td>Routine care</td>
<td>Maximise SV and rise CVP by 3 mmHg with fluid challenges (200mL hydroxethyl starch) assessed by oesophageal Doppler</td>
<td>Not able to calculate</td>
<td>Reduced gut mucosal hypoperfusion, major complications hospitalization and ICU stay in treatment group.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Procedure Description</td>
<td>Survival Analysis</td>
<td>Results</td>
<td></td>
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<tr>
<td>Durham</td>
<td>Trauma specific diagnostic criteria</td>
<td>58</td>
<td>Routine care, but patients monitored with a PA catheter</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><strong>DO₂I &gt; 600 mL min⁻¹ m⁻² and/or VO₂I &gt; 150 mL min⁻¹ m⁻² using fluid therapy and dopamine or dobutamine if targets not met</strong></td>
<td>1.17 (0.22-6.33)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><strong>None.</strong></td>
<td>1.17 (0.22-6.33)</td>
<td></td>
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</tr>
<tr>
<td>Bender</td>
<td>Infra-renal aortic reconstruction, Lower limb revascularisation</td>
<td>104</td>
<td>Routine care as directed by the anaesthesiologist, PA catheter only in some patients</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td><strong>PAOP 8-14 mmHg, CI &gt; 2.8 L min⁻¹ m⁻², SVR &lt; 1100 dyne.sec cm⁻⁵</strong></td>
<td>1.04 (0.06-17.08)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><strong>None.</strong></td>
<td>1.04 (0.06-17.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinclair</td>
<td>Fractured neck of femur</td>
<td>40</td>
<td>Maintenance intravenous fluid therapy. Oesophageal Doppler used for monitoring, otherwise routine care</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Maximise SV with fluid challenges and increase corrected flow time &gt; 0.35s assessed by oesophageal Doppler</td>
<td>0.47 (0.04-5.69)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>None.</strong></td>
<td>0.47 (0.04-5.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziegler</td>
<td>Aortic reconstruction, limb salvage surgery</td>
<td>72</td>
<td>PA catheter used, only maintenance intravenous fluids given</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><strong>PAOP &gt; 12mmHg S₂O₂ &gt; 65% using fluid boluses, vasodilators and dobutamine</strong></td>
<td>1.97 (0.31-12.54)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><strong>None.</strong></td>
<td>1.97 (0.31-12.54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ueno</td>
<td>Partial hepatectomy for hepatocellular carcinoma</td>
<td>34</td>
<td>Routine care including CI 2.8-4.0 l/min/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>CI &gt; 4.5 L min⁻¹ m⁻²</strong></td>
<td>Not able to calculate</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>DO₂I &gt; 600 mL min⁻¹ m⁻²</strong></td>
<td>Not able to calculate</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><strong>VO₂I &gt; 170 mL min⁻¹ m⁻²</strong></td>
<td>Not able to calculate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Reduced incidence of hyperbilirubinaemia and liver failure in treatment group.</strong></td>
<td>Not able to calculate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valentine</td>
<td>Aortic surgery</td>
<td>120</td>
<td>Routine care without PA catheter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>PA catheter placed in protocol patients</strong></td>
<td>3.11 (0.04-5.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Increased number of</strong></td>
<td>3.11 (0.04-5.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilson</td>
<td>List of surgical or medical criteria for general surgical patients</td>
<td>138</td>
<td>Routine care</td>
<td>PAOP &gt;12 using human albumin 4.5% DO$_2$I &gt; 600 mL m$^{-2}$ using fluids, and adrenaline (n=92) or dopexamine (n=92). Analysis is based on treatment groups combined vs. control</td>
<td>0.16 (0.04-0.64)</td>
<td>The use of dopexamine significantly reduced complications and hospital stay.</td>
</tr>
<tr>
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</tr>
<tr>
<td>Polonen</td>
<td>Elective cardiac surgery</td>
<td>393</td>
<td>Routine care</td>
<td>PA catheter S$_O_2$ &gt; 70% Serum Lactate &lt; 2mmol L$^{-1}$</td>
<td>0.38 (0.08-1.81)</td>
<td>Reduced hospital stay and organ failure at discharge in the treatment group.</td>
</tr>
<tr>
<td>Takala</td>
<td>List of surgical or medical criteria</td>
<td>412</td>
<td>Haemodynamic stabilisation</td>
<td>No specific additional targets. Dopexamine given in two predefined doses. Analysis is based on treatment groups combined vs. control</td>
<td>0.84 (0.45-1.57)</td>
<td>None.</td>
</tr>
<tr>
<td>Lobo</td>
<td>List of surgical or medical criteria</td>
<td>37</td>
<td>Patients monitored with a PA catheter. Treatment to PAOP 12-16 mmHg using fluids, and DO$_2$I 520-600 mL m$^{-2}$ using dobutamine</td>
<td>DO$_2$I &gt; 600 mL m$^{-2}$ using additional dobutamine</td>
<td>0.33 (0.07-1.65)</td>
<td>Clinical and infectious complications were significantly reduced in the protocol group.</td>
</tr>
<tr>
<td>Venn</td>
<td>Fractured neck of femur</td>
<td>90</td>
<td>Patients monitored with CVP or oesophageal Doppler</td>
<td>CVP group patients had fluid boluses in response to changes of CVP measurement. Doppler group patients had fluid boluses to maximize SV.</td>
<td>0.72 (0.18-2.95)</td>
<td>A significant reduction in time fit for hospital discharge in treatment group.</td>
</tr>
</tbody>
</table>

Other values:
- CI > 2.8 L min$^{-1}$ m$^{-2}$
- PAOP 8-15 mmHg
- SVR < 1100 dyne.sec/cm$^5$
- (0.31-30.73) adverse intraoperative events in the protocol group.
- 0.16 (0.04-0.64) The use of dopexamine significantly reduced complications and hospital stay.
<table>
<thead>
<tr>
<th>Author</th>
<th>Population Details</th>
<th>Number Monitored</th>
<th>Monitoring</th>
<th>Management</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan</td>
<td>Major elective surgery (anticipated blood loss &gt; 500 mLs)</td>
<td>100</td>
<td>Patients monitored with oesophageal Doppler</td>
<td>Fluid boluses given to maximize SV</td>
<td>Unable to calculate Earlier return of bowel function, decreased length of stay in the treatment group</td>
</tr>
<tr>
<td>Sandham</td>
<td>Age &gt; 60, major elective surgery, ASA III or IV</td>
<td>1994</td>
<td>Routine care</td>
<td>Pulmonary artery catheter in the treatment group to target DO$_2$I 500 to 600 mL min$^{-1}$m$^{-2}$, CI 3.5 to 4.5 L min$^{-1}$, MAP 70 mmHg, PAOP 18 mmHg, HR &lt; 120 bpm</td>
<td>1.01 (0.73-1.41) Increased pulmonary embolism rate in the treatment group.</td>
</tr>
<tr>
<td>Stone</td>
<td>Age&gt;60, major elective abdominal surgery</td>
<td>100</td>
<td>All patients monitored with the oesophageal Doppler to maximize SV</td>
<td>Dopexamine infusion at 0.25 mcg kg$^{-1}$min$^{-1}$ (double blind)</td>
<td>1.53 (0.24-9.59) All patients had significantly lower mortality than predicted.</td>
</tr>
</tbody>
</table>
The Use of Dopexamine Hydrochloride to Increase Oxygen Delivery Perioperatively

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Perioperative increases in oxygen delivery may reduce morbidity and mortality in certain groups of surgical patients. However positive inotropic drugs, such as dobutamine and epinephrine themselves, may increase oxygen demand. Dopexamine hydrochloride is a new dopamine analogue with action at β₂-adrenoceptors and DA₁ receptors, but it possesses no direct α-adrenoceptor activity. We assessed the suitability of dopexamine to increase oxygen delivery perioperatively in eight patients having vascular surgery and studied its effects on oxygen demand. Oxygen delivery was increased toward 600 mL min⁻¹ m⁻² by intravenous (IV) fluid infusion and IV titration of dopexamine hydrochloride. Oxygen delivery could be increased preoperatively (375 ± 43 to 552 ± 50 mL min⁻¹ m⁻², P < 0.05) with >600 mL min⁻¹ m⁻² being achieved in five patients. This increase was achieved without significant increase in total body oxygen consumption (114 ± 10 to 123 ± 7 mL min⁻¹ m⁻², P > 0.05) or rate pressure product (13.7 ± 2.8 × 10³ to 13.5 ± 2.1 × 10³ mm Hg beats/min, P > 0.05). Postoperatively oxygen delivery was increased again without an increase in oxygen consumption (126 ± 10 mL min⁻¹ m⁻², P > 0.05) or rate pressure product (14.2 ± 0.9 × 10³ mm Hg beats/min, P > 0.05). Dopexamine hydrochloride may provide a method for increasing oxygen delivery perioperatively with only limited increase in total body or myocardial oxygen demand.

Mortality and morbidity are reduced in patients having major surgery if cardiorespiratory variables are increased to the supranormal levels of survivors (1,2), particularly when these increases are achieved preoperatively (3,4). After insuring that the hemoglobin concentration and arterial saturation are optimal, inotropic drugs and vasodilators are often given. The inotropic drugs commonly used in this context have been dobutamine and epinephrine (3,4). However both these inotropic drugs increase oxygen consumption in normal individuals (5–10), and their use may needlessly increase oxygen demand in these stable preoperative patients (11). Other inotropic and vasoactive drugs may have more suitable hemodynamic and metabolic profiles for use perioperatively, but as yet no information is available. We have investigated the possibility and metabolic cost of using dopexamine to increase oxygen delivery in patients undergoing major vascular surgery.

Dopexamine is a dopamine analogue with action at β₂-adrenoceptors and DA₁ receptors and only moderate activity at β₁ and DA₂ receptors. Dopexamine possesses no direct α-adrenoceptor activity, but norepinephrine reuptake is inhibited (12). Dopexamine has been investigated in patients with cardiac failure in whom it causes peripheral vasodilation and increased cardiac index (13) without a significant increase in myocardial oxygen consumption (14,15); renal, hepatic, and splanchnic blood flows are also increased (16,17). Dopexamine may have a suitable hemodynamic profile for use preoperatively where increase in blood flow to vital organs is required without an increase in myocardial or total body oxygen consumption.

Methods

Eight patients who were booked for elective major vascular procedures were included in the study (Table 1). Hospital ethics committee approval for the study was obtained and all patients gave informed consent. The patients were admitted to the Intensive Care Unit (ICU) 12–24 h before their operation. Under local anesthesia a pulmonary artery thermodilution catheter and radial arterial line were inserted, and a peripheral intravenous infusion commenced; the electrocardiograph (ECG) was recorded continuously. The patients...
Supervision of anesthesia was by the anesthesiologist designated to the case and apart from attempting to maintain PAOP and Hb, no other constraints were placed on conduct of anesthesia. Anesthesia was induced with 3 µg/kg fentanyl, 0.3 mg/kg etomidate, and 0.01 mg/kg vecuronium IV and was maintained with 7 µg/kg fentanyl, oxygen/NO2, and enflurane, with bolus doses of vecuronium as required. Crystalloids and blood products were administered to attempt to maintain baseline values for PAOP and Hb. Thirty minutes after induction of anesthesia and before arterial cross-clamping (if used) cardiorespiratory values were recorded (intraoperative).

Postoperatively, patients were returned to the ICU and cardiorespiratory values were recorded at 2, 6, and 12 h. Fluid and blood products were given to maintain the preoperative PAOP and Hb, and doxepamine hydrochloride was titrated to the preoperative oxygen delivery. When lactate had fallen to less than 2.0 mmol/L (this is the upper limit of the normal range in our ICU) doxepamine hydrochloride was discontinued; at 6 h postdiscontinuation of the doxepamine hydrochloride, a last set of cardiorespiratory values were recorded.

Data were analyzed by repeated measures analysis of variance for each variable; if significance was achieved Fisher’s PLSD test was used for multiple comparison. The major emphasis in this study was changes from baseline; therefore, all results indicated as significant in the text are as compared to baseline. A statistical significance was taken as $P < 0.05$. All values in the text are mean ± SEM.

## Results

All the patients (Table 1) required doxepamine to increase their oxygen delivery preoperatively. Doxepamine was stopped, on average, 16 h postoperatively (range 0–29 h). The preoperative dose of doxepamine was $1.7 ± 0.46$ µg·kg⁻¹·min⁻¹. Three patients failed to achieve an oxygen delivery of 600 mL·min⁻¹·m⁻², two
because of increases in HR >20% above baseline, and one because the maximum dose of dopexamine was given. One patient who was scheduled for peripheral vascular surgery had such improved blood flow to the limb after dopexamine was started that the operation was canceled. Three patients were in long-standing atrial fibrillation before beginning dopexamine; two converted to sinus rhythm preoperatively during dopexamine infusion. No patients developed chest pain or ECG changes. Dopexamine was discontinued in one patient due to short-lived hypotension after induction of anesthesia.

The results for the major cardiorespiratory values (cardiac index, oxygen delivery, oxygen consumption, and rate-pressure product) are shown in Figure 1. Results for other variables are shown in Table 2. Cardiac index and oxygen delivery could be increased preoperatively with dopexamine. There was no concomitant increase in oxygen consumption or rate-pressure product. Intraoperatively the increase in cardiac index was maintained, but oxygen delivery fell due to a decrease in hemoglobin concentration. Oxygen consumption fell significantly, but there was no significant decrease in rate-pressure product. Postoperatively, cardiac index was maintained at elevated levels and oxygen delivery also increased. Oxygen consumption and rate-pressure product returned to baseline values postoperatively.

Discussion

This study demonstrates the perioperative cardiorespiratory effects of dopexamine hydrochloride infusion given to increase oxygen delivery in patients requiring vascular surgery. Most importantly, we found that the increase in oxygen delivery could be achieved without increases in oxygen consumption or rate-pressure product. Previously, dopexamine has been given intra- and postoperatively to patients undergoing coronary bypass surgery to increase oxygen delivery (18). In that study significant increases in oxygen delivery were seen at a dopexamine infusion of 2 μg·kg⁻¹·min⁻¹ compared to placebo, but the dopexamine was only started after induction of anesthesia and postoperative increases in oxygen delivery were not as much as in our study.

The changes we observed preoperatively in cardiac index, oxygen delivery, and SVRI were much the same as other investigators have found for similar doses of dopexamine (13,19). These studies were undertaken in patients with primary cardiac conditions, but the abnormally low baseline cardiac index in our patients suggests that they too had significant cardiac pathology. In our study, the cardiac index could be maintained at elevated levels perioperatively, although oxygen delivery fell intraoperatively due to blood loss. The maintenance of significantly increased levels of cardiac index and oxygen delivery after the dopexamine was discontinued was an unexpected finding. This may be due to a longer lasting effect of dopexamine hydrochloride than has been reported before, or it may be due to a normal increase in cardiac index and oxygen delivery in the postoperative period (1). In previous studies, the effectiveness of long-term infusions of dopexamine to increase CI has been varied (19–21), but the postinfusion period has not been reported previously.

Most studies using dopexamine have shown a dose-related increase in HR (13), but this may not be long lasting (19). Although two patients did have a 20% increase in HR preoperatively, we did not observe an
increase in mean HR until 6 and 12 h postoperatively. This may have been due to the emphasis in our study on the prevention of a decrease in left ventricular filling pressures (22). The lack of increased overall mean HR was partly due to the conversion of two patients from atrial fibrillation to sinus rhythm with dopexamine. Dopexamine is less arrhythmogenic than other catecholamines (12,23); animal studies have demonstrated an antiarrhythmogenic effect (23).

The most important feature of this study is that the increase in cardiac index and oxygen delivery was achieved without increase in whole body oxygen consumption or rate-pressure product. Apart from an intraoperative decrease in oxygen consumption, probably due to sedative effects of anesthesia or possibly an effect of temperature (24), there were no significant changes in oxygen consumption. In particular there was no significant increase in oxygen consumption preoperatively, implying that there was no increase in total body oxygen demand. Although we did not measure myocardial oxygen consumption directly, an estimate can be made from the rate-pressure product which showed no significant changes in our study implying no change in myocardial oxygen demand. This agrees with previous studies showing that myocardial oxygen consumption does not increase with dopexamine (14,15). Studies of other inotropes have shown an increase in oxygen consumption in otherwise well patients, and have suggested that this is due to peripheral catecholamine actions and effects on myocardial oxygen consumption (5–10). We feel that the lack of an increase in oxygen demand in our patients in the preoperative phase may show a potential advantage of dopexamine over other inotropic agents.

Unlike Shoemaker, we did not find a higher oxygen consumption postoperatively than preoperatively (3); this may have been due to the different inotropic drug used or a different sedation regimen (24). Some investigators have suggested that increased oxygen consumption postoperatively may be a particular benefit of increasing oxygen delivery during surgery (3) allowing more rapid ‘repayment’ of a tissue oxygen debt (25). In our patients, the lactate returned to normal levels within 6 h, suggesting that the postoperative oxygen debt was paid back within this time. This may have occurred without an obvious increase in oxygen consumption due to a generalized improvement in oxygen supply/demand (26) when dopexamine is given pre- and intraoperatively. We suggest that dopexamine may be a suitable drug to increase oxygen delivery perioperatively, because increases can be achieved without an increase in oxygen demand.

References
11. Boyd O, Bennett ED. Is oxygen consumption an important clin-
A Randomized Clinical Trial of the Effect of Deliberate Perioperative Increase of Oxygen Delivery on Mortality in High-Risk Surgical Patients

Owen Boyd, MRCP; R. Michael Grounds, MD, FFARCS; E. David Bennett, FRCP

Objective.—To assess the effect of deliberate perioperative increase in oxygen delivery on mortality and morbidity in patients who are at high risk of both following surgery.

Design.—Prospective, randomized clinical trial.


Patients.—A total of 107 surgical patients, who were assessed as high risk from previously identified criteria, were studied during an 18-month period.

Interventions.—Patients were randomly assigned to a control group (n=54) that received best standard perioperative care, or to a protocol group (n=53) that, in addition, had deliberate increase of oxygen delivery index to greater than 600 ml/min per square meter by use of dopexamine hydrochloride infusion.

Outcome Measures.—Mortality and complications were assessed to 28 days postoperatively.

Results.—Groups were similar with respect to demographics, admission criteria, operation type, and admission hemodynamic variables. Groups were treated similarly to maintain blood pressure, arterial saturation, hemoglobin concentration, and pulmonary artery occlusion pressure; however, once additional treatment with dopexamine hydrochloride had been given, the protocol group had significantly higher oxygen delivery preoperatively (median, 597 vs 399 ml/min per square meter; P<.001) and postoperatively (P<.001). Results indicate a 75% reduction in mortality (5.7% vs 22.2%; P=.015) and a halving of the mean (±SEM) number of complications per patient (0.66 [±0.16] vs 1.35 [±0.20]; P=.008) in patients randomized to the protocol group.

Conclusion.—Perioperative increase of oxygen delivery with dopexamine hydrochloride significantly reduces mortality and morbidity in high-risk surgical patients.

IN THE 1970s and 1980s, Shoemaker and colleagues reported that they were able to identify a group of high-risk patients that had mortality rates of between 30% and 40% following surgery. They also confirmed the earlier work by Clowes and Del Guerdo that survivors of major operations had consistently higher postoperative cardiac output and oxygen delivery values of survivors, and they demonstrated that if routine parameters, such as blood pressure and urine output, were stabilized, parameters related to blood flow had important prognostic implications. Thus, in 1978, it was suggested that the high mortality rate found in this group of high-risk surgical patients might be reduced if the flow-related cardiovascular values noted in the survivors became additional goals for perioperative treatment for all such surgical patients. In 1988, Shoemaker and co-workers published the results of a randomized study of 58 patients, showing that mortality and morbidity could indeed be reduced if the cardiac output and oxygen delivery values of survivors were used to target additional therapy. Since then, no other randomized studies of high-risk surgical patients have been published. Despite the lack of contradictory data, considerable doubt has been cast on the value of this type of treatment for surgical patients; only a small number of relatively young patients were studied, the groups may not have been matched well, and the treatment regimen used was unclear. Further concerns have been raised regarding the safety of this type of therapy because invasive procedures are required that have not always been shown to be useful, and inotropes, which are used to increase cardiac output and oxygen delivery, may also increase cardiac oxygen demand, placing patients at risk for myocardial ischemia. As a consequence, this type of goal-directed therapy, where in addition to standard best treatment cardiac output and oxygen delivery are deliberately increased, has not been widely adopted in surgical patients, and it has been suggested that further clinical trials are required.

We have recently shown in a pilot study that dopexamine hydrochloride might be a suitable agent for increasing perioperative oxygen delivery, as oxygen delivery can be increased without significantly increasing oxygen demand, an effect that has been reported to occur with other agents. Dopexamine is a novel dopamine analogue with action at β-adrenoceptors and DA receptors and only moderate activity at β- and DA receptors; it has no direct α-adrenoceptor activity, but norepinephrine reuptake is inhibited. Dopexamine consequently produces peripheral vasodilation with a simultaneous increase in cardiac index (CI) without significant increase in myocardial oxygen consumption (VO2). In addition, renal, hepatic, and splanchic blood flows are specifically increased.

This article reports the results of a randomized, prospective, controlled study to test the hypothesis that deliberately increasing oxygen delivery (DO2I) during the perioperative period by use of intra-
venous dopexamine will reduce mortality and morbidity in a group of surgical patients who are known to be at high risk of both.

MATERIALS AND METHODS

Summary

Patients were randomly allocated to a protocol or control limb of the study. Those patients randomized to the control group were treated with what is considered to be the best conventional therapy, which included dopamine, inotropes, and vasodilators as required, as well as continuous fluid management to maintain cardiac filling pressures. Postoperative artificial ventilation was provided when indicated. In addition to this, patients randomized to the protocol group had DO2I deliberately increased to a target of greater than 600 mL/min per square meter as suggested by Shoemaker and coworkers.7 In the protocol group, dopexamine was used to deliberately increase cardiac output and DO2I with limits placed on the dopexamine infusion rate to avoid tachycardia and possible coronary ischemia. No treatment that would normally have been given to any patient enrolled in this study was withheld; specifically, vasodilating drugs and dopamine were given prophylactically and where clinically indicated when this was the normal practice of the surgeons, anesthetologists, or intensive care team. Use of these vasoactive medications in the postoperative period was recorded. Mortality and morbidity were recorded to 28 days postoperatively.

Patient Selection

A total of 107 patients were enrolled in a randomized, prospective clinical trial at The General Intensive Care Unit (ICU), St George's Hospital, London, England, during an 18-month period from November 1990 to May 1992. Institutional ethics committee approval was obtained and patients gave informed consent for participation in the study. Patients were identified as high risk using a table of high-risk criteria (Table 1), and were enrolled in the study if, in addition, the operation was expected to last, or had lasted, more than 1.6 hours. The patients were then randomized to either a protocol or control limb of the study (Fig 1). Because treatment was given to attain a specific target for DO2I, the study could not be blinded for the investigators. However, the surgical teams managing the patient were not aware of any particular patient's allocation.

Preoperative Treatment and Assessments

On admission to the ICU, an intraarterial catheter (Abbocath-T 20G or 22G, Abbott Laboratories Ltd, North Chicago, Ill) was placed in the patient's radial or femoral artery, and a pulmonary artery occlusion catheter (catheter 93A-131-7F, Edwards Division, Baxter Healthcare Corp, Irvine, Calif) was inserted via the internal jugular, subclavian, or femoral vein, depending on the proposed operation. Correct placement was checked by appropriate pressure traces and confirmed by chest roentgenography. The electrocardiogram was recorded continuously. Systemic arterial, pulmonary arterial, and central venous pressures were monitored continuously, and cardiac output was measured by thermodilution from the average of triplicate injections of 5 mL of cold 5% dextrose (Supermon 7210, Kontron Instruments, Milan, Italy). Arterial blood gas and arterial and mixed venous oxygen saturation levels were measured directly (IL 1382 Blood Gas Manager and IL 482 Co-oximeter, Instrumentation Laboratories, Lexington, Mass) as was whole blood lactate (LMA4s, Analox Instruments Ltd, London, England).

The following measurements were made after admission to the ICU and after insertion of monitoring devices, with the patient lying quietly in bed and prior to any further intervention: heart rate (HR), systolic and diastolic arterial pressure, systolic and diastolic pulmonary arterial pressure, right atrial pressure, pulmonary arterial occlusion pressure, cardiac output, arterial oxygen saturation (SaO2), pulmonary artery oxygen saturation (SvO2), hemoglobin concentration (Hb), and whole blood lactate concentration. Body surface area was calculated from measurements of height and weight by standard nomograms. A Goldman cardiac index indirect score was calculated for each patient.28 These measurements were labeled as "admission" (Fig 1).

Cardiac index, mean arterial pressure, and mean pulmonary arterial pressure were calculated, and DO2I and VO2I were calculated from the following standard formulae:

- DO2I (mL/min per m²) = CI (L/min per m²) × SaO2 (%)/Hb (g/L) × 0.0134
- VO2I (mL/min per m²) = CI (L/min per m²) × (SaO2 - SvO2)/Hb (g/L) × 0.0134

All patients were treated in the following way prior to surgery.29 A modified fluid gelatin solution (Gelofusine, Consolidated Chemicals Ltd, Wrexham, England) was given intravenously until the pulmonary artery occlusion pressure was 12 to 14 mm Hg;30 until there was no further increase in cardiac output, or until urine output exceeded 100 mL/h; blood products were infused to increase the patient's hemoglobin to greater than or equal to 120 g/L;31 if the SaO2 was less than 94%, supplemental oxygen was given by face mask.32 Once these targets (Table 2) had been achieved, all variables were remeasured and the results were recorded as "baseline" (Fig 1).

In patients randomized to the control group, the values at baseline were then maintained until the patients were transferred to the operating room. In patients randomized to the protocol group, further treatment with dopexamine was given if the DO2I had not reached 600 mL/min per square meter (Table 2). Dopexamine was infused into a central vein starting at a dose of 0.5 μg/kg per minute, and this dose was doubled every subsequent 30 minutes to a maximum dose of 8 μg/kg per minute or until a DO2I of 600 mL/min per square meter was achieved. Increase in the rate of infusion of dopexamine was to be limited by attainment of the DO2I target or by chest pain, significant ST segment depression on electrocardiogram, or an

Table 1.—Admission Criteria for Identification of High-Risk Patients*

<table>
<thead>
<tr>
<th>Admission Criteria</th>
<th>Protocol, No. (%) (n=53)</th>
<th>Control, No. (%) (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous severe cardiopulmonary illness (eg, acute myocardial infarction, COPD, stroke)</td>
<td>27 (50.9)</td>
<td>29 (53.7)</td>
</tr>
<tr>
<td>Extensive surgery planned for carcinoma (eg, esophagectomy, gastrectomy, cystectomy)</td>
<td>13 (24.5)</td>
<td>10 (18.5)</td>
</tr>
<tr>
<td>Acute massive blood loss (&gt;8 U)</td>
<td>6 (11.3)</td>
<td>5 (9.3)</td>
</tr>
<tr>
<td>Age &gt;70 y with limited physiological reserve in one or more vital organs</td>
<td>20 (37.7)</td>
<td>23 (42.6)</td>
</tr>
<tr>
<td>Septicemia (positive blood cultures or septic focus)</td>
<td>4 (7.5)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Respiratory failure (PaO2 &lt; 8 kPa on an FIO2 &gt; 0.4 or mechanical ventilation &gt;48 h)</td>
<td>1 (1.9)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Acute abdominal catastrophe with hemodynamic instability (eg, pancreatitis, perforated viscus, peritonitis, gastrointestinal bleed)</td>
<td>10 (18.9)</td>
<td>10 (18.5)</td>
</tr>
<tr>
<td>Acute renal failure (urea &gt;20 mmol/L, creatinine &gt;260 μmol/L)</td>
<td>2 (3.8)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Late-stage vascular disease involving aortic disease</td>
<td>31 (58.5)</td>
<td>32 (59.3)</td>
</tr>
<tr>
<td>Mean No. of admission criteria per patient</td>
<td>2.13</td>
<td>2.07</td>
</tr>
</tbody>
</table>

*No differences between groups were statistically significant. COPD indicates chronic obstructive pulmonary disease; FIO2, fractional inspired oxygen concentration.
increase in HR greater than 20% from the baseline level. At the limit of doxepamine titration, a further data set was recorded as "preoperative data" (Fig 1). For the control patients, baseline data were the same as preoperative data.

Perioperative Management

Introporarily administered doxepamine, if started, was continued at the same preoperative infusion dose; neither the anesthesiologist nor the surgeon was aware of a patient's allocation, and no other instructions were given to the anesthesiologist with regard to anesthetic management. The patients either were premedicated with morphine and atropine intramuscularly 1 hour preoperatively or had no premedication. Induction of anesthesia was with either propofol or thiopental sodium followed by fentanyl citrate for analgesia and vecuronium bromide for muscle relaxation. All patients were mechanically ventilated with oxygen, nitrous oxide, and isoflurane, with appropriate maintenance doses of fentanyl citrate and vecuronium bromide. The conduct of the anesthesia was left to the individual anesthesiologist assigned to the case; any treatment that the anesthesiologist or surgeon wished to give the patients was allowed at any stage.

Postoperative Treatment and Assessments

Patients were readmitted to the ICU after surgery and an immediate postoperative "0 hours" data set (Fig 1) was recorded. Patients who were admitted to the study postoperatively were randomly allocated to the protocol or control group, but it was not the purpose of this trial to randomize patients between preoperative and postoperative admission. In the patients admitted postoperatively, a pulmonary artery catheter was inserted and the treatment, according to the appropriate randomization, was instituted within 2 hours of the end of the operation.

In both protocol and control groups, the postoperative strategy was to retain and then maintain the same targets determined preoperatively (Table 2) by change in inspired oxygen concentration, blood transfusion, or intravenous fluid infusion as necessary. Clinical treatment of the patients was undertaken by the ICU team while the investigators controlled manipulation of the oxygen delivery to the required targets. Any necessary treatment was permitted to any patient at any stage. In the protocol group, DO$_2$ was increased toward 600 mL/min per square meter by addition or increase in the dose of doxepamine. The same limitations on doxepamine infusion were used as had been adopted preop-

Table 2.—Treatment Goals

<table>
<thead>
<tr>
<th>Variable</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>For Both Study Groups</td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>80-110</td>
</tr>
<tr>
<td>Pulmonary arterial occlusion pressure, mm Hg</td>
<td>12-14</td>
</tr>
<tr>
<td>Arterial oxygen saturation, %</td>
<td>&gt;94</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>&gt;120</td>
</tr>
<tr>
<td>Urine output, mL/kg per h</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Additional for Protocol Patients</td>
<td></td>
</tr>
<tr>
<td>Oxygen delivery index, mL/min per m$^2$</td>
<td>&gt;600</td>
</tr>
</tbody>
</table>

Fig 1.—Diagnostic representation of trial regimen and data recording times. ICU indicates intensive care unit; DO$_2$, oxygen delivery index.

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Most of the complications had clear-cut causes confirmed from hospital records or data measurements taken at the measurement times set out below (I<5 mmol/L is the upper limit of the normal range in our ICU). Although most monitoring was continuous while the patients remained on the ICU, data measurements were recorded on the patients at 0, 2, 6, 12, 18, and 24 hours postoperatively (Fig 1). Patient care in the ICU was continued in the usual way until the ICU team, not aware of any differences in demographic characteristics, Table 1 shows that there were no significant differences in the control groups and compared by a log-rank statistic. Fisher’s Exact Test was used to correct absolute data. Normally distributed cardiorespiratory data from the protocol and control groups were compared by Student’s t test for admission, preoperative, and postoperative data. Postoperative data were analyzed by the method of generating summary data for hemodynamic variables from 0 to 18 hours (full data sets were available for patients up to 18 hours), the integral of each variable with time being calculated for each patient and the results compared for protocol and control patients. Bonferroni’s method was used to correct t tests for three comparisons for each variable. Data that were manipulated to achieve a specific maximal target were consequently not normally distributed, and the Mann-Whitney U test was therefore used to compare CI, DO2, and VO2.

Table 3.—Postoperative Complications

<table>
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<th>Complications</th>
<th>Protocol, No. (%)</th>
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<tr>
<td>Respiratory failure (mechanical ventilation &gt;48 h)</td>
<td>(n=53)</td>
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<tr>
<td>Acute renal failure (urine output &lt;500 mL/24 h despite adequate pulmonary arterial occlusion pressure)</td>
<td>(5.7)</td>
<td>(13.0)</td>
</tr>
<tr>
<td>Septicemia (pyrexia &gt;38.5°C and septic focus or positive blood cultures)</td>
<td>(1.9)</td>
<td>(5.6)</td>
</tr>
<tr>
<td>Cardiorespiratory arrest</td>
<td>(5.7)</td>
<td>(4.7)</td>
</tr>
<tr>
<td>Pulmonary edema (roentgenographic diagnosis)</td>
<td>(7.5)</td>
<td>(18.5)</td>
</tr>
<tr>
<td>Pleural fluid (roentgenographic diagnosis)</td>
<td>(5.7)</td>
<td>(2.7)</td>
</tr>
<tr>
<td>Wound infection (positive wound swab cultures)</td>
<td>(5.7)</td>
<td>(5.6)</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>(1.9)</td>
<td>(0.7)</td>
</tr>
<tr>
<td>Acute myocaridal infarction (electrocardiographic diagnosis)</td>
<td>(1.9)</td>
<td>(4.7)</td>
</tr>
<tr>
<td>Abdominal abscess (positive cultures from intraperitoneal collection)</td>
<td>0</td>
<td>(1.9)</td>
</tr>
<tr>
<td>Postoperative hemorrhage (overt blood loss requiring &gt;2 U transfusion) with normal clotting profile</td>
<td>(1.9)</td>
<td>(8.4)</td>
</tr>
<tr>
<td>Gastric outlet obstruction (roentgenographic diagnosis)</td>
<td>(3.8)</td>
<td>0</td>
</tr>
<tr>
<td>Cerebrovascular accident (clinical diagnosis)</td>
<td>0</td>
<td>(3.7)</td>
</tr>
<tr>
<td>Pulmonary embolism (ventilation perfusion scan, with consistent clinical history)</td>
<td>0</td>
<td>(3.7)</td>
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<tr>
<td>Chest infection (clinical diagnosis)</td>
<td>(9.4)</td>
<td>(13.0)</td>
</tr>
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<td>Pneumonia (clinical diagnosis)</td>
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<tr>
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</tr>
<tr>
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*No individual differences were statistically significant.

**Results**

**Clinical Data**

A total of 107 patients were enrolled in the study, and all were included in the data analysis that was performed on an intention-to-treat basis;  \( P < 0.05 \) was considered significant in two-sided tests. Results are quoted as mean (±SEM), median with 25th to 75th centile range, or percentage as appropriate. Kaplan-Meier survival curves were constructed for the protocol and control groups and compared by a log-rank statistic. Fisher’s Exact Test was used to compare absolute data. Normally distributed cardiorespiratory data from the protocol and control groups were compared by Student’s t test for admission, preoperative, and postoperative data. Postoperative data were analyzed by the method of generating summary data for hemodynamic variables from 0 to 18 hours (full data sets were available for patients up to 18 hours), the integral of each variable with time being calculated for each patient and the results compared for protocol and control patients. Bonferroni’s method was used to correct t tests for three comparisons for each variable. Data that were manipulated to achieve a specific maximal target were consequently not normally distributed, and the Mann-Whitney U test was therefore used to compare CI, DO2, and VO2.

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or urgent surgical procedures \((P=.42)\); 30 (57%) of the protocol patients and 26 (52%) of the control patients underwent vascular operations \((P=.70)\); 17 (32%) of the protocol patients and 20 (37%) of the control patients underwent abdominal operations \((P=.69)\); and six in each group underwent other major operations \((P=.99)\).

As anticipated from the vasodilatory properties of dopexamine, the patients in the protocol group received significantly more fluid preoperatively than patients in the control group \((P<.01)\), as shown in Table 5. There were, however, no significant differences between the preoperative pulmonary artery occlusion pressure in the protocol or control groups (Table 6). Table 5 also shows that there was no difference in the fluid treatment given in the two study groups in the first 24 hours postoperatively. While there was no significant difference in treatment with a vasodilatory medication other than dopexamine between the two groups, the control group received more vasodilatory medication than the protocol group postoperatively. This confirms that both groups were aggressively managed to maintain therapeutic targets and suggests that the control patients were less cardiovacularly stable than the protocol patients in the first 24 hours postoperatively.

There were no complications related to placement of the pulmonary artery catheter or placement of any other measuring device. Apart from the expected increase in HR once dopexamine was started in the protocol patients, there were no harmful or potentially harmful side effects related to the use of dopexamine. In the protocol group, the mean \(\pm SE\) dose of dopexamine hydrochloride administered preoperatively was \(1.18 \pm 0.16\) \(\mu\)g/kg per minute and postoperatively was \(1.32 \pm 0.21\) \(\mu\)g/kg per minute. In patients who received dopexamine, infusion was continued for a median of 6.5 hours (25th centile, 3 hours; 75th centile, 16 hours) postoperatively. In the patients admitted postoperatively and randomized to the protocol group, a similar dose of dopexamine hydrochloride \((1.20 \pm 0.8)\) \(\mu\)g/kg per minute) was given, but the infusion was given for longer, 17 hours (25th centile, 14 hours; 75th centile, 19 hours). The APACHE II scores, median score of 14 (25th centile, 11; 75th centile, 16) for the control group vs median score of 12 (10, 15) for the protocol group \((P=.029)\), reflected the higher protocol group mortality in the control group. These scores were calculated after perioperative intervention and therefore cannot be used to form the basis of a demographic comparison between the groups.

Twenty-six of 107 patients were admitted postoperatively, 10 to the protocol group and 16 to the control group \((P=.26)\). Of these 26, four patients met entry criteria only during the operation, one with respiratory failure and three with more extensive resections for carcinoma than anticipated. The remaining 22 patients were taken directly to the ICU postoperatively. No patient met criteria only during the operation; eight of these could not be admitted to the ICU preoperatively because no bed was available, 11 were only recognized as fulfilling entry criteria after induction of anesthesia, and three had severe hemodynamic instability. For patients admitted postoperatively, there were no statistical differences in age, sex distribution, concurrent disease, or Goldman cardiac risk index between patients randomly assigned to the protocol or control groups. However, there was a lower Goldman cardiac risk index score in the patients admitted postoperatively to the study (median score, 9 [25th centile, 4; 75th centile, 15]) compared with those admitted preoperatively (median score, 11 [5, 17]) \((P=.076)\).

### Cardiorespiratory Data

Table 6 shows that there were no significant differences in mean arterial pressure, mean pulmonary arterial pressure, right atrial pressure, or pulmonary arterial occlusion pressure, in either the preoperative or the postoperative phase, between the two groups. These results show that the targets set for the trial regimen were met in both trial groups and that the groups were well matched for these "routine" parameters. The results also confirm the poor ability of these parameters to predict outcome. As expected from the pharmacologic effects of dopexamine, the HR was higher after dopexamine had been started in the protocol group. Although for the groups as a whole this did not reach statistical significance \((P=.14)\), 11 patients did have titration of dopexamine limited by a rise in HR of greater than 20% above baseline, as required by the study regimen.

Table 7 and Fig 2 show that on admission to the ICU there were no significant differences in CI, DO\(_1\), or VO\(_2\) between the groups. As expected, once the titration of dopexamine had been completed preoperatively, there were significantly higher CI and DO\(_1\) \((P<.001)\) in the protocol group. Postoperatively, the CI and DO\(_1\) in the protocol group remained higher \((P<.001)\), but it was not possible...
and nine patients were not treated preoperatively; 11 patients had the indocyanine green fluorescent following infusion of dopexamine in the HR of more than 20% preoperatively; greater than 600 mL/min per square meter; and 15 patients reached a DO₂I of less than 600 mL/min per square meter in most protocol patients. Although there did appear to be a small elevation of VO₂I as dopexamine was started, this did not reach statistical significance.

An important finding was the absence of significant differences in VO₂I preoperatively or postoperatively between the two groups. Although there did appear to be a small elevation of VO₂I as dopexamine was started, this did not reach statistical significance.

Preoperatively, eight protocol patients, compared with four control patients (P = .24), reached a DO₂I of greater than 600 mL/min per square meter following infusion of modified fluid gelatin alone; 15 patients reached a DO₂I of greater than 600 mL/min per square meter following infusion of dopexamine preoperatively; 11 patients had the infusion of dopexamine limited by a rise in HR of more than 20% preoperatively; and nine patients were not treated entirely in accordance with the preoperative regimen for the protocol patients. Of these nine patients, four received dopexamine preoperatively, but the infusion rate of dopexamine was not increased as planned; one of these four had a painful abdominal aortic aneurysm, and after a rise in mean arterial pressure, dopexamine infusion was not increased further; two almost attained target DO₂I (584 and 596 mL/min per square meter); and one had no further increase in DO₂I as planned; one of these four patients was randomized to the protocol group, but despite low DO₂I (<600 mL/min per square meter) did not receive dopexamine; one of these had uncontrolled hemorrhage and was transferred urgently to the operating room, two had almost attained target DO₂I (570 and 588 mL/min per square meter), and two were transferred to the operating room at the instruction of the surgeons before dopexamine infusion had been started.

### Table 7

<table>
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<th>Preoperative</th>
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</table>

*Significant difference between protocol and control for postoperative data, P < .001.

Mortality and morbidity were the major outcome measures for this study and have been analyzed on an intention-to-treat basis. Figure 3 shows the survival curves for the two patient groups. There was a significantly (P = .015) lower mortality in the protocol group (5.7%) compared with the control group (22.2%). Of the 12 patients in the control group who died, nine had multiple organ dysfunction syndrome, two had acute myocardial infarction, and one had a pulmonary embolism. Of the three protocol patients who died, two had multiple organ dysfunction syndrome and one had an acute
myocardial infarction. Given that previous studies have shown a mortality rate of 25% to 40% in these high-risk patients, our control group mortality of 22.5% suggests that these patients were well treated on our ICU, and further suggests that the protocol group mortality of 5.7% represents a reduction in mortality as a result of the treatment given. The biggest difference in mortality was seen in patients who had abdominal surgery; none of 17 patients in the protocol group died and five (25%) of 20 patients in the control group died (P=.049). The corresponding figures for vascular surgery are three (10%) of 30 protocol patients and six (23%) of 26 control patients (P=.29), and for other types of surgery, none of six protocol patients and one (17%) of six control patients (P=.50).

Table 8 shows that there was a significantly lower number of complications per patient in the protocol group compared with the control group (P=.005). Full details of the complications divided by study group are shown in Table 8. Although no individual differences reached significance, all complications on our checklist, except gastric outlet obstruction, the occurrence of pleural fluid, and wound infection, occurred more frequently in the control group. Although not significant, there was lower ICU stay and hospital stay in the protocol group compared with the control group. When stays are compared more meaningfully in those patients who survived, there were trends to shorter median hospital stay (12.5 vs 16 days) and shorter median ICU stay (40 vs 45 hours) in the protocol group, but these did not reach statistical significance. With the distribution of duration of stay found in our study, it would have required more than 500 patients to show statistical significance.

A total of 81 patients were admitted to the study preoperatively, 43 in the protocol group and 38 in the control group. Figure 3 shows a significantly (P=.041) better survival for patients allocated preoperatively to the protocol group (7.0%) compared with patients allocated preoperatively to the control group (23.7%). There were fewer complications (mean ±SEM, 0.70 ±0.19) in patients allocated preoperatively to the protocol group than in patients allocated preoperatively to the control group (1.45 ±0.24) (P=.009). In the 26 patients admitted to the study postoperatively, there were three deaths in those allocated to the control group and none in those allocated to the protocol group (P=.062). There was a mean (±SEM) of 0.60 ±0.31 complication per patient in those allocated to the protocol group compared with 1.13 ±0.33 complications per patient in those allocated to the control group (P=.446). These analyses were performed on an intention-to-treat basis; however, as noted, nine patients included in these analyses as being randomized to the protocol group preoperatively were not treated entirely in accordance with the treatment regimen for protocol patients. All three deaths occurring in the protocol group were from this group of nine patients. Therefore, the mortality rate of these patients admitted preoperatively and treated exactly in accordance with the treatment regimen for protocol patients is 0% compared with 23.7% for patients randomized preoperatively to the control group (P=.003).

COMMENT

The results of this randomized, controlled, prospective study show a 75% reduction in mortality in the patients treated with a deliberate perioperative increase of CI and DO₂. This reduction is despite the fact that there were no apparent differences between the patients randomly allocated to the two groups for either baseline or other co-morbidity risk factors. No patient admitted preoperatively and treated entirely in accordance with the treatment regimen died. Those patients who died did so from a variety of different types of organ failures that developed in the days following surgery, not from an acute catastrophe during the immediate postoperative period. It was these patient deaths and an associated number of complications that were lower in the protocol group. Our data suggest that deliberately increasing CI and DO₂ perioperatively leads to significant reduction in both mortality and morbidity in those patients who are at high risk of both following surgery.

The results of our study are very similar to those reported by Shoemaker et al who showed a control mortality of 38% compared with 52% (P=.015) for patients undergoing vascular surgery, a reduction of 4%. However, our study had slightly different goals for treatment than used previously and used doxapamine as opposed to other drugs to increase DO₂. In the study by Shoemaker et al targets were given for CI (>4.5 L/min per square meter) and VO₂ (>170 mL/min per square meter), as well as for DO₂ (>600 mL/min per square meter), but the similarity of our final results suggests that the most important therapeutic target is DO₂. Several other groups have shown the benefits of deliberately increasing DO₂, but in different clinical situations. In a controlled trial in 51 patients with septic shock, Tuchschmidt et al showed a reduction in mortality from 72% in a normally treated group to 50% in a protocol group, but this did not reach significance. Berlauk and colleagues showed a reduced morbidity in 89 patients who had vascular surgery, although the authors con-
firm that these patients did not fit the criteria of "high risk" and were treated to attain different targets. Recently, a significant reduction in mortality in trauma patients, most of whom were suffering from gunshot wounds, has been reported.41

In contrast to the few randomized trials that have investigated any possible beneficial effect of increasing DO\textsubscript{I} on patient outcome, there have been many studies concerned with any mechanism whereby an effect may arise. Most of these studies have linked a higher DO\textsubscript{I} with an increase in the body's use of oxygen. It has been shown that hidden oxygen demand can be revealed if tissue perfusion is increased in critically ill patients and that in many types of critical illness VO\textsubscript{I} may depend on DO\textsubscript{I}.42-46

Other investigators have demonstrated postoperative rises in VO\textsubscript{I} and survivors have higher postoperative VO\textsubscript{I} compared with those patients who subsequently die.43 It has further been suggested that postoperative increases in DO\textsubscript{I} are required to compensate for an impaired oxygen debt arising during surgery and that it is by this mechanism that increasing DO\textsubscript{I} may exert a beneficial effect.42-46

Unlike other studies, we did not specifically titrate therapy to VO\textsubscript{I}. We have previously pointed out the difficulties associated with using VO\textsubscript{I} as a therapeutic goal in critically ill patients,44 owing to effects of sedation,41 temperature,42 and other drugs43,44 all of which may be particularly important in postoperative patients. We thus set out to deliberately increase DO\textsubscript{I} alone to facilitate increased oxygen uptake if this was required by the patient. Although we observed a slightly higher VO\textsubscript{I} postoperatively in protocol patients compared with control patients (Fig 2), the small differences did not reach significance, and it appears that by increasing DO\textsubscript{I} we were not influencing the patient's total body VO\textsubscript{I}. The difference in our results for VO\textsubscript{I} and those found by others may be due to the difficulties in recording small regional changes in VO\textsubscript{I} that have occurred, to differences in the patient's underlying condition, or to an effect of the drugs used to increase DO\textsubscript{I}. In the postoperative period, our patients were sedated41 and initially had temperatures below 37°C,43 both of which may have masked any rise in VO\textsubscript{I}. As we have reported previously,14 dopexamine appears to have only a small effect on VO\textsubscript{I} compared with agents such as epinephrine and dobutamine, which have both been shown to increase resting VO\textsubscript{I} in healthy volunteers.41,51

The use of these agents in previous studies may therefore have confused the interpretation of changes in VO\textsubscript{I}. Our data show that increasing DO\textsubscript{I} alone will reduce mortality and morbidity even if VO\textsubscript{I} does not apparently increase, and we suggest that VO\textsubscript{I} may be an inappropriate target for therapy.45

Our study differs from those published not only in regard to the agents used and the specific goals of therapy, but also in regard to the limits placed on drug infusions. Tachycardia is known to be predictive of postoperative cardiac morbidity,45 and an increase in HR was anticipated in response to dopexamine infusion.22 We therefore placed an arbitrary limit of a 20% increase in HR in our study. We suggest that physiological limits, such as the occurrence of tachycardia, should be included in regimens designed to attain therapeutic goals. This may prevent all patients from achieving the therapeutic goal, but avoids the possibility of causing significant side effects such as coronary ischemia.

Additional studies may further characterize the type of patient that may benefit most from a deliberate perioperative increase in DO\textsubscript{I} and the exact methods used to achieve the therapeutic goal. The high-risk criteria used in this study are broad, and it is likely that refinements to these criteria, possibly combined with physiological screening, may identify a group of patients particularly at risk. The use of a general target of a DO\textsubscript{I} of 600 mL/min per square meter for all patients may be inappropriate, some patients may require a higher value and some may achieve benefit at a lower value. The methods by which the exact requirements for each patient can be found require further investigation. Many studies of the potential benefits of invasive monitoring have been undertaken on patients having vascular surgery, often aortic surgery, but our data suggest that greatest improvements in mortality might be seen in patients having abdominal surgery. These observations require further study for confirmation.

Our study included patients admitted preoperatively and postoperatively, and it was not our purpose to investigate differences between preoperative and postoperative admission. No attempt was made to randomize patients between preoperative and postoperative groups, and thus they may not have been comparable. Indeed, there is a suggestion that the postoperatively admitted patients may have been at slightly lower risk because the gather index was lower, and in most cases the surgeons commenced surgery without confirming availability of a postoperative intensive care bed, implying that the surgical team felt that the patients were at lower risk. It is definitely methodologically easier to place intravenous lines and titrate therapy to goals designed to attain therapeutic goals, but a comparative study will need to be performed.

In summary, we have demonstrated that a reduction in mortality rate and postoperative complications can be achieved in patients who are considered to be at high risk of both when undergoing surgery if, in addition to normal treatment, a deliberate increase in DO\textsubscript{I}, using dopexamine, is added as a further goal of treatment. Our data further suggest that a target for DO\textsubscript{I} of 600 mL/min per square meter is an appropriate goal for therapy, although this may not be obtainable in all patients. There appears to be no need for specific targets for VO\textsubscript{I}. An increased VO\textsubscript{I}, if needed by the patient, is facilitated by a reservoir effect of higher DO\textsubscript{I} and improved tissue perfusion. We propose that drug infusion rates should be limited by
physiological changes to avoid the potential risks of myocardial ischemia, even if targets have not been achieved. We observed no complications from the use of doxepamine in our high-risk patients and suggest that doxepamine may be a suitable agent for perioperatively increasing $\text{DO}_2$.

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We acknowledge the medical, surgical, and nursing staff at St. George's Hospital for their cooperation and assistance during this study; without their help we would not have been able to proceed. We thank J. Alt-Graham, FANZCA, J. Mackay, FRCA, and J. Lee, FRCA, for allowing us to refer to their previously unpublished results; and J. M. Bland, PhD, reader in medical statistics, for statistical advice.

References


A Comparison of the Efficacy of Dopexamine and Dobutamine for Increasing Oxygen Delivery in High-Risk Surgical Patients

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St George's Hospital, London, United Kingdom

SUMMARY

Peri-operative increase of oxygen delivery has been shown to reduce mortality in high-risk surgical patients. This study compares the effectiveness of dopexamine and dobutamine when used to increase cardiac output as part of a regimen to increase oxygen delivery. Sixteen surgical patients were randomly allocated to receive either dopexamine or dobutamine, which was increased to a stable dose defined as either oxygen delivery index >600 ml/min/m², or tachycardia >20% above baseline, other dysrhythmias or angina. At this "stable" dose there were significant increases in cardiac index (2.4 ± 0.2 vs 3.7 ± 0.3 l/min/m²) and oxygen delivery (380 ± 73 vs 579 ± 40 ml/min/m²) in the dopexamine group (P<0.05); but not the dobutamine group. Five out of eight patients receiving dopexamine and three out of eight receiving dobutamine reached target oxygen delivery. Three dobutamine patients, but no dopexamine patients, had angina or dysrhythmias. In preoperative high-risk surgical patients, dopexamine can allow greater increases in oxygen delivery than dobutamine, due to cardiac effects that limit the dobutamine infusion rate.

Key Words: HEART: cardiac output, dopexamine, dobutamine; SURGERY: oxygen consumption, oxygen delivery

We have recently shown that by increasing the cardiac output and the oxygen delivery during the perioperative period with intravenous infusion of fluid and then dopexamine HCl, we have been able to reduce the mortality in high-risk surgical patients. This reduction in mortality from 22.2% to 5.7%, with an associated halving of morbidity, confirmed the results of other studies on surgical patients where cardiac output and oxygen delivery were increased during the peri-operative period. These studies have shown a decreased mortality in high risk surgical patients, patients with hip fracture, and trauma patients; and reductions in morbidity in patients undergoing peripheral vascular surgery. However, all these previous studies have used dobutamine hydrochloride, or combinations of inotropes, to increase cardiac output and oxygen delivery, whereas our recent study used dopexamine hydrochloride. Dopexamine HCl and dobutamine HCl have different pharmacological actions and different spectrums of vascular response, but no direct comparison between the use of these agents in the perioperative period has been performed. This is particularly important as increased mortality has been seen when dobutamine HCl has been used in an attempt to increase oxygen consumption by increasing oxygen delivery in a general group of critically ill patients.

Dobutamine HCl is a mixture of two isomers which stimulate cardiac β₁ adrenoceptors and α and β₂ adrenoreceptors. In previous studies it has been shown to be an inotropic agent causing an increase in cardiac output and stroke volume with only a mild systemic vasodilation. Dobutamine HCl has been investigated in patients with cardiac failure, septic shock and in the peri-operative period, and its inotropic action has been confirmed. Dopexamine HCl, however, is a dopamine analogue with action at β₂ adrenoreceptors and DA₁ receptors but only moderate activity at β₁ and DA₂ receptors. Dopexamine possesses no direct α-adrenoreceptor activity, but noradrenaline reuptake is inhibited, leading mainly to vasodilatation with only mild inotropic effects. Dopexamine HCl has been investigated in patients with cardiac failure where it has been shown to cause peripheral vasodilatation and increased cardiac index.

The different pharmacological profile of dopexamine
HCl and dobutamine HCl suggests that there may be important differences between these two drugs when used for the peri-operative manipulation of the cardiovascular system in high-risk surgical patients. We have compared the cardiovascular and oxygen transport effects of dobutamine HCl with those of dopexamine HCl, to answer the clinically relevant question of which agent is most suitable for increasing peri-operative oxygen delivery, in high-risk surgical patients.

METHOD

Sixteen high-risk surgical patients, defined as being at high-risk by previous studies, who had given informed consent, were randomly allocated to receive either dopexamine HCl or dobutamine HCl to increase oxygen delivery preoperatively. The study was approved by our institutional ethics committee, and randomization was undertaken on a weekly schedule. Only patients with previously uncontrolled dysrhythmias were excluded from the study. The patients were admitted to the Intensive Care Unit (ICU) 12 to 24 hours prior to their operation and under local anaesthesia a pulmonary artery thermodilution catheter (93A-131-TF, Edwards Division, Baxter Healthcare Corp, Irvine, Calif) and radial arterial line (Abbocath-T 20G or 22G, Abbott Laboratories Ltd, North Chicago, Ill) were inserted; the ECG was recorded continuously. The patients’ regular medication was continued until surgery. Patients receiving β-blockers were not included in the study. The patients’ height and weight were recorded for calculation of their body surface area.

Cardiorespiratory parameters

The following cardiorespiratory variables were recorded: heart rate (HR), mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP) and right atrial pressure (RA) and pulmonary artery occlusion pressure (PAOP). The cardiac output was measured by thermodilution by average of results of four 5 ml injectates of cold (6 to 12°C) 5% dextrose (Supermon 7210, Kontron Instruments, Milan, Italy), and cardiac index (CI), systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI) were derived using standard formulae and the body surface area. Arterial (SaO₂) and mixed venous (SvO₂) oxygen saturations were measured (IL482 Co-oximeter, Instrumentation Laboratories, Lexington, Mass) from samples drawn simultaneously, the haemoglobin (Hb) concentration in arterial blood was recorded. Oxygen delivery index (DO₂I), oxygen consumption index (VO₂I) and oxygen extraction ratio (OER) were calculated, using the following standard formulae:

\[
\text{DO}_2\text{I} = \text{Cl} \times \text{SaO}_2 \times \text{Hb} \times 0.134 \\
\text{VO}_2\text{I} = \text{Cl} \times (\text{SaO}_2 - \text{SvO}_2) \times \text{Hb} \times 0.134 \\
\text{OER} = (\text{VO}_2\text{I}/\text{DO}_2\text{I}) \times 100
\]

Preoperative phase

Initial cardiorespiratory data were obtained and intravenous modified fluid gelatin solution (Gelofusine, Consolidated Chemicals Ltd, Wrexham, England) was administered to obtain a PAOP of 12-15 mmHg. ‘‘Baseline’’ cardiorespiratory values were taken as those after fluid administration and prior to doxexamine or dobutamine infusion. Preoperatively the target for DO₂I was to equal or exceed 600 ml/min/m². If this DO₂I was not achieved with intravenous fluid then dopexamine HCl or dobutamine HCl was started intravenously depending on the patient’s randomization. During this phase PAOP was maintained at 12-15 mmHg by further administration of modified fluid gelatin solution. Dopexamine HCl was started at 0.5 µg/kg/min and increased to 1.0, 2.0 and 4.0 µg/kg/min each 20 minutes until a DO₂I of greater than 600 ml/min/m² had been achieved. Dobutamine HCl was started at 2 µg/kg/min and increased to 5, 10 and 20 µg/kg/min each 20 minutes until an oxygen delivery index of greater than 600 ml/min/m² had been achieved. The starting infusion rates were chosen because in unpublished pilot studies 1.0 µg/kg/min of dopexamine HCl appeared to lead to similar cardiovascular effects as 5.0 µg/kg/min of dobutamine HCl. The dose titrations were limited by the occurrence of cardiac side-effects, or an achievement of a DO₂I of greater than 600 ml/min/m²; if these occurred the infusion rate of the dobutamine or dopexamine was reduced to the previous infusion increment and this was termed the ‘‘stable dose’’. Cardiac side-effects were defined for the purposes of the study as an increase in HR greater than 20% above baseline, significant ST depression on the ECG, anginal chest pain or clinically important dysrhythmia such as the onset of atrial fibrillation, other supraventricular tachycardia, ventricular tachycardia, multifocal ventricular ectopic beats, or greater than 10 ventricular ectopic beats per minute. At the end-point of dose titration cardiorespiratory values were recorded at the maximum stable dose of the dopexamine or dobutamine.

Statistical analysis

Results are presented as mean ± SEM. Percentage changes in the measured parameters were calculated from baseline (after fluid administration) to the
values at the highest stable dose of dopexamine or dobutamine. Both the percentage changes and the absolute values of the parameters recorded were compared by Student's t-test between the dopexamine and the dobutamine group. Paired Student's t-tests were used to compare the oxygen delivery index, cardiac index, oxygen extraction ratio and oxygen consumption index at baseline and after a stable dose of dopexamine or dobutamine had been achieved for the patients receiving either dopexamine or dobutamine. P < 0.05 was taken as significant, and Bonferroni's method was used to correct for multiple comparisons.

RESULTS

Sixteen patients were admitted to the study. In the dopexamine group, the mean age was 69 ± 3 years (range 60-85) and in the dobutamine group was 71 ± 2 years (range 62-81) (Table 1). Initial measurement of haemodynamic parameters was made in all patients on admission to the ICU and after infusion of fluid to attain a PAOP of 12 to 15 mmHg ("Baseline"). There were no statistical differences in these values between the two groups either at admission or at baseline, although cardiac index and oxygen delivery index were lower in the dopexamine group compared to the dobutamine group (Table 2). There were no differences in the volumes of modified fluid gelatin solution administered to the two groups, either prior to starting the inotrope infusion, 512 ± 83 ml for the dopexamine group and 650 ± 144 ml for the dobutamine group, or, during the inotrope infusion, 146 ± 33 ml for the dopexamine group and 125 ± 33 ml for the dobutamine group.

In no patient was DO2I able to be increased to greater than 600 ml/min/m² by intravenous fluids alone. Therefore all required infusion of either dopexamine HCl or dobutamine HCl. Details of the titration of dopexamine and dobutamine are shown in

| TABLE 1 |
| Details of patients, operations and drug dosage |

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<th>Age</th>
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<th>Max dose (µg/kg/min)</th>
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<td>Greater than 20% rise in heart rate (90 to 120 bpm)</td>
</tr>
<tr>
<td>76</td>
<td>Peripheral vascular reconstruction</td>
<td>20</td>
<td>20</td>
<td>600 ml/min/m² attained</td>
</tr>
<tr>
<td>70</td>
<td>Bowel resection for carcinoma</td>
<td>5</td>
<td>5</td>
<td>600 ml/min/m² attained</td>
</tr>
<tr>
<td>75</td>
<td>Operation cancelled due to angina</td>
<td>2</td>
<td>0</td>
<td>Angina, VEs and SV tachycardia</td>
</tr>
<tr>
<td>Dobutamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>68</td>
<td>Peripheral vascular reconstruction</td>
<td>1</td>
<td>1</td>
<td>600 ml/min/m² attained</td>
</tr>
<tr>
<td>60</td>
<td>Abdominal aortic aneurysm repair</td>
<td>1</td>
<td>1</td>
<td>600 ml/min/m² attained</td>
</tr>
<tr>
<td>83</td>
<td>Peripheral vascular reconstruction</td>
<td>1</td>
<td>1</td>
<td>Greater than 20% rise in heart rate (105 to 132 bpm)</td>
</tr>
<tr>
<td>65</td>
<td>Peripheral vascular reconstruction</td>
<td>2</td>
<td>2</td>
<td>Greater than 20% rise in heart rate (82 to 102 bpm)</td>
</tr>
<tr>
<td>76</td>
<td>Peripheral vascular reconstruction</td>
<td>1</td>
<td>1</td>
<td>600 ml/min/m² attained</td>
</tr>
<tr>
<td>65</td>
<td>Peripheral vascular reconstruction</td>
<td>1</td>
<td>1</td>
<td>600 ml/min/m² attained</td>
</tr>
<tr>
<td>64</td>
<td>Femoro-Femoral and Femoro-popliteal grafts</td>
<td>4</td>
<td>4</td>
<td>Greater than 20% rise in heart rate (62 to 82 bpm)</td>
</tr>
<tr>
<td>72</td>
<td>Abdominal aortic aneurysm repair</td>
<td>2</td>
<td>2</td>
<td>600 ml/min/m² attained</td>
</tr>
</tbody>
</table>

SV = supra-ventricular, VE = ventricular ectopic, bpm = beats/min.

| TABLE 2 |
| Changes in oxygen delivery, oxygen consumption, oxygen extraction ratio and cardiac output in the two groups during the study. Initial values after admission to the Intensive Care Unit, values at baseline following fluid administration, and values at the maximum stable dose of dopexamine and dobutamine are shown, mean ± SEM. |

<table>
<thead>
<tr>
<th>Dopexamine</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>Baseline</td>
</tr>
<tr>
<td>Oxygen delivery index (ml/min/m²)</td>
<td>362 ± 37</td>
</tr>
<tr>
<td>Oxygen consumption index (ml/min/m²)</td>
<td>112 ± 10</td>
</tr>
<tr>
<td>Oxygen extraction ratio (%)</td>
<td>32 ± 3</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.3 ± 0.7</td>
</tr>
</tbody>
</table>

* = P < 0.05 from baseline to maximum stable dose for each drug.
Table 1. The mean stable dose of dobutamine was 5.9±2.1 μg/kg/min and the mean stable dose of dopexamine was 1.6±0.4 μg/kg/min. The actual changes in oxygen delivery index are shown in Figure 1. Of the eight patients receiving dopexamine, five reached the target oxygen delivery index of 600 ml/min/m², the other three being limited in the dose titration by a rise in heart rate of greater than 20% above baseline. No patient receiving dopexamine HCl developed significant dysrhythmic cardiac events, and none developed angina. Only three of the patients receiving dobutamine reached the target of 600 ml/min/m², two of the others had their dobutamine titration limited by a rise in heart rate of greater than 20% above baseline and the other three had significant angina or dysrhythmic cardiac events that required the dose of dobutamine to be reduced. Of particular note, in three of the patients who received dobutamine HCl, the oxygen delivery index fell when the dobutamine HCl was started.

Figure 2 shows the percentage changes in various cardiorespiratory parameters for the patients receiving dopexamine and dobutamine. The increase in cardiac index, oxygen delivery index and stroke volume index was significantly greater with dopexamine than dobutamine, and the decrease in systemic vascular resistance index was significantly greater with dopexamine than dobutamine. None of the other differences reached significance. The actual change in cardiac index, oxygen delivery index and oxygen extraction ratio were significant, compared with baseline, for the patients receiving dopexamine (Table 2) while none of these oxygen transport parameters showed significant changes with dobutamine infusion.

DISCUSSION

Over the last ten years the results of a number of randomized, controlled studies have been published which have investigated the role of "goal-directed" therapy, whereby critically ill or high-risk surgical patients have been treated to achieve specific cardiovascular values ("goals"), during some stage of their illness, often around the time of operation. Although most studies have shown some benefit from this approach, in a recent study where dobutamine was used to increase cardiac output, there was an increased mortality in the treatment group\(^1\). There are a number
problems in comparing the published studies, including differences in the type of patients studied, differences in the timing of treatment during the illness and differences in the drugs used. It was in an effort to address this last point that this study was undertaken.

Four groups of patients have been included in studies of “goal-directed” therapy: patients undergoing surgery, patients with trauma, patients with sepsis, and general groups of patients who are critically ill. Studies on peri-operative patients have all shown an improved outcome in the treatment arm of the study. In studies of high-risk peri-operative patients, Boyd and colleagues, and Shoemaker et al., showed significant reduction in postoperative mortality. Earlier, Schultz et al. had shown significant reduction in mortality in patients undergoing operation for fractured neck of femur, but the treatment used in this study is not absolutely clear. In a study of patients undergoing vascular surgery, Berlauk and colleagues showed a reduction in peri- and postoperative cardiac events, but the reduction in mortality did not reach statistical significance. Studies of trauma patients have shown reduced post-trauma organ failure, and improved survival in elderly patients.

Less convincing results have been achieved in the studies of those patients who have proven sepsis. Edwards et al. showed improved outcome in patients with septic shock compared with historical controls, and Tuchschmidt and colleagues demonstrated improved survival in the group treated with “goal-directed” therapy, but this did not reach statistical significance. In a more recent study examining a heterogeneous group of critically ill patients, Hayes and colleagues showed a higher mortality in patients in whom “goal-directed” therapy was undertaken. Their study differs from those so far described, particularly those on peri-operative patients, in so much as the patients were admitted to the study at a later stage of their illness, once complications had developed. Furthermore, the investigators tried to attain the goals for cardiac index, oxygen delivery and oxygen consumption, suggested by Shoemaker et al., and this required high infusion rates of dobutamine HCl. The control group was also treated to elevate cardiac output if this was below 2.8 L/min/m², showing that they too were treated in a goal-directed fashion, although the goals were different and lower rates of dobutamine HCl infusion were required. This was a well conducted study and is important because the differences in patients, study design, and drugs used might start to point the way to identifying which patients may benefit from “goal-directed” therapy, and also which drugs and which goals should be used.

Many of the patients in the groups that appear to benefit from this type of proactive management will be elderly with coexisting clinical conditions. In particular they are likely to have a high incidence of cardiovascular disease, and it is therefore essential to avoid proactive treatment which is itself harmful. The results of the current study show that it is possible to achieve a significantly greater increase in oxygen delivery with dopexamine HCl than dobutamine HCl. The difference and apparent poor performance of dobutamine HCl is largely a result of the number of patients in the dobutamine HCl group that had their titration of dobutamine HCl limited by cardiac side-effects. Only three patients reached an oxygen delivery index of 600 ml/min/m² in the dobutamine HCl group compared with five in the dopexamine HCl group. No patient in the dopexamine HCl group needed to have the dopexamine HCl dose reduced because of the occurrence of cardiac dysrhythmias, whereas three patients in the dobutamine HCl group needed to have the dobutamine HCl reduced after sustaining clinically significant tachycardia or angina. The remaining patients—three in the dopexamine HCl group and two in the dobutamine HCl group—had to have the inotrope dosage limited by a rise in heart rate above 20% of the baseline value.

There are a number of studies that compare the effects of dopexamine HCl and dobutamine HCl in humans. It is difficult to compare the other studies with this one owing to differences in age and diagnosis. Mousedale et al. compared the effects of dopexamine HCl and dobutamine HCl at apparently matched doses on heart rate, blood pressure and renal parameters in young, healthy volunteers and showed a marked tachycardia with dopexamine HCl. This is opposite to the findings in our study but is perhaps explained by our careful attention to maintaining cardiac pre-load and intravascular fluid status. In view of the vasodilator properties of both dopexamine HCl and dobutamine HCl, a reflex tachycardia is expected if ventricular filling pressures are not maintained. There may also be differences between the responses of normal volunteers and patients with pre-existing cardiac disease which might partly explain the apparent discrepancy.

Jaski et al. compared dopexamine HCl and dobutamine HCl in ten patients with cardiac failure, and demonstrated an improvement in cardiac function with both agents. However, their patients only had a mean age of 53 years and they excluded patients with pre-existing angina. Baumann et al. showed that both dopexamine HCl and dobutamine HCl improved cardiac function in a study of 33 patients with cardiac failure who had a mean age 60 years. In their study,
however, patients known to have had cardiac dysrhythmias were excluded. There appeared to be little to differentiate the two agents except a greater vasodilator effect with dopexamine HCI. The patients specifically excluded by these study protocols, and the lower mean age, make the results difficult to compare with ours. Our study was designed as a clinically based study of "goal-directed" therapy for high-risk surgical patients and as such the only specific cardiac exclusion criteria were pre-existing, uncontrolled cardiac dysrhythmias. These differences in the patients studied might explain the apparent superiority of dopexamine HCl for increasing cardiac output without side-effects.

The limiting tachycardia and dysrhythmias that we saw in our study in the patient group receiving dobutamine HCl do not appear to have been reported before. It is noteworthy, however, that Shoemaker et al were unable to complete a planned study using dobutamine HCl to increase cardiac output as 20% of their patients developed a tachycardia of 140 beats/min. Even at a dose of 7.5 μg/kg/min the mean increase in heart rate from baseline was 20%10. It is possible that the high rate of cardiac side-effects seen with dobutamine HCl in our study may have been reduced if the infusion increments had been smaller, although at the lower doses it appears unlikely that we would have been able to achieve our oxygen delivery goals.

Other studies have demonstrated an increase in myocardial oxygen consumption with dobutamine HCl infusion11-13, and have shown non-homogeneous changes in coronary blood flow following infusion of dobutamine HCl, particularly in patients with coronary artery disease14. This effect of dobutamine HCl has been used recently to demonstrate myocardial ischemia as an alternative to exercise testing15. Dopexamine, on the other hand, does not appear to significantly increase myocardial oxygen consumption when given at a dose that will increase cardiac output16,17. It is also possible that dopexamine HCl has a specific anti-dysrhythmic effect18. Fourteen of our 16 patients were having operations for peripheral vascular disease and the incidence of coronary disease was likely to be high, even if it was not symptomatic because of low exercise ability. The one patient who had anginal chest pain following infusion of dobutamine HCl, although suffering from a previous myocardial infarction, did not usually suffer from angina.

Because we were not able to achieve such a large increase in oxygen delivery with dobutamine HCl, it is difficult to compare the changes in other parameters in a meaningful way. It is, however, important to note that there was an 11% change in heart rate in both groups of patients despite the fact that the mean oxygen delivery index increased so much less in the dobutamine HCl group. In the dobutamine HCl group the increase in cardiac output was mainly due to the increase in heart rate rather than increase in stroke volume and this has been found previously with dobutamine HCl19. In our study dopexamine HCl appears to have increased cardiac output and oxygen delivery by both vasodilatory and mild inotropic action, which confirms earlier work20,21. It is possible that if dobutamine HCl and a vasodilator had been used, similar results to those seen with dopexamine HCl may have been achieved, but the titration of two agents to achieve slightly different end-points will be much more complicated. Our study compared a fixed initial infusion and subsequent increase of dopexamine HCl with a similar regimen for dobutamine HCl. Although we had previously noted similar cardiovascular effects for 1.0 μg/kg/min of dopexamine HCl and 5.0 μg/kg/min of dobutamine HCl (Boyd, unpublished observations, 1989), different results may have been achieved if a lower starting infusion rate for dobutamine HCl had been used, or the subsequent increase of infusion rate had been undertaken in smaller steps.

In conclusion we have shown that in preoperative high-risk surgical patients, dopexamine HCl leads to significantly greater increases in cardiac output and oxygen delivery than dobutamine HCl. The lack of effect of dobutamine HCl is largely due to the cardiac side-effects that limited the infusion rate. Although a study of differences in outcome is required, we currently suggest that dopexamine HCl rather than dobutamine HCl should be used preoperatively for increasing oxygen delivery due to its greater effectiveness and lower incidence of cardiac side-effects.

ACKNOWLEDGEMENT

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REFERENCES

A cost analysis of a treatment policy of a deliberate perioperative increase in oxygen delivery in high risk surgical patients

Abstract

Objective: To investigate the cost implications of a treatment policy of a deliberate perioperative increase of oxygen delivery in high risk surgical patients.

Design: A cost-effectiveness analysis comparing 'protocol' high risk surgical patients in whom oxygen delivery was specifically targeted towards 600 ml/min/m² with 'control' patients.

Interventions: In a randomised, controlled clinical trial we previously demonstrated a significant reduction in mortality (5.7% vs 22.2%, \( p = 0.015 \)) and morbidity (0.68 ± 0.16 complications vs 1.35 ± 0.20, \( p = 0.008 \)) in 'protocol' high risk surgical patients in whom oxygen delivery was specifically targeted towards 600 ml/min per m² compared with 'control' patients. This current study retrospectively analysed the medical care and National Health Service resource use of each patient in the trial. Departmental purchasing records and business managers were consulted to identify the unit cost of these resources, and thereby the cost of treating each patient was calculated.

Results: The median cost of treating a protocol patient was lower than for a control patient (£6,525 vs £7,784) and this reduction was due mainly to a decrease in the cost of treating postoperative complications (median £213 vs £668). The cost of obtaining a survivor was 31% lower in the protocol group.

Conclusion: Perioperative increase of oxygen delivery in high risk surgical patients not only improves survival, but also provides an actual and relative cost saving. This may have important implications for the management of these patients and the funding of intensive care.

Key words Cardiac output · Complications · Cost · Dopexamine · High risk patients · Intensive care · Morbidity · Mortality · Oxygen delivery · Resource use · Surgery

Introduction

Developed nations are spending increasing proportions of their gross domestic product on health care, and an increasing percentage of this on intensive care, although there are wide variations in the actual amount spent per capita in different countries. All too often there is little direct evidence that this increased expenditure leads to any improvement in patient outcome in terms of survival, reduced morbidity or even quality of life. Therefore, new pharmacological agents and treatment protocols must increasingly be placed in context by considering their impact on the use of National Health Service resources [1]. This may be particularly important when considering new treatments for patients on intensive care as they can be prohibitively expensive [2], may increase the length of stay on intensive care and costs can escalate rapidly [3, 4].
One area where clinical studies have shown benefit by 'prophylactic' intensive care is in the management of the high risk surgical patient. Each year approximately 3.3 million operations are performed in England alone [5]. Recently it has been shown that at least 22,000 deaths occur within 30 days of operation [6]. Eighty-four percent of these deaths occur in patients aged 60 years or over, and the median day of death is 6 days postoperatively [6]. The costs for specific operative groups, and specifically for the patients who die, are unknown. However, advances in surgical possibilities and the growth in the elderly population mean that these costs are likely to increase significantly in the future.

One possible treatment approach has been to increase perioperative cardiac output and tissue oxygen delivery, aiming for the values naturally obtained by the survivors of surgery [7]. This is a so-called 'goal orientated' approach to management. Studies have shown a decreased mortality following very early intervention in the course of illness or prior to surgical intervention, although similar results have not been obtained in patients in the later stage of their illness [8, 9]. Randomised, controlled trials in high risk surgical patients [10, 11], patients with hip fracture [12] and trauma patients [13], have all shown reductions in mortality; and reductions in morbidity have been seen in patients undergoing peripheral vascular surgery [14] and following gun-shot trauma [15]. Trials using historical controls have shown similar results [10, 16–18].

In the largest trial of high risk surgical patients, we previously demonstrated a significant reduction in mortality (5.7% vs 22.2%, \( p = 0.015 \)) and morbidity (0.68 ± 0.16 complications vs 1.35 ± 0.20, \( p = 0.008 \)) in 'protocol' high risk surgical patients in whom oxygen delivery was specifically targeted towards 600 ml/min per m² compared with 'control' patients [11]. This current study retrospectively analyses the cost implications of the results of our earlier work. We are not aware of any studies that have attempted to analyse the cost implications of intensive care interventions in this way.

**Methods**

The financial costs of the treatment programmes were analysed and compared in three stages. Firstly, the clinical records of the 107 patients recruited in the trial [11] were reviewed in order to identify use of National Health Service resources; secondly, the unit cost of the individual resources were used to obtain a total cost for each patient; thirdly, the patients treated with a goal orientated approach were compared with the control patients.

**Identification of the use of resources**

As part of the documentation for the clinical trial, data on preoperative and postoperative intensive care stay, and postoperative surgical ward stay were collected. The clinical trial records were reviewed to obtain these data, together with those details pertaining to the therapy that was given in addition to the clinical trial interventions on the intensive care unit, particularly in respect of treatment of postoperative complications. The clinical trial records and hospital notes made it possible to identify and quantify the National Health Service resources that were used to manage the complications, and for investigations, interventions and drug treatments. The individual cost of treating each complication in each patient who had a complication was calculated on a per patient basis.

**Cost of resources used**

The cost of each resource was obtained at 1993/4 prices from St George's Hospital, London. The costs of investigations were obtained from the departments concerned. The cost of disposable equipment was obtained from the purchasers. The cost of drugs used was obtained from the hospital pharmacy, and although the doxapamine used for the clinical trial was provided free for the duration of the trial, we have included its acquisition cost. Hotel costs for the surgical ward and intensive care stay were obtained from the hospital business managers. The use of most capital equipment was included in the 'hotel' costs for intensive care and surgical ward stay. However the use of additional capital equipment that was required specifically as part of the treatment used, and the maintenance of this equipment, were costed separately. The cost for the surgery undertaken was not included in the total cost, as this study considers the cost implications of the perioperative management, not the surgery. If a further operative procedure were included as part of the management of a complication then this surgery was charged at the hourly rate obtained from the operating theatre business manager.

**Comparison of the resources used**

A comparison of cost was made between the two groups in the clinical study in terms of total cost, and in respect of different phases of treatment (i.e. preoperative, postoperative on intensive care, postoperative on the ward, and with regard to treatment of complications). Cost-effectiveness analysis took into account the mortality outcome data from the clinical study. A cost for obtaining a survivor (by dividing the total cost for each group by the number of survivors) was therefore calculated and compared. A sensitivity analysis to evaluate the impact of clinical outcomes where there was an element of doubt (i.e. those that were non-significant) was also carried out.

**Results**

**Identification of resources used**

The clinical trial documentation combined with the inpatient hospital records enabled National Health Service resources used by the patients to be quantified.

**Cost of resource use**

Contact with purchasers and business managers enabled the cost of the resources under consideration to be calculated for all cases. Table 1 shows the unit cost of capital equipment and the maintenance of this equipment. Only equipment that was considered as an additional requirement for participation in the study...
over and above what would normally be required for running an intensive care unit is included. Thus monitoring equipment for each bed is included but a blood gas analyser, which would be required for the running of any intensive care is not, and is, instead, included in the hotel costs (Table 2). The daily use of monitoring equipment was obtained by considering its purchase price and life-expectancy, giving an average cost of £82.19 per day. Table 2 shows the unit cost of consumables used during the study, including 'hotel' costs for intensive care and ward care.

Comparison of study groups

The study groups were compared at the different phases of their routine perioperative management, i.e. preoperative intensive care management, postoperative intensive care management and postoperative ward management (Table 3). Since there was very little difference in the routine study treatment for the two patient groups, the differences in costs result from differences in length of intensive care and ward stay. The infusion of dopexamine that was required in some of the 'protocol' patients to increase oxygen delivery contributed negligibly to the total costs.

The cost of management of complications was considered separately. Table 4 shows the costs of treating specified complications in the control and protocol groups. Because each patient was considered individually, the costs of treating each individual complication was not necessarily the same for control and protocol patients. Indeed 12/18 complications were found to be more expensive to treat in the control patients and 4/18 were more expensive in the protocol patients. Also, the occurrence of a complication did not mean that an additional cost was incurred in treating that complication. For example, acute myocardial infarction required no specific treatment to be given to three patients, as this was thought to be a terminal event by the surgical team in direct charge of the patients' management. Also, it should be noted that specific treatment for a complication may already have been given as part of a treatment for another complication incurred by the same patient – such treatments were not counted twice, leading to some apparent anomalies in Table 4, such as the apparent cost of treatment for acute myocardial infarction being zero. Not included in the cost of treating complications is any additional hospital stay required as this was already included in the hospital costs in Table 3. The median cost for treating complications in the two groups was £212.96 for protocol patients and £668.40 for control patients. This difference was due both to the higher incidence of complications in the control group and the higher cost of treating individual complications in this group.

The total costs for patients in the two groups are shown in Table 5. Table 5 also gives details of an estimate of cost-effectiveness by presenting the overall costs in terms of the surviving patients in each group. In the protocol group, both the total cost spent on patients and the cost per survivor were less. The differences in costs arose as a result of differences in the significantly improved survival and reduced complications, and due to the non-significant decreases in intensive care and ward stay among patients in the protocol group previously reported [11] (Table 6). These outcomes are the cost drivers for the two groups. Since the differences in intensive care and ward stays between the

---

### Table 1 Costs of capital equipment and maintenance

<table>
<thead>
<tr>
<th>Capital equipment</th>
<th>Cost (£)</th>
<th>Life-expectancy (years)</th>
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</thead>
<tbody>
<tr>
<td>Monitoring equipment on intensive care</td>
<td>150,000</td>
<td>5</td>
</tr>
<tr>
<td>Syringe driver</td>
<td>1,000</td>
<td>5</td>
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<tr>
<td>Volumetric pump</td>
<td>700</td>
<td>5</td>
</tr>
<tr>
<td>Ventilator</td>
<td>20,000</td>
<td>12</td>
</tr>
<tr>
<td>Lactate analyser</td>
<td>4,000</td>
<td>5</td>
</tr>
<tr>
<td>Maintenance of equipment (per day)</td>
<td>14</td>
<td></td>
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</table>

### Table 2 Costs of consumables

<table>
<thead>
<tr>
<th>Consumable</th>
<th>Cost (£)</th>
</tr>
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<tbody>
<tr>
<td>Blood count</td>
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</tr>
<tr>
<td>Clotting screen</td>
<td>2.50</td>
</tr>
<tr>
<td>Biochemistry</td>
<td>11.00</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>13.62</td>
</tr>
<tr>
<td>ECG</td>
<td>30.00</td>
</tr>
<tr>
<td>Blood cross-match (per unit)</td>
<td>4.67</td>
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<tr>
<td>Blood grouping</td>
<td>9.00</td>
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<tr>
<td>Two channel pressure monitor</td>
<td>16.97</td>
</tr>
<tr>
<td>Pulmonary artery catheter, cardiac output set and insertion set</td>
<td>120.51</td>
</tr>
<tr>
<td>16G cannula</td>
<td>14.23</td>
</tr>
<tr>
<td>20G cannula</td>
<td>10.29</td>
</tr>
<tr>
<td>Line site dressing</td>
<td>2.00</td>
</tr>
<tr>
<td>Lactate analysis (syringe etc)</td>
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</tr>
<tr>
<td>Blood gas measurement (syringe etc)</td>
<td>0.25</td>
</tr>
<tr>
<td>Colloid (500 ml)</td>
<td>3.34</td>
</tr>
<tr>
<td>Crystalloid (1000 ml)</td>
<td>0.76</td>
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<tr>
<td>Dopexamine hydrochloride (50 mg/5 ml)</td>
<td>21.00</td>
</tr>
<tr>
<td>Syringe (50 ml for drug administration)</td>
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</tr>
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<td>Red cells (unit)</td>
<td>30.65</td>
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<tr>
<td>Platelets (unit)</td>
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<td>Morphine (10 x 1 ml)</td>
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<td>Propofol (5 x 20 ml)</td>
<td>22.28</td>
</tr>
<tr>
<td>Surgery (h)</td>
<td>1000.00</td>
</tr>
<tr>
<td>Intensive care hotel costs (h)</td>
<td>33.00</td>
</tr>
<tr>
<td>Ward care hotel costs (day)</td>
<td>309.00</td>
</tr>
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</table>
Table 3 Costs (£) of preoperative, additional intraoperative and postoperative care for protocol and control patients. Median, 25th and 75th centile range

<table>
<thead>
<tr>
<th></th>
<th>Protocol patients</th>
<th>Control patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative costs</td>
<td>576.83 (576.83, 576.83)</td>
<td>569.93 (569.93, 569.93)</td>
</tr>
<tr>
<td>Intraoperative costs*</td>
<td>7.80 (7.80, 7.80)</td>
<td>0</td>
</tr>
<tr>
<td>Postoperative hospital costs</td>
<td>5,640.19 (3,316.27, 17,248.16)</td>
<td>6,458.23 (3,334.19, 15,487.32)</td>
</tr>
</tbody>
</table>

* Attributable to the cost of dopexamine

Table 4 Costs (£) of treatment of individual complications in protocol and control patients, see text for details. Median (range)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Protocol</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory failure</td>
<td>159 (80–558)</td>
<td>160 (80–957)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>980 (12–1844)</td>
<td>631 (6–5040)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>261 (261)</td>
<td>261 (261–5,987)</td>
</tr>
<tr>
<td>Cardiorespiratory arrest</td>
<td>131 (0–393)</td>
<td>392 (0–472)</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>173 (21–173)</td>
<td>144 (0–182)</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>27 (0–161)</td>
<td>1,090.50 (0–2,181)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>85 (85–2,126)</td>
<td>85 (85–2,127)</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>445 (445)</td>
<td>693.50 (445–942)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Abdominal abscess</td>
<td>2,845 (2,845)</td>
<td>1,340.50 (278–2,304)</td>
</tr>
<tr>
<td>Gastric outlet obstruction</td>
<td>89 (89)</td>
<td>278 (278)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>253 (228–278)</td>
<td>117 (65–169)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>278 (228–278)</td>
<td>117 (65–169)</td>
</tr>
<tr>
<td>Chest infection</td>
<td>160 (160)</td>
<td>160 (160)</td>
</tr>
<tr>
<td>Psychosis</td>
<td>91 (91)</td>
<td>91 (91–116)</td>
</tr>
<tr>
<td>Distal ischaemia</td>
<td>1,044 (87–2000)</td>
<td>2,413 (186–2513)</td>
</tr>
<tr>
<td>Other</td>
<td>61 (61)</td>
<td>47 (47)</td>
</tr>
</tbody>
</table>

Table 5 Total costs, cost savings and cost-effectiveness analysis for patients in the protocol and control groups of the study. Median, 25th and 75th centile

<table>
<thead>
<tr>
<th>Cost (£)</th>
<th>Protocol</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cost/patient</td>
<td>6,525.38 (4,201.46, 17,468.92)</td>
<td>7,784.17 (4,660.13, 16,155.72)</td>
</tr>
<tr>
<td>Cost/surviving patient</td>
<td>6,916.90 (4,453.55, 18,517.05)</td>
<td>10,008.22 (5,991.59, 20,771.64)</td>
</tr>
</tbody>
</table>

two groups were not significant, a sensitivity analysis was performed.

The analysis in Fig. 1 shows the impact on potential cost savings as a result of different lengths of intensive care and ward stay among protocol patients. If the length of hospital stay for protocol patients were to be increased from 40 h to 46 h in the intensive care and from 12 days to 14 days on the ward, as was the case for control patients, then the cost saving per protocol patient would be reduced from £1,259 to £422 and the cost saving per surviving protocol patient would be reduced from £3,091 to £2,205. The sensitivity analysis also shows that a protocol patient would cost the same as a control patient if their length of hospital stay were to be increased to 49 h in the intensive care unit and 15 days on the ward. Similarly, a surviving protocol patient would cost the same as a surviving control patient if their length of hospital stay were to be increased to 60.5 h in the intensive care unit and 19 days on the ward. Hence, the length of hospital stay for a protocol patient would have to be substantially increased before potential cost savings were no longer made.

Discussion

This study evaluates the cost implications of perioperatively increasing oxygen delivery in high risk surgical patients, by retrospectively comparing the costs of protocol and control patients in our previously published clinical trial [11]. The evaluation demonstrates that the
Table 6 Major results from the randomised controlled trial of a deliberate increase in oxygen delivery in high risk surgical patients [11]

<table>
<thead>
<tr>
<th></th>
<th>Protocol</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (%)</td>
<td>5.7</td>
<td>22.2</td>
<td>0.015</td>
</tr>
<tr>
<td>No. of complications (mean ± SE)</td>
<td>0.68 ±0.16</td>
<td>1.35 ±0.20</td>
<td>0.008</td>
</tr>
<tr>
<td>Intensive care stay, hours (median, 25th and 75th centile)</td>
<td>40(19,120)</td>
<td>46(20,98)</td>
<td>0.58</td>
</tr>
<tr>
<td>Ward stay, days (median, 25th and 75th centile)</td>
<td>12(7,40)</td>
<td>14(7,37)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Fig. 1 Impact of variation in length of hospital stay on the potential cost saving per protocol patient

The median total cost for patients in whom oxygen delivery was deliberately increased towards a target value of 600 ml/min per m² was £6,525.38, compared with £7,784.17 for control patients. Most of the difference was due to the non-significant difference in hospital stay and to the significant difference in treating complications between the two groups. Cost-effectiveness analysis showed that there was a 31% reduction in costs for obtaining a survivor in patients in whom oxygen delivery was deliberately increased, from £10,008.22 to £6,916.90. Break-even points for the non-statistically significant cost drivers would require protocol patients to stay 4 h longer on the intensive care unit and 1.5 days longer on the ward than control patients, quite the opposite to the results of the original study (Table 6).

There are very few studies that have investigated the effects of new research on cost. Shoemaker showed that costs were significantly reduced in his study in the group in whom oxygen delivery had been specifically increased [10]. Although these results show a similar trend to our own, they are difficult to compare directly as there is no detail given of what was included in the final figure or how this was arrived at; presumably costs were based on charges made to patients. Recently, the large variations between charges and actual costs that arise due to variations in hospital pricing policies, have been emphasised [19]. In our study, although some of the costs included were based on charges made by one service, e.g. radiology, to another, e.g. surgery, we considered direct healthcare costs incurred at St George's Hospital, rather than the prices charged to purchasers.

In estimating the costs in the current study a number of assumptions have been made. Not included in this analysis was 'routine' preoperative care on the surgical ward. This care was the same for both study groups and standard for this type of surgery. Also, there are varying lengths of preoperative stay that were not documented and were multifactorial in cause. Furthermore, surgery costs have not been included, except for the costs of re-operation for the treatment of a complication, because this analysis is concerned with the cost effects of the perioperative care and not the surgery.

There are a number of limitations to this study. Firstly, the analysis is based on clinical data censored at 28 days postoperatively. Secondly, the analysis does not consider the impact of increased survival on future healthcare costs. Thirdly, the study concentrates on direct healthcare costs to the National Health Service. The evaluation did not include direct costs to patients, their families and non-healthcare providers, indirect costs due to lost productivity, and other intangible costs. Fourthly, the valuation of costs used in this study is based on St George's Hospital in London, UK for the year 1993/94. Differences in costs between St George's Hospital and other institutions, and variations among patients, may necessitate modification of the actual costs presented in this study before they are applied to other institutions. However, the costs identified as part
of this study are very much in line with those used in other studies [20–22]. Furthermore, it would require a large and unexpected difference in the cost of a particular resource before the conclusions of this study became invalid.

There are now a number of randomised, controlled clinical trials that have investigated the hypothesis that increasing oxygen delivery in the perioperative period might lead to improved outcomes. Studies on perioperative patients have all shown an improved outcome in the treatment arm of the study [10–12, 14]. In studies of high-risk perioperative patients Boyd and colleagues [11], and Shoemaker et al. [10], both showed a significant reduction in postoperative mortality. Earlier, Schultz et al. showed a significant reduction in mortality among patients undergoing operation for fractured neck of femur, but the treatment used in this study is not absolutely clear [12]. In a study of patients undergoing vascular surgery, Berlauk and colleagues [14] showed a reduction in perioperative and postoperative cardiac events, but the reduction in mortality did not reach statistical significance. Studies of trauma patients have shown reduced post-trauma organ failure [15] and improved survival in elderly patients [13]. However, when trying to rationalise these research findings with current clinical practice it is often perceived that there will be increased financial costs. This study demonstrates that this is not necessarily so, and shows that the increased financial cost of improved therapy can ultimately result in net cost savings due to the reduced costs of treating complications and of a shorter hospital stay.

In conclusion, this study shows that a treatment policy aimed at deliberately increasing oxygen delivery in the perioperative period in high-risk surgical patients results in reduced hospital costs and, as we have shown previously, reduces mortality. Findings such as these have important implications for the direction of future research, the management of high-risk surgical patients and the funding of intensive care.

References

Enhancement of Perioperative Tissue Perfusion as a Therapeutic Strategy for Major Surgery

Owen Boyd, MRCP, FRCA; E. David Bennett, FRCP

Multiple organ dysfunction syndrome (MODS) accounts for most surgical deaths which occur some days postoperatively. Current hypotheses concerning the pathophysiology of MODS place tissue hypoxia and reperfusion as a central feature of the initiation and continuation of the syndrome. Surgical patients are at risk of developing overt and covert tissue hypoxia and hypoperfusion due to anesthetic, surgical, and other factors; and it is known that surgical patients with poor cardiovascular reserve have a worse outcome postoperatively. A number of clinical studies have attempted to intervene early in surgical patients to prophylactically improve tissue perfusion in the perioperative period by augmentation of cardiac output. These studies demonstrate a reduction in mortality and morbidity in these groups of patients. A similar approach has been tried in other groups of critically ill patients, at a later state in the evolution of their illness; these studies have not shown any improvement in outcome. In surgical patients, data show that those with more coexisting pathology and worse cardiac function may benefit most from a treatment approach aimed at improving tissue perfusion; furthermore, this may result in cost savings. The implications for the management of the higher risk surgical patient are obvious. It may no longer be acceptable to undertake surgery in these patients without facilities to monitor and improve cardiac output and tissue perfusion. (New Horiz 1996; 4:453–465)

Key Words: surgery; mortality; morbidity; outcome; review; tissue perfusion; cardiac output; oxygen delivery; oxygen consumption; cost

INTRODUCTION

The perioperative surgical patient is in a unique position compared with other patients admitted to ICUs. When medical patients and postoperative patients are admitted from other floors, some time has usually elapsed between the primary insult and worsening of the patient's condition, often with the onset of the systemic inflammatory response syndrome (SIRS), or multiple organ dysfunction syndrome (MODS) (1). Although the exact pathophysiology of SIRS and MODS is not known, alterations in microcirculatory flow resulting in tissue hypoxia is important in the onset and maintenance of the syndromes and as one of the factors involved in the resulting organ damage (2–4). Established tissue hypoxia has, therefore, already developed in many patients admitted to the ICU. This is not the case for perioperative patients, and therapeutic interventions to prevent or modify the effects of tissue hypoxia can be undertaken either before or immediately after surgery.

This article reviews the evidence that a preventative strategy to avoid tissue hypoxia in surgical
patients results in improved outcome. We explore the evidence that in many cases of postoperative morbidity and mortality, tissue hypoperfusion is the underlying cause. We describe initial uncontrolled, and more recently controlled, randomized studies on perioperative patients in which strategies to prevent tissue hypoxia have been employed. We contrast these studies with others that used similar therapeutic techniques, but included patients much later in the course of their disease. Finally, we consider the implications of treating high-risk surgical patients in this preventative fashion on the use of healthcare resources, and provide new data which identify the types of patients who may benefit most.

PERIOPERATIVE PHYSIOLOGIC RESPONSES TO SURGERY — THE LINK BETWEEN TISSUE HYPOPERFUSION AND MORTALITY

In 1872, Pfluger (5) stated that "arterial oxygen content, arterial pressures, velocity of blood stream, mode of cardiac work, mode of respiration are all incidental and subordinate; they all combine to service the cells." However, it was not until many years later that techniques of cardiac catheterization became available to allow analysis of the defects that occurred in this system around the time of surgery. In 1959, Boyd and colleagues (6) identified two groups of patients based on cardiac function following cardiopulmonary bypass. When the cardiac index was >2.5 L/min/m², all patients survived, but if the cardiac index decreased to <2.5 L/min/m², 66% of the patients died. The authors suggest that high cardiac output and high oxygen transport to the tissues are of major importance for survival following cardiac surgery. Clowes and Del Guercio (7) reported similar results from a group of patients undergoing thoracic surgery. Immediately following surgery, 84% of patients had increased cardiac output, and all survived; however, the 16% of patients whose cardiac output did not all died. Very similar results were found in a study (8) of patients with peritonitis where 36% of patients were unable to maintain elevated cardiac output and all these patients subsequently died. Early work, therefore, suggested that the appropriate response to surgery was elevation of cardiac index, and that if this response failed or was attenuated, the patient died.

Along very similar lines, several studies showed that limited cardiovascular reserve, usually a history of myocardial infarction or cardiac failure, significantly increases perioperative mortality. In 1977, Goldman and colleagues (9) published a predictive index of cardiac mortality in patients undergoing noncardiac operations, and demonstrated that patients who were elderly, with cardiac failure, and with history and/or signs of cardiac disease were at greatest risk. Much more recently, the importance of myocardial factors that predispose to cardiac mortality in the perioperative period have been thoroughly documented. Mangano (10) showed that of 25 million noncardiac operations performed annually in the United States, 7 to 8 million patients are at risk of postoperative cardiac mortality and morbidity.

Further attempts to define the nature of the physiologic changes around the time of surgery were undertaken by Shoemaker, Bland, and colleagues. They published a series of papers (11, 12) in which the temporal sequence of changes in hemodynamic parameters was described. They showed that survivors and nonsurvivors differed in their postoperative cardiovascular responses to surgery. Each of the parameters tested could be given a coefficient based on its ability to predict survival, and this coefficient could be taken as a measure of the potential usefulness of that particular variable (13). They found that the most commonly monitored vital signs, i.e., heart rate (HR), temperature, central venous pressure, and hemoglobin concentration, were the poorest at differentiating between survivors and nonsurvivors. However, the more rarely measured variables, those relating to tissue perfusion, were the best predictors of patient outcome (13). This work confirmed that survivors had higher postoperative cardiac output and oxygen delivery (Do2) than those patients who subsequently died (14, 15). Furthermore, they proved that the more commonly measured and recorded variables, such as blood pressure and HR, did not differ between survivors and nonsurvivors until the preterminal stages.

The investigations cited above have all considered global cardiac function and its implications for survival; however, it has been suggested for some time that not all the organs of the body are equally important. Many recent studies (16, 17) have hypothesized a central role for alterations in splanchnic perfusion in the development of SIRS and MODS. There are several methods, e.g., tissue Po2 probes, Doppler flow probes, and hepatic vein catheterization, which are available to monitor splanchnic perfusion, but the gastrointestinal tonometer is the most straightforward to use for routine surgical
patients. The gastrointestinal tonometer measures the Pco2 of the intestinal contents. This value, in conjunction with the arterial bicarbonate concentration, is used to calculate the intramucosal pH (pHi). In critically ill patients, the pHi value can be used as an independent predictor of mortality, and is thought to indicate the presence of splanchnic hypoperfusion (18-20). Other studies have specifically investigated the development of a low pHi during surgery. Fiddian-Green and Gantz (21) showed that a low pHi in the sigmoid colon following elective aortic aneurysm repair was of poor prognostic significance. Similar results were found in patients undergoing cardiac surgery (22). More recently, Mythen and Webb (23) showed that the development of a low pHi intraoperatively is associated with increased postoperative complications and increased cost, due to the treatment of postoperative SIRS and MODS.

In summary, patients who survive major operative procedures appear able to maintain tissue perfusion by increasing their cardiac output and Do2 in the perioperative period, compared with those patients who subsequently have major complications or die.

HOW TO PREVENT PERIOPERATIVE TISSUE HYPOPERFUSION?

Once a link between perioperative hypoperfusion and increased mortality has been established, the question of what to do about it arises. During the perioperative period, a number of changes alter the normal physiologic responses of the cardiorespiratory system, and change metabolic demands (Fig. 1). It is also clear that most patients do not suffer clinically from the consequences of tissue hypoperfusion, and are able to compensate adequately for these changes; nonetheless, there are a significant minority of patients who cannot do so. During the perioperative period, there are several changes which alter the normal physiologic responses of the cardiorespiratory system, and change metabolic demands. The physiologic changes caused by positive-pressure ventilation, reduction in functional residual capacity, and reduced muscle tone all tend to reduce tissue perfusion. Many of the drugs given during the perioperative period also have the potential to reduce tissue perfusion, redistribute blood flow, and override normal compensatory mechanisms such as hypoxic vasoconstriction. Conversely, changes in metabolic demand affect the requirement for tissue perfusion. Inevitably, there will be an inflammatory response secondary to the trauma of surgery and healing that will require adequate perfusion. Postoperative stress responses, the maintenance of normothermia, the effects of starvation, and altered requirement for specific organ function all have metabolic consequences requiring, in gross terms, increase in tissue perfusion. There are, therefore, swings in metabolic demand and the ability to meet this demand during the perioperative period. If a balance of the supply and demand is not maintained, tissue hypoxic damage will result. Most patients who undergo surgery will be able to compensate for these changes themselves. Problems are likely to occur if a) the cardiorespiratory system is unable to meet changes in demand placed on it, and b) if specific organ systems are compromised so that very mild changes in perfusion cause significant damage to the organ.

Few of the metabolic demands of surgery are amenable to therapeutic intervention. Although some studies (24, 25) using regional anesthesia to modify the stress response of surgery appear to...
show some benefit, other studies (26, 27) in apparently similar patient groups do not. There remain many more methods in which the changes in tissue perfusion during the perioperative period can be influenced. First, patients with pre-existing cardiorespiratory dysfunction can have their cardiovascular status optimized initially by medical management and acutely by fluid titration to maximize cardiac function, drugs to optimize ventricular preload and afterload, and inotropic agents to increase myocardial contractility. Second, in anticipation of increased metabolic demand, global oxygen availability can be increased. Third, knowing that some organ systems may be more susceptible to hypoperfusion and that some organs may have proportionally greater increases in metabolic demands, therapy targeted toward increasing oxygen availability to these organs specifically can be instituted.

All three of these approaches have been used in clinical studies, but the unifying hypothesis is one of increasing cardiorespiratory function and reserve, and increasing tissue perfusion. Two apparently conflicting problems remain. Many patients identified as having reduced cardiorespiratory reserve will also have ischemic cardiac disease, and traditionally these patients have been managed perioperatively to limit any possibility of increased cardiac work (28). Rationalizing this conflict between increasing tissue perfusion and limiting cardiac work in the clinical setting is one of degree, and in most situations it might be reasonable to provide for the increased metabolic demands of the tissues while avoiding tachycardias. The second conflict occurs when the approaches for prevention of tissue hypoxic injury in the perioperative patient are applied to other groups of intensive care patients, specifically those in whom tissue hypoxic injury may already have become established. The published literature on the subject is very confusing and frequently all studies, where tissue perfusion has become one of the targets for treatment, have been considered together (29, 30). Later in this review we compare the studies on groups of perioperative patients and those on other groups of critically ill patients.

NONRANDOMIZED STUDIES OF INCREASED TISSUE PERFUSION IN PERIOPERATIVE PATIENTS

Studies to investigate the effect of improving tissue perfusion in the perioperative period have been conducted comparing results with historical controls and in randomized, controlled clinical trials. Babu and colleagues (31) evaluated 75 patients undergoing elective vascular reconstructions. They showed that only 33% of patients had normal left ventricular function and required no therapeutic intervention to optimize their cardiac status. The other patients had impaired left ventricular function responding to volume load (27%), afterload reduction (13%), inotropic support (17%), or combination therapy (9%), and outcome was improved compared with historical controls.

In 1978, it was proposed that the patterns of cardiovascular responses exhibited by survivors of surgery should become the goals of treatment for all patients in the perioperative period, actual numerical values being derived from the median values of survivors (32). In 1982, Shoemaker et al. (33) published results of a trial of 100 consecutive perioperative patients. Patients were allocated to a protocol or control group by a predetermined temporal schedule. The control group was treated by a regimen designed to attain normal routine and cardiovascular targets, whereas the protocol group was treated to attain the same routine targets but greater cardiac output and $D_O_2$. Thus, routine parameters such as blood pressure (>120/80 mm Hg), HR (60–120 beats/min), and urine output (>30 mL/hr) were the same for both groups, but goals for cardiac index (2.8–3.5 L/min/m² for control patients and >4.5 L/min/m² for protocol patients) and $D_O_2$ (400–550 mL/min/m² for control patients and >600 mL/min/m² for protocol patients) were greater in the protocol patients. The results showed a lower complication rate in the protocol patients (a mean of 0.92 complications per patient vs. 1.60 complications per patient, $p < .05$); and a lower mortality rate in the protocol patients (13% vs. 48%, $p < .05$) (33).

Whittmore and colleagues (34) investigated the use of the pulmonary artery (PA) catheter for control of fluid management in patients undergoing elective abdominal aortic aneurysm repair. They titrated fluid to increase the pulmonary artery occlusion pressure to a point at which the cardiac output peaked, or to a maximum of 12 to 14 mm Hg with a cardiac index of >2.5 L/min/m². Results of the study showed that only 1 patient died within 30 days of the operation, a mortality rate of 0.9%, compared with a reported mortality rate of 6%. While appropriate fluid therapy probably is vital to the successful treatment of high-risk patients, another study emphasizes that this must be taken in the context of the effects of that therapy on cardiac output. Grindlinger et al. (35) also studied patients...
undergoing abdominal aortic aneurysm repair, but in addition to careful titration of fluid in the preoperative period, they gave vasodilators to 1 of 3 groups in the intraoperative period. Their data showed that this intervention resulted in a decrease in cardiac output, and led to a higher incidence of myocardial infarction.

Goldman and co-workers (9) emphasized the high incidence of reinfarction in patients in the perioperative period, and Rao and colleagues (36) analyzed the effect that a change in practice had on mortality in patients who had previously suffered a myocardial infarction. Retrospective data collected from 1973 to 1976 showed a reinfarction rate of 7.7%. In 1977, a change in policy toward invasive hemodynamic monitoring was undertaken: PA catheters were inserted preoperatively and fluids, vasodilators, and inotropes were given to optimize the patients' cardiac status. Results from 1977 to 1982 showed a significant reduction in reinfarction rate to 1.9% (p <.005).

RANDOMIZED STUDIES OF AN INCREASE IN TISSUE PERFUSION IN PERIOPERATIVE PATIENTS

Despite the evidence of significant improvement in the outcome for high-risk surgical patients that has accumulated from nonrandomized trials and the repeated calls for randomized studies (37, 38), only a few such studies have been performed.

The mortality rate following surgical management of hip fracture is known to be high, estimates ranging from 13% to 40% (39). In 1985, Schultz and colleagues (39) published the results of a randomized clinical trial of 70 patients undergoing operative repair of hip fracture. Thirty-five patients were managed conventionally (“nonmonitored”) and 35 patients were “monitored” to assess a number of cardiovascular parameters preoperatively. Fluids, inotropes, and vasodilators were given preoperatively to the monitored group to correct cardiac index and other physiologic parameters to a defined physiologic profile. Although the investigators were not specifically attempting to increase \( \overset{o}{D}_o \) as part of their therapeutic regimen, and indeed did not calculate or measure \( \overset{o}{D}_o \), the net result of their therapy was to increase oxygen availability in their monitored group. This treatment resulted in a significant reduction in postoperative mortality in the monitored group, from 29% in the nonmonitored group to 2.9% (p <.05).

Shoemaker’s nonrandomized studies, described above, were followed by the report of results of a randomized study using the same entry criteria and treatment goals (40). Fifty-eight high-risk surgical patients were randomized either to a protocol or a control group. Patients in the control group were treated conventionally, but protocol patients had their cardiovascular physiology manipulated pharmacologically to increase tissue \( \overset{o}{D}_o \) to 600 mL/min/m\(^2\), the median value reached by survivors in earlier studies (32). The results of the study showed reduction in mortality, morbidity, and ICU stay in the patients in the protocol group. The mean number of complications per patient in the protocol group was 0.39 compared with 1.3 in the control group (p <.05), and the protocol group mortality rate was 4% compared with 33% in the control group (p <.01) (40).

In 1991, Berlauk et al. (41) published the results of a randomized trial of patients undergoing limb-salvage arterial surgery. The study enrolled 89 patients into three study groups: group 1 had a PA catheter inserted up to 12 hrs before surgery in the surgical ICU, group 2 had a PA catheter inserted within 3 hrs of the operation, and the third group did not have a PA catheter. In groups 1 and 2, similar hemodynamic intervention was undertaken to achieve a PA occlusion pressure of 8 to 15 mm Hg, a cardiac index of >2.8 L/min/m\(^2\), and a systemic vascular resistance of <1100 dyne-sec/cm\(^4\). The results of the study showed that the groups were well matched preoperatively with regard to demographic details and co-existing disease. However, the groups that had the additional hemodynamic intervention had fewer adverse intraoperative events (p <.05), less postoperative cardiac morbidity (p <.05), and less early graft thrombosis (p <.05) than the control group, and mortality was lower, although not significantly so (p = .08). Fleming and colleagues (42), studied 67 patients with multiple trauma. Increasing \( \overset{o}{D}_o \) in their protocol group, they demonstrated a reduction in organ failures and a nonsignificant reduction in mortality rate, from 44% to 24% (p = .08). The same group (43) has recently published the results of a second prospective, randomized trial on the effects of increasing cardiac output, \( \overset{o}{D}_o \), and oxygen consumption (\( \overset{o}{V}_o \)) in patients with severe trauma. In the protocol group, efforts were made to reach the resuscitation goals within 24 hrs of admission and maintain them for 48 hrs thereafter. Very similar results to the earlier study were found, with a lower incidence of organ failures in the protocol group (0.74±0.28 vs.
1.62±0.28, $p < .05$), and a significant reduction in mortality rate (18% vs. 37%, $p = .03$).

In 1993, our group (44) published the results of a study of 107 high-risk surgical patients, using similar definitions of high risk to Shoemaker and colleagues (Table 1). We had previously confirmed in three surveys, two conducted before commencement of the major study and one conducted on patients treated in our institution who were retrospectively found to fit the study entry criteria but were not enrolled in the study, that the mortality rate of patients who satisfied these entry criteria was 30%. Those patients randomized to the control group were treated in the ICU with what is considered to be the best conventional therapy which included dopamine and vasodilators as required, as well as continuous fluid management to maintain cardiac filling pressures, and blood transfusion to maintain hemoglobin concentration. In addition to this, patients randomized to the protocol group had their $\text{DO}_2$ index deliberately increased to a target value of 600 mL/min/m² as suggested by Bland and co-workers (32). In the protocol group, dopexamine HCl was used to deliberately increase $\text{DO}_2$, with limits being placed on the dopexamine infusion rate to avoid tachycardia. No treatment that would normally have been given to any patient enrolled in this study was withheld; specifically, vasodilating drugs and dopamine were given prophylactically and where clinically indicated when this was the normal practice of the surgeons, anesthesiologists, or intensive care team. Mortality and morbidity were recorded to 28 days postoperatively, and statistical analysis of data was performed on an intention-to-treat basis.

The results of the study showed a significant reduction in mortality rate ($p = .015$) in the protocol group (5.7%) compared with the control group (22.2%). Of the 12 patients in the control group who died, nine had MODS, two had acute myocardial infarction, and one had a pulmonary embolism. Of the three protocol patients who died, two had MODS and one had an acute myocardial infarction. There was also a significantly lower number of complications per patient in the protocol group compared with the control group ($p = .008$). In those patients who survived, there were trends to shorter hospital stay (median 12.5 vs. 16 days) and shorter ICU stay (median 40 vs. 45 hrs) in the protocol group, but these did not reach statistical significance.

With the introduction of the experimental technique of gastric intramucosal pH tonometry in perioperative patients (22), there has been increasing interest in the effect of surgery on gut mucosal perfusion. Knowing that pHi decreased during cardiac surgery, Mythen and Webb (45), studied the effect of plasma volume expansion on gut mucosal pH and on outcome in cardiac surgical patients. Patients in their protocol group received boluses of 6% hydroxyethyl starch solution to obtain a maximal cardiac stroke volume measured by intracardial Doppler ultrasound. Treatment was not directly targeted to the pHi result. Results showed that the incidence of low pHi was reduced in the protocol group, and this group also had fewer complications and a reduced hospital stay. This study is in agreement with those mentioned above, showing that improved cardiac performance, in this case achieved by careful monitoring of fluid therapy, improves outcome. Furthermore, this study strongly suggests that this is due to reduction of tissue hypoperfusion.

Although there are differences in the patients in each study and slight differences in the exact targets for treatment, these data show that deliberately increasing tissue perfusion perioperatively or immediately after trauma, by increasing cardiac output and $\text{DO}_2$, leads to significant reduction in both mortality and morbidity.

**STUDIES OF AN INCREASE IN TISSUE PERFUSION IN OTHER GROUPS OF CRITICALLY ILL PATIENTS**

As mentioned above, the idea of specifically increasing tissue perfusion has been extended from...
perioperative patients to include treatment of patients with other critical illnesses. A number of nonrandomized and randomized studies have been performed, and generally results have not shown an reduction in mortality. We suggest that this is due to the fact that in these patients, tissue hypoxic changes resulting from tissue hypoperfusion have already become established and are irreversible.

In 1989, Edwards et al. (46) published an uncontrolled study in which they used the goals identified for perioperative patients (32), for the treatment of patients with septic shock. Following volume expansion of the circulation, infusions of epinephrine, dopamine, and dobutamine were given to achieve increases in $\dot{D}O_2$ and $\dot{V}O_2$. Using the regimen, $\dot{D}O_2$ increased from a mean of 605 ± 40 to 843 ± 27 mL/min/m², and the mortality rate was only 52% compared with an historical mortality rate of >80%. These initially promising results have not been confirmed in randomized trials. Tuchschmidt and colleagues (47), performed a randomized study of patients with septic shock. Resuscitation of the patients was by a printed algorithm to a cardiac index >3.0 L/min/m² in the 25 “normally” treated control subjects and to a cardiac index >6 L/min/m² in the 26 “optimally” treated subjects. Overall, the mortality rate of 72% in the normally treated group, and 50% in the optimally treated group, was not significantly different ($p = .14$). Bone et al. (48) used prostaglandin E₃ (PGE₃) to improve tissue perfusion in 100 patients with ARDS. PGE₃ augmented the circulation of the patients, increasing cardiac output and stroke volume, but showed no improvement in mortality rate. At 30 days, 30 protocol and 24 control patients had died, total deaths related to the syndrome were 30 of 50 patients in the PGE₃ group and 28 of 50 patients in the control group.

In a more recent study examining a heterogeneous group of critically ill patients, none of whom were admitted early to the ICU, Hayes and colleagues (49) showed a higher mortality rate in patients in whom $\dot{D}O_2$ was specifically increased. Their patients were admitted to their ICU an unspecified number of days postoperatively or after they had developed ARDS or other organ failures. The goals of cardiac index >4.5 L/min/m², $\dot{D}O_2$ >600 mL/min/m², and $\dot{V}O_2$ >170 mL/min/m², were the same as those suggested for perioperative patients (32). They then treated their protocol group with fluids and infusion of dobutamine in an attempt to achieve all three targets. The inhospital mortality rate was 34% for patients in the control group and 54% for patients in the protocol group ($p = .04$), suggesting that aggressive treatment to achieve the targets might itself have been harmful.

Yu et al. (50) examined the effect of increasing $\dot{D}O_2$ on patients with sepsis, septic shock, hypovolemic shock, or ARDS. Each group had identical management, except that protocol patients had $\dot{D}O_2$ targeted to >600 mL/min/m² and control patients had $\dot{D}O_2$ targeted to 450 to 500 mL/min/m². Analyzed on an intention-to-treat basis, the mortality rate was 34% for each group, although subset analysis showed that patients in either group with higher $\dot{D}O_2$ had improved survival. Yu et al. (51) also undertook a study of surgical patients, but these were not admitted preoperatively and had evidence of tissue hypoxic injury at enrollment: 80% had sepsis or septic shock, 48% had ARDS, and 16% had prolonged hypovolemic shock. In the protocol group, a resuscitation goal of an $\dot{D}O_2$ >600 mL/min/m² was used. The results are presented as an analysis of subgroups, but analysis of all the data on an intention-to-treat basis shows a mortality rate of 38% in the protocol group compared with 41% in the control group. Although the resuscitation treatment did not appear to be harmful, mortality rate was not reduced.

A slightly different approach was taken byGattinoni and colleagues (52). In a multicenter study, they allocated 762 patients to one of three groups: a control group was treated normally for that ICU, a cardiac index group had treatment targeted toward a cardiac index >4.5 L/min/m², and an oxygen-saturation group had treatment targeted toward a mixed venous saturation >70%. There was no difference in mortality rate between the three groups: 48.4% in the control group, 48.6% in the cardiac index group, and 52.1% in the oxygen-saturation group ($p = .638$). In this study, although the targets used for treatment were slightly different, the aim was to avoid tissue hypoxia and once again no improvement in mortality was seen. As in the study of Hayes et al. (49), if their patients were admitted postoperatively they had already developed ARDS or other organ failures.

**RANDOMIZED STUDIES OF PERIOPERATIVE AND OTHER CRITICALLY ILL PATIENTS COMPARED**

There are a number of methodologic differences between the studies on perioperative patients and those on other groups of critically ill patients. These concern the exact targets that are used for treatment and the drugs that have been given in an
attempt to achieve those targets. However, we suggest that the most significant difference between the studies is in the type of patient enrolled and the time postoperatively that optimization was started. The studies on groups of critically ill patients all intervened on patients once the effects of tissue hypoperfusion had become clinically evident. Seventy-six percent of the patients studied by Hayes and colleagues (49) had septic shock or sepsis syndrome. Eighty percent of the patients studied by Yu et al. (51) had sepsis, and 54% had ARDS. One of the criteria for enrollment into the study of Gattinoni and colleagues (52) was the failure to respond to ICU treatment for >48 hrs. This late intervention may well have resulted in the disappointing effects of treatment.

In a paper published in Lancet in 1992, Gutierrez and colleagues (53) demonstrated the difference in effectiveness of early or late intervention with treatment to prevent tissue hypoperfusion. Using pHi as a therapeutic index, they enrolled 260 general critically ill patients with an Acute Physiology and Chronic Health Evaluation (APACHE) II score of between 15 and 25 into a trial where boluses of fluid and infusion of dobutamine were given to increase tissue oxygen availability and correct an abnormally low pHi value. The patients were divided into two groups depending on the initial pHi result. Patients with a normal pHi initially, who were assumed not have evidence of tissue hypoperfusion, showed a reduction in hospital mortality from 58% to 42% (p < .01) compared with the control group. However, in the patients who had evidence of tissue hypoperfusion at start of the trial, as demonstrated by a low pHi, there was no difference in mortality, 64% for the control group vs. 63% in the group treated to improve tissue perfusion.

It is possible to separate the clinical trials of specific therapy aimed at improving tissue perfusion into those in which therapy was started before, or very shortly after, the onset of tissue hypoperfusion, and those in which therapy was started after tissue hypoperfusion had become established. Seven trials involving 1031 patients can be identified as having late intervention (47–53); and seven trials enrolling 647 patients as early intervention (39–44, 53). As described above, the trial of Gutierrez and colleagues occurs in both groups (53). To compare the results of all the trials, we have calculated the odds ratio and confidence intervals for a reduction in mortality in the trial groups treated with the therapy targeted toward increased tissue perfusion.

The study of Mythen and Webb (45) cannot be included in this analysis as one group had a mortality rate of zero. The data are presented in Figure 2. In showing the data of these clinical trials in this way, we have merely reproduced the results as presented in the published results of the trials, we have not attempted to analyze details of the quality of the study design, etc. The results tabulated this way clearly show that studies in which tissue perfusion was increased before established tissue hypoxic damage result in a reduction in mortality, the odds ratio for the data combined is 0.34 (95% confidence interval, 0.23–0.49); and studies in which tissue perfusion was augmented late show no reduction in mortality, odds ratio for the data combined is 1.05 (95% confidence interval, 0.82–1.34).
WHO IS A HIGH-RISK SURGICAL PATIENT?

In this article so far, we have emphasized the difference in the results of studies that have aimed to maintain tissue perfusion and those that have aimed to restore tissue perfusion. We have drawn the conclusion from the published randomized studies that maintaining tissue perfusion improves outcome, while attempting to restore perfusion does not. The studies maintaining tissue perfusion have all considered high-risk surgical patients, although the actual definitions have varied from those with single disease or operation types, to those with lists of entry criteria; we used a list of definitions, adapted from Shoemaker et al. (40), to help identify our study patients preoperatively (Table 1). Many operative patients appear to meet one or more of these criteria and to admit them all to ICUs preoperatively might be impossible. The question therefore arose: was there any way to identify patients who might be at particularly high risk?

We hypothesized that if increasing $\text{Do}_2$ was responsible for the improvement in survival seen in our protocol patients (44), it would be more likely to improve patients who started with a lower $\text{Do}_2$ initially. We also thought that patients who had a greater number of admission criteria (Table 1) might also be at increased risk. To investigate these hypotheses, we have retrospectively analyzed data from our original study to relate outcome to the initial $\text{Do}_2$ of the patient, and to the number of admission criteria.

The $\text{Do}_2$ percentiles for the 25th, 50th, and 75th centiles for the patients admitted preoperatively, at the time of admission to the ICU and before any intervention, were found (Table 2). The 28-day mortality rates for patients in these groups were then calculated and the results are presented in Figure 3. It can be seen that as admission $\text{Do}_2$ increases, the overall mortality rate decreases; this is in agreement with other studies and suggests that patients with a less impaired cardiovascular system are able to compensate for potential hypoxic changes during surgery. The results also show (Fig. 3) that, for the lower admission $\text{Do}_2$ there is a marked reduction in mortality when $\text{Do}_2$ is specifically increased in the protocol group, although this is only significant for the 25th percentile. These results are consistent with the hypothesis that cardiovascular reserve is important for postoperative survival, and that specifically increasing $\text{Do}_2$ and tissue perfusion improves outcome.

In a separate retrospective analysis, the outcome of patients was analyzed depending on whether the patients had one or more admission criteria present at enrollment into the study (Table 1). The results are shown in Figure 4. It can be seen that the distribution of the number of admission criteria was the same for patients randomized to the control or protocol group. Overall morbidity, as measured by the number of complications, and mortality increase as the number of admission criteria increase. Dividing patients into the protocol and control groups, it is seen that for all the groupings of admission criteria number, mortality and morbidity are reduced in patients in the protocol group.

These new results of retrospective analyses of data from our clinical trial suggest that the greatest influence of increasing $\text{Do}_2$ in the perioperative period may be seen in patients with the lowest initial $\text{Do}_2$ and the greater number of admission criteria. This is consistent with our hypothesis that sicker patients with more limited cardiovascular reserve...
HEALTHCARE IMPLICATIONS OF INCREASING TISSUE PERFUSION IN HIGH-RISK SURGICAL PATIENTS

Developed nations are spending increasing proportions of their Gross Domestic Product on health care, and an increasing percentage of this on intensive care, although there are wide variations in the actual amount spent per capita in different countries. All too often, there is little direct evidence that this increased expenditure leads to any improvement in patient outcome in terms of survival, reduced morbidity, or even comfort. It is therefore becoming accepted that new pharmacologic agents and treatment approaches must be placed in context by considering their impact on the use of resources (54). This may be particularly important when considering new treatments for patients in an ICU, as new treatments can be prohibitively expensive (55) and costs can escalate rapidly if treatments increase the time of stay in an ICU (56, 57). The cost for specific operative groups and specifically for the patients who die is unknown, but advances in surgical possibilities and the growth in the elderly population mean that these costs are likely to increase significantly over the years.

The results of studies on prevention of the onset of tissue hypoxic damage have shown a reduction in mortality, and also in morbidity. The treatment of postoperative complications is known to be expensive, and with this in mind we wondered if there was a reduction in costs if patients were treated to augment their cardiovascular systems. Our group has published the preliminary results (58) of a retrospective survey of the costs of treating patients in our randomized, controlled study (44). Resources consumed by the patients in the study were recorded prospectively and the costs of these resources were obtained at 1993/94 prices. The results show that the average cost of treating a patient in the protocol group was £9,894, and the average cost of treating a patient in the control group was £11,331, the difference in costs was largely due to the difference in treating postoperative complications. There was therefore an actual reduction in cost in patients whom a more aggressive treatment regimen was undertaken. There was also increased survival; the costs for obtaining a survivor was £10,488 for protocol patients and £14,568 for control patients.

There are a number of limitations to this study. First, the analysis is based on clinical data censored at 28 days postoperatively. Second, the analysis

benefit most from an increase in their $\text{Do}_2$, and tissue perfusion perioperatively, as they are unable to compensate for perioperative changes in oxygen availability and demand spontaneously.
does not consider the impact of increased survival on future healthcare costs. Third, the study concentrates on direct healthcare costs to the National Health Service. The evaluation did not include direct costs to patients, their families, and non-healthcare providers, indirect costs due to lost productivity, and other intangible costs. Fourth, the valuation of costs used in this study is based on St. George's Hospital in London, UK for the year 1993/94. Differences in costs between St. George's Hospital and other institutions, and variations among patients, may necessitate modification of the actual costs presented in this study before they are applied to other institutions. We have also not compared the costs of treating patients in our study, for whom full data were available, with patients who may have met our study entry criteria but were treated on other floors, for whom full data were not available.

Our cost-effectiveness analysis may have important implications. In anesthetic practice, as well as in other areas of patient care, it is often considered that the opportunities for cost saving are not that great; however, this ignores the influence that anesthetic practice may have on the use of other hospital resources and on "downstream" benefit that may be quite temporally separated from the initial anesthetic and operation (59). Our analysis shows that the downstream benefit may be quite marked.

CONCLUSION

Most patients who undergo surgery will have sufficient cardiovascular reserve to provide for the changes in metabolic demand that occur perioperatively. However, as patients get older and the incidence of concurrent disease rises, cardiovascular reserve falls, and it becomes increasingly difficult for the cardiovascular system to cope with changes in metabolic demand. Furthermore, complex, longer surgery with more tissue trauma and more complicated anesthetic requirements is likely to result in more widespread changes in metabolic requirements, and greater demands on the cardiovascular system. The consequence may be an imbalance between oxygen and nutrient availability, and metabolic demand. This situation marks the onset of relative tissue hypoperfusion and tissue hypoxic injury, with the possible development of SIRS and MODS.

The unique situation of the perioperative patient allows therapeutic intervention to prevent the onset of relative tissue hypoperfusion, rather than just react to the consequences. Three therapeutic strategies can be used: a) to improve cardiovascular performance, b) to increase global $\text{DO}_2$ in anticipation of increased demand, and c) to attempt to increase perfusion of organ systems thought to be most at risk. Clinical studies, using a combination of these approaches, have shown a benefit in terms of reduced mortality and morbidity. They have also shown that depending on the proposed surgery and the patient's cardiovascular impairment, careful titration of intravascular fluid may not be sufficient on its own to prevent tissue hypoperfusion. The results for trials on perioperative patients contrast sharply with the results of studies that have used a similar therapeutic strategy after the onset of tissue hypoxic damage; in these studies, no reduction in mortality or morbidity has been demonstrated.

The potential importance of these results for the perioperative management of higher-risk surgical patients and the use of healthcare resources is huge. It may no longer be acceptable to operate on these patients without preoperative and postoperative facilities for full investigation and monitoring of the cardiovascular system, and the available knowledge to act on the results to improve tissue perfusion. The implications for the provision of adequate beds and facilities, and for suitably trained medical and nursing staff are obvious. However, improved patient outcome and possibly reduced cost may be the benefit. Future investigation must accurately identify the patients who are most at risk of postoperative mortality and morbidity, and rationalize the combinations of therapeutic strategies that we have proposed for each patient.

REFERENCES

5. Pfluger E: Uber die Diffusion des Sauerstoffs, den Ord und die grenze der Oxydationsprozesse im thierischen organismus. Pfluger's Arch Gesamte Physiologie Menschen Thiere 1872; 43–64
cardiopulmonary bypass. *Ann Surg* 1959; 150:613–625


The Dependency of Oxygen Consumption on Oxygen Delivery in Critically Ill Postoperative Patients Is Mimicked by Variations in Sedation*

Owen Boyd, M.R.C.P.; Michael Grounds, F.F.A.R.C.S.; and David Bennett, F.R.C.P.

The finding of a dependence of oxygen consumption on oxygen delivery in critically ill patients has encouraged interventions to increase oxygen delivery index (DoI) to overcome tissue hypoxia. In individuals other factors may influence oxygen consumption index (VoI) and DoI and may cause an apparently dependent relationship. We studied the effects of sedation and temperature on the VoI/DoI relationship in 13 perioperative patients. Pooled data showed significant correlations between VoI and DoI (r>0.6, p<0.05) but also between VoI and sedation score (r>0.7, p<0.05), but not VoI and temperature (r<0.5). When VoI was standardized for the effects of sedation score (SS), the relationship between VoI and DoI was lost (r<0.5). Seven of 13 patients had significant (p<0.05) correlations between VoI and SS and six of 13 between VoI and DoI; when standardized for the effect of varying sedation, no relationships were significant. When interpreting oxygen transport data from critically ill patients, the effects of sedation but not temperature must be taken into account; otherwise a false impression of a dependent relationship between VoI and DoI may cause unnecessary treatment.

DoI = oxygen delivery index; LAC = lactate; SS = sedation score; temp = body temperature; VoI = oxygen consumption index

In healthy individuals at normal or high levels of oxygen delivery (DoI), oxygen consumption (VoI) is relatively constant, but in pooled data, as the DoI falls, a critical point is reached after which VoI also decreases. In critically ill patients, the situation is different. It has been demonstrated that in adult respiratory distress syndrome, septic shock, and in a wider range of critical illness, there is a dependence of oxygen consumption on oxygen delivery to much greater levels of delivery. This relationship has been termed "supply dependence."

The demonstration that at supply-dependent levels of oxygen delivery there are raised lactate levels, and that a hidden oxygen debt can be exposed by pharmacologic means has prompted the suggestion that if supply dependence can be found, oxygen delivery should be increased. It is suggested that "supply dependence" is evidence of tissue hypoxia and that higher levels of oxygen delivery and consumption may prevent some of the possible sequelae of critical illness. The existence of a supply-dependent state is shown in individual patients by an oxygen delivery challenge, and indeed therapy aimed at increasing both oxygen delivery and consumption has been shown to reduce mortality in surgical patients and patients with sepsis. However, unnecessary increase in the oxygen delivery may be both difficult to achieve and undesirable.

In an individual patient, the interpretation of oxygen transport data can be difficult. Other factors affecting the patient may change both oxygen delivery and consumption producing an "apparent" supply dependence. We have observed that patients recovering from a variety of major operative procedures show an increase in both delivery and consumption, and that this relationship forms an apparent supply dependence. We were concerned that the picture of an apparent supply-dependent state may have prompted inappropriate treatment and believed that other factors may have been affecting the oxygen delivery/consumption relationship in our postoperative patients.

This study was undertaken to test the hypothesis that changing sedation level and body temperature may have been responsible for the apparent supply-dependent state seen in postoperative patients. If such an effect could be demonstrated, it would be of major importance in interpreting oxygen transport data, as many critically ill patients are sedated to some degree, and these patients frequently have abnormal body temperatures.

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Table 1—Descriptive Features of the 13 Patients, Including Whether the Patients Had Been Admitted Preoperatively to the ITU (Preop) or Received Inotropes (Inotropes)

<table>
<thead>
<tr>
<th>Patient No./Age, y/Sex</th>
<th>APACHE II Score</th>
<th>Nature of Operation</th>
<th>Preop</th>
<th>Inotropes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/87/F 80</td>
<td>13</td>
<td>A-P resection</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2/81/M 15</td>
<td>15</td>
<td>Cystectomy and colectomy</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3/73/M 17</td>
<td>17</td>
<td>Femoral to distal graft</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4/69/M 16</td>
<td>16</td>
<td>Peripheral vascular reconstruction</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5/69/F 11</td>
<td>11</td>
<td>Femoral to distal graft</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6/74/M 11</td>
<td>11</td>
<td>Fem-pop graft with crossover graft</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7/64/M 14</td>
<td>14</td>
<td>Femoral to anti tibial graft</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>8/67/F 11</td>
<td>11</td>
<td>Cystectomy and colectomy</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>9/81/F 17</td>
<td>17</td>
<td>Abdominal aortic aneurysm repair</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>10/76/M 18</td>
<td>18</td>
<td>Laryngectomy</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>11/75/F 29</td>
<td>29</td>
<td>Colectomy and splenectomy</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>12/67/M 17</td>
<td>17</td>
<td>Abdominal aortic aneurysm repair</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>13/57/M 6</td>
<td>6</td>
<td>Femoral to distal graft</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**METHODS**

**Subjects**

Thirteen patients having major operative procedures were studied prospectively (Table 1) after informed consent had been obtained. The patients were admitted preoperatively or immediately postoperatively to the Intensive Care Unit, St George's Hospital, London. Each patient was monitored with a flow-directed pulmonary artery catheter (American-Edwards 93A-131-7F) via the right internal jugular vein and a radial artery arterial line; the ECG, arterial pressure, and pulmonary arterial pressure were monitored continuously. Cardiac output was determined by thermodilution (Kontron 7210), and the cardiac index (CI) was calculated from the body surface area. Body temperature (Temp) was measured by the pulmonary artery catheter thermistor. Oxygen saturation of arterial (SaO2) and mixed venous (SvO2) blood was analyzed directly (IL 482 CO-oximeter). Hemoglobin (Hb) was measured spectrophotometrically (IL 482 CO-oximeter). Mixed venous whole blood lactate (LAC) was measured (Analox LM4s), a significantly raised lactate level in our unit is taken as greater that 1.5 mmol/L. The sedation score (SS) was assessed on a scale of 1 to 6: 1, patient anxious and agitated or restless or both; 2, patient is cooperative, orientated, and tranquil; 3, patient responds to commands only; 4, there is brisk response to light glabellar tap or auditory stimulus; 5, a sluggish response; and 6, no response to glabellar tap or auditory stimulus.

**Data Analysis**

Measurements were made preoperatively, intraoperatively, and postoperatively. At each data point the following were recorded: CI, SaO2, SvO2, Hb, LAC, Temp, and SS. The oxygen delivery index (Do2I), oxygen consumption index (Vo2I) and oxygen extraction ratio (OER) were calculated from standard formulas. For the purposes of analysis, Temp was banded into 0.5°C bands. The Vo2I data were manipulated to standardize for changes in sedation score, temperature, and Do2I. From the regression Vo2I on SS for each patient (Table 2, part A), an expected oxygen consumption can be calculated for each SS for each patient; this expected oxygen consumption can be subtracted from the actual oxygen consumptions observed at each sedation score, to give an estimate of the variation of the observed from the expected oxygen consumption.

If there is indeed a supply-dependent pattern of oxygen transport, observed consumptions greater than those anticipated from the regression line would be expected to be associated with greater oxygen deliveries. Addition of the mean actual oxygen consumption of that patient’s observations gives an oxygen consumption that is standardized for sedation score (ss Vo2I). Similar calculations can be made for temperature to give an oxygen consumption standardized for temperature variations (temp Vo2I), and for Do2I to give an oxygen consumption standardized for Do2I (dd Vo2I). The data can be standardized similarly for the pooled patient group. This method of standardization of Vo2I for changes in SS, Temp, and Do2I allows

Table 2—The Regression Relationships between Oxygen Consumption and Sedation Score (A) and Temperature (B) for the Individual Patients*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Slope A</th>
<th>r A</th>
<th>p A</th>
<th>Slope B</th>
<th>r B</th>
<th>p B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-11.94</td>
<td>0.74</td>
<td>0.01</td>
<td>-5.13</td>
<td>1.00</td>
<td>. .</td>
</tr>
<tr>
<td>2</td>
<td>-11.95</td>
<td>0.88</td>
<td>0.01</td>
<td>16.06</td>
<td>0.31</td>
<td>0.60</td>
</tr>
<tr>
<td>3</td>
<td>-19.52</td>
<td>0.89</td>
<td>0.01</td>
<td>26.33</td>
<td>0.95</td>
<td>0.01</td>
</tr>
<tr>
<td>4</td>
<td>-16.47</td>
<td>0.81</td>
<td>0.01</td>
<td>5.54</td>
<td>0.22</td>
<td>0.60</td>
</tr>
<tr>
<td>5</td>
<td>-16.54</td>
<td>0.94</td>
<td>0.01</td>
<td>15.84</td>
<td>0.55</td>
<td>0.33</td>
</tr>
<tr>
<td>6</td>
<td>-12.71</td>
<td>0.85</td>
<td>0.01</td>
<td>48.89</td>
<td>0.72</td>
<td>0.17</td>
</tr>
<tr>
<td>7</td>
<td>-37.47</td>
<td>0.58</td>
<td>0.22</td>
<td>65.79</td>
<td>0.38</td>
<td>0.45</td>
</tr>
<tr>
<td>8</td>
<td>-9.89</td>
<td>0.30</td>
<td>0.06</td>
<td>27.78</td>
<td>0.30</td>
<td>0.62</td>
</tr>
<tr>
<td>9</td>
<td>-23.75</td>
<td>0.76</td>
<td>0.08</td>
<td>45.24</td>
<td>0.85</td>
<td>0.07</td>
</tr>
<tr>
<td>10</td>
<td>-5.27</td>
<td>0.18</td>
<td>0.67</td>
<td></td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td>11</td>
<td>-11.70</td>
<td>0.89</td>
<td>0.11</td>
<td>18.78</td>
<td>0.95</td>
<td>0.19</td>
</tr>
<tr>
<td>12</td>
<td>-22.00</td>
<td>0.93</td>
<td>0.07</td>
<td>-3.43</td>
<td>0.37</td>
<td>0.63</td>
</tr>
<tr>
<td>13</td>
<td>-21.66</td>
<td>0.72</td>
<td>0.04</td>
<td>16.69</td>
<td>0.85</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*The slopes of the regression lines (Slope), correlation coefficients (r), and significances (p) are shown. Significant correlations are boldfaced (p<0.05).
graphic representation of relationship between the remaining parameters once the influence of one of the variables had been excluded.

Linear regression analyses were used to assess the relationship between variables, both for individual patients and for pooled data, and both for actual and standardized results. A major emphasis was placed on the analysis of relationships from individual patients rather than the pooled data as it was considered individuals may vary in their responses to variations in oxygen delivery, sedation level, and temperature. Analysis of variance was used to assess the significance of changes in VO₂, DO₂I, and OER at different SS and Temp bands. Significance was taken as p<0.05.

Results

The descriptive features of the 13 patients are summarized in Table 1. None of the patients had evidence of adult respiratory distress syndrome (ARDS) or septicemia. Four to 14 (mean, 7.6) measurements were made for each patient over a 24-h time period.

For the pooled data there was a significant correlation between SS and VO₂I (slope −13.8, r=0.77, p<0.01) and a less good correlation between Temp and VO₂I (r=0.458, p<0.01). Figure 1 shows a positive correlation between DO₂I and VO₂I for the pooled data (r=0.614, p<0.01) with a line slope of 0.22. There was a less striking negative correlation between DO₂I and LAC (r=0.485, p<0.01) and no correlation between VO₂I and LAC (r=0.260).

The data for the individual patients are shown in Tables 2 and 3, and Figure 2. In all patients, there is a positive correlation between DO₂I and VO₂I (>0.60, in all but three patients); this relationship reaches significance in 6 of the 13 patients (p<0.05) (Fig 2 and Table 3, part A). Table 2 shows the relationship between oxygen consumption and both SS and Temp for the individual patients. Seven of the patients displayed significant negative correlations between

Table 3—The Oxygen Delivery/Consumption Relationships for the Different Patients*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Slope A</th>
<th>r A</th>
<th>p A</th>
<th>Slope B</th>
<th>r B</th>
<th>p B</th>
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<td>0.07</td>
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<td>0.33</td>
<td>0.03</td>
<td>0.13</td>
<td>0.75</td>
</tr>
</tbody>
</table>

*Slope A shows the relationship of actual oxygen delivery to oxygen consumption, slope B shows the relationship of actual oxygen delivery to oxygen consumption standardized for sedation from the equations for the regression lines for sedation score and oxygen consumption for each individual patient. The slopes of the regression lines (Slope), correlation coefficients (r), and significances (p) are shown. Significant correlations are boldfaced (p<0.05). See also Figures 2 and 4.
There was little change in the relationship between SS and Vo2I, when Vo2I was standardized for the effects of Do2I. The line slope was slightly reduced to -8.4 with r = 0.519 (p < 0.01) for the pooled data, and of the seven patients who had significant relationships prior to this standardization, six still had significant relationships between SS and dd Vo2I.

The means and standard errors for Vo2I, Do2I, and OER were calculated for each SS (Table 4) and Temp band for the pooled data. At different SS there were significant variations in Vo2I (except for SS 4 vs 2 and 3, or SS 5 vs 6). Do2I only had significant variations at SS 6 vs 1, 2, and 3, and SS 2 vs 4, OER had an intermediate number of significant variations. At the different Temp bands, there were significant variations between Vo2I and OER at 34.1 to 34.5°C and 34.6 to 36.0°C and subsequent Temp bands, but not between Do2Is at different Temp bands.

**Discussion**

This study was designed to examine the relationship between Do2I and Vo2I in perioperative patients, and to look for other factors which might influence this relationship. We have considered, as have others, that the relationships between variables within individual patients may be more relevant than these relationships for the pooled data. We have shown an apparently supply-dependent relationship between oxygen delivery and oxygen consumption with raised lactate levels in our patients. However, once the effects of varying sedation are taken into account, and once the oxygen consumption has been standardized for this effect, the supply-dependent relationship is lost. We have also shown that in our patients the effects of changes in sedation on Vo2I are much greater than the effects of changes in Do2I or temperature.

Contrary to earlier observations, we found little relationship between varying temperature and oxygen consumption, although in ileal tissue oxygen uptake increases 2.7-fold for a 10°C rise in temperature. This unexpected finding may have been due to a positive relationship being hidden in our data because oxygen consumption may be paradoxically high at low temperatures due to postoperative rewarming. Our finding of a lack of significant or consistent relation-

**Table 4—Vo2I (ml/min/m²), Do2I (ml/min/m²), and OER (percent) at Different Sedation Scores**

<table>
<thead>
<tr>
<th>Sedation Score</th>
<th>Vo2I ± SE (ml/min/m²)</th>
<th>Do2I ± SE (ml/min/m²)</th>
<th>OER ± SE (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>156.0 ± 2.1</td>
<td>371.7 ± 55.5</td>
<td>43.7 ± 6.2</td>
</tr>
<tr>
<td>2</td>
<td>125.4 ± 3.1</td>
<td>368.5 ± 11.0</td>
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</tr>
<tr>
<td>3</td>
<td>112.2 ± 2.8</td>
<td>335.4 ± 16.0</td>
<td>34.9 ± 1.6</td>
</tr>
<tr>
<td>4</td>
<td>121.3 ± 10.1</td>
<td>301.7 ± 24.3</td>
<td>40.7 ± 3.0</td>
</tr>
<tr>
<td>5</td>
<td>84.4 ± 17.1</td>
<td>298.0 ± 1.0</td>
<td>28.2 ± 5.8</td>
</tr>
<tr>
<td>6</td>
<td>70.0 ± 2.7</td>
<td>267.2 ± 13.1</td>
<td>27.2 ± 1.5</td>
</tr>
</tbody>
</table>

**Figure 3.** The oxygen delivery/standardized oxygen consumption relationship for the pooled data. Oxygen consumption is standardized with data from the pooled relationship of oxygen consumption and sedation score; ss Vo2I = 0.084 Do2I + 82.3, r = 0.366, p < 0.01.

**Figure 4.** The oxygen delivery/standardized consumption relationships for the individual patients (see text for details).
ships between temperature and oxygen consumption for the individual patients prevented any further analysis of oxygen consumption standardized for the effects of temperature.

Four previous studies have considered the possibility of other factors affecting oxygen transport; variations in oxygen transport which mimic supply dependence can be demonstrated to occur spontaneously in ICU patients and in ICU patients having physiotherapy, and earlier data have shown that there are wide swings in metabolic rate in ICU patients. Others have demonstrated that morphine decreases oxygen consumption in postoperative and other critically ill patients and have postulated that this may in part be due to its sedative action. Although these authors did not specifically measure sedation level the variations that they observed may all have been due to changes in sedation level. We are concerned that the effect of changing sedation may mimic "supply dependence" and may prompt inappropriate therapy and intervention in postoperative ICU patients. Our data may provide a method for standardizing the changes in VOJ for sedation score and hence allow the same patient to be observed with regard to oxygen transport data over different levels of sedation.

Apparent supply dependence has been demonstrated in patients with sepsis, adult respiratory distress syndrome, chronic congestive cardiac failure, and pulmonary hypertension. The patient populations studied imply that sedation must have been used in all but two of the studies, but only three of the remaining ten studies mention sedation at all and it is not possible to draw conclusions as to changes in sedation from the presented data. The changes in sedation may have been quite great: Gilbert et al specifically mention that they only excluded patients with agitation, restlessness, or seizures, three patients studied by Mohsenifar et al had to have pancuronium bromide, and four of the studies collected data on their patients over periods longer than 24 h. From the others it is possible to calculate approximately the slope of this relationship by considering the mean baseline and mean peak values for DOJ and VOJ. The slopes for the regression lines vary from 0.08 to 0.32, and the slopes for the calculated values vary from 0.09 to 0.46. The slope of our regression line for the pooled data prior to standardization for sedation is 0.22. The similarity between our nonstandardized results and those in the previous studies may imply that some of the effects of changing sedation that we have observed may have contributed to their apparent supply-dependent relationships.

Two recent studies have emphasized that the apparent supply-dependent relationship in patients with ARDS, sepsis, and postoperative patients might be caused by the mathematical linkage of oxygen delivery and oxygen consumption, by the appearance of cardiac output in the formulas for both variables. In postoperative patients, the slopes of the oxygen delivery/consumption relationships, when oxygen consumption is measured by the difference between inspired and expired gases, range from —0.07 to 0.08. These slopes are very similar to those found in our study once oxygen consumption had been standardized for varying sedation level (Table 3, part B). Four of our patients had slopes that were greater than 0.10 despite standardization of oxygen consumption, although none of these was significant. We did not investigate the contribution of mathematical linkage in our study, but this may have accounted for the trend to a positive oxygen delivery/standardized consumption relationship in some of our patients. On the other hand, the average small positive relationship found in these two studies may have had a contribution of varying sedation level that they did not measure.

This study does not disprove the theory of a "supply dependence" of oxygen consumption on oxygen delivery. We have shown, however, that the effect of varying sedation level on the oxygen delivery/consumption relationship can mimic supply dependence, and that the effect of sedation on VOJ is more important than the effect of DOJ. We are unable in this study to exclude the effects of other factors on the oxygen delivery/consumption relationship such as mathematical linkage, but we have not found a major effect of temperature change. We recommend that when interpreting oxygen transport data from individual patients and from investigation work the effect of varying sedation is taken into account.

REFERENCES
1 Shibutani K, Komatsu T, Kubal K, Sanchala V, Kumar V, Bizzarri
Oxygen Consumption and Delivery in Critically Ill Patients


Is Oxygen Consumption an Important Clinical Target?

O. Boyd and E. D. Bennett

Introduction

In the late 1960s and early 1970s a new syndrome was recognized following episodes of sepsis, ruptures of aortic aneurysm and multiple trauma. It consisted of development of progressive failures of vital organs: liver, kidneys, lungs and heart, starting from 1 to 3 days after the initial insult and culminating usually in death 14 to 21 days later, and was named multiple organ failure (MOF). The syndrome carried a mortality of greater than 80%. The exact cause and sequence of the events that arose at the time of the insult and resulted in MOF remain obscure, but hypotension, poor perfusion and relative hypoxia were thought to be important initiating events. It was in this context that the increase of arterial saturation by the addition of positive end-expiratory pressure (PEEP) became important and the physiological effects of PEEP in patients ventilated for adult respiratory distress syndrome (ARDS) were studied by Powers et al. [1]. They showed that the addition of PEEP caused changes in cardiac output and thus oxygen delivery (DO₂) and similar changes in the whole body oxygen consumption (VO₂) [1]. This work was interpreted as showing that VO₂ depended on DO₂ and hence VO₂ in a supply dependent patient. Shoemaker et al. [3] showed that VO₂ was an important predictor of survival in high risk surgical patients and that the survivors had supranormal

![Fig. 1 The VO₂/DO₂ relationship for healthy humans (solid line) and patients with ARDS (dashed line). (From [2] with permission)](image)
oxygen transport parameters, and his group demonstrated the usefulness of this approach in studies where VO2 was added to normal parameters of treatment. Mortality, complications and hospital stay were reduced if oxygen transport parameters were added as targets of treatment post-operatively and more significantly pre-operatively. Recently, reduced mortality has been shown in a controlled trial of septic patients [4].

However, doubts remain about the interpretation of oxygen transport parameters in the clinical setting. We are concerned that too much emphasis is placed on treatment targeted to increasing VO2. VO2 may be altered by a number of factors and we hypothesize that treatment targeted to increasing vital organ perfusion may be more beneficial to a particular patient than treatment aimed primarily at increasing VO2. We present a review of the studies which have suggested a supply dependence of VO2 on DO2 and consider evidence from our group and others that the interpretation of these studies may not be so straightforward. We suggest that some therapies may increase oxygen demand without providing adequately distributed supply and find that we can interpret the literature to suggest that blood flow is more important than VO2.

The Evidence for Supply Dependence

The Effects of PEEP. Powers et al. [1] demonstrated in 71 data sets from 33 patients with ARDS, that as DO2 fell in response to increases in PEEP there were falls in VO2. When data from all the patients was analyzed as a group, there was good correlation between DO2 and VO2. In some patients, DO2 increased with the application of PEEP and in these patients VO2 increased but the correlation was much less good (r = 0.64). Danek et al. [5] also considered the effects of the application of PEEP to patients with ARDS and showed in 11 patients that after stepwise increases in PEEP there were falls in DO2 and concomitant falls in VO2. These authors studied two other patient groups: a group with ARDS was studied longitudinally over 3 to 9 days and showed significant positive correlation between DO2 and VO2, but a group without the diagnosis of ARDS failed to show a similar significant correlation. This last group consisted of patients with various medical diagnoses that included pulmonary hypertension and heart failure.

Spontaneous Fluctuations. Variations in DO2 and VO2 over the whole of a patient's stay in ICU has been studied by two groups. Mohsenifar et al. [6] analyzed the pooled data for the population studied and Clarke et al. [7] analyzed data from the individual patients. Mohsenifar et al. [6] studied 10 patients with ARDS and observed variations in DO2 and VO2. At least two determinations were made each day but the length of the observation period was not stated. The results were interpreted as showing a supply dependent relationship between DO2 and VO2 up to a DO2 of 21 ml/min/kg after which VO2 appeared to plateau. A correlation coefficient of r = 0.76 for VO2/DO2 was found below 21 ml/min/kg. Edwards' group has observed variations in DO2 and VO2 in patients with ARDS but has interpreted the data on an individual patient basis [7]. They increased DO2 by a combination of fluid therapy, blood products and vasoactive drugs as part of a treatment proto-
col which prevented the use of PEEP if there were falls in DO$_2$, and they observed the changes in VO$_2$. They modeled various curves to the individual patients' data and found in 17 of 20 patients the curve of optimal fit showed VO$_2$ to increase as DO$_2$ increased. In one patient, VO$_2$ decreased with DO$_2$ greater than 1000 ml/min/m$^2$, and in 2 patients there was no significant relationship. This study was unable to define a plateau on the VO$_2$/DO$_2$ relationship.

**Fluid Therapy.** Fluid therapy was known to increase cardiac output in patients with ARDS [8] and the same group studied the effects of hypertonic mannitol on DO$_2$ and VO$_2$ in patient with ARDS [9]. Eleven patients were studied, 2 twice, and a bolus and maintainance dose of mannitol was given over 1 hour. Cardiorespiratory parameters were recorded before and after the mannitol. They showed increase in DO$_2$ in 11 measurement sets; in all but one VO$_2$ also increased. DO$_2$ decreased in 2 measurement sets but VO$_2$ still increased. They also showed an increase in oxygen extraction ratio and an increase in the oxygen diffusing capacity following mannitol therapy. Kaufman et al. [10] studied 5 patients with hypovolemia and 8 patients with septic shock all of whom were only included in the study if DO$_2$ increased following fluid therapy. All patients in the hypovolemic group and 7 of 8 in the septic group showed increases in VO$_2$ as DO$_2$ increased. Other workers have investigated the response to fluid therapy [11]. Hetastarch or albumin was given to 20 septic patients and they were divided into 3 groups for analysis. Group A with a raised lactate showed an increase in VO$_2$ as DO$_2$ was increased and the extraction ratio rose. Group B with a normal lactate showed no increase in VO$_2$. Group C, which did not respond to fluid therapy with a rise in DO$_2$ but did have a raised lactate, showed a fall in VO$_2$ as DO$_2$ fell. There was also a slight fall in extraction ratio. Interestingly, group C had the best survival.

**Pharmacological Interventions.** Various groups have studied the effect of pharmacological intervention on the VO$_2$/DO$_2$ relationship. Eight patients with congestive cardiac failure had resting DO$_2$ and VO$_2$ measured, and in all but 1 patient, a further 4 data points were recorded at increasing doses of nitrate [12]. At maximum nitrate dose, there were increases in DO$_2$, VO$_2$ and extraction ratio. The authors emphasized the changes in the values for DO$_2$ and VO$_2$ in their analysis. For the patient group as a whole, these are well correlated ($r=0.84$). Eleven patients with pulmonary hypertension were given nifedipine and were interpreted as showing supply dependence [13].

Vincent et al. [14] have advocated the use of a short term dobutamine infusion as an oxygen delivery challenge to assess the effects of increasing DO$_2$ on VO$_2$. This group studied 73 patients, 24 with heart failure and 49 with sepsis. Cardiorespiratory parameters were measured before and after a 30 min infusion of dobutamine at a rate of 5 µg/kg/min. The patients were divided into those with raised lactate and those with normal lactate, and were analyzed as individuals. This study was interpreted as showing a supply dependent pattern of VO$_2$/DO$_2$ relationship in the patients with raised lactate but not those with a normal lactate. Bihari et al. [15] were concerned that the use of catecholamines might bias results to show an apparent dependence of VO$_2$ on DO$_2$, due to potential increase in metabolic rate when catecholamines are given and he used prostacyclin (PGI$_2$) to increase the DO$_2$ to identify the presence of supply dependence in sepsis and acute respiratory failure by
an 'oxygen flux test'. This study showed that in 20 of 27 critically ill patients, VO₂ increased as DO₂ increased. This effect was not seen in healthy human volunteers also given PGI₂. It was also found that in the 13 patients who subsequently died, VO₂ increased more (19%) than in the 14 patients with similar severity of illness who survived (5%). Extraction ratio increased, from 34% to 37%, in the 13 patients who died, while in the 14 who survived, it fell.

There is one study that compares the effect of fluid loading, blood transfusion and catecholamines infusion in 54 patients with sepsis in the same institution [16]. Group I (n = 20) received fluid loading with hetastarch and albumin, group II (n = 17) received blood transfusion and group III (n = 17) received dopamine or dobutamine therapy. Each group was subdivided into those with a raised and those with a normal lactate. Group III showed increases in VO₂ as DO₂ was increased in both subgroups, although the VO₂ increased more in the high lactate group. The oxygen extraction ratio fell in both sub-groups. In group II, there was a significant increase in VO₂ as DO₂ increased in the raised lactate group but not the normal lactate group although the absolute changes, 18 and 13 ml/min/m², were similar. Again the oxygen extraction ratio fell in both groups. In group I, VO₂ fell in the normal lactate sub-group and rose in the high lactate sub-group with a rise in the oxygen extraction ratio.

**Summary.** These studies have been interpreted throughout the literature as demonstrating a supply dependence of VO₂ on DO₂ in critically ill patients. However, we are not convinced that these studies always necessarily confirm the presence of supply dependence.

**Mathematical Linkage**

In all the studies presented above, VO₂ and DO₂ were calculated using measurement of cardiac output, hemoglobin concentration and hemoglobin saturations. The VO₂/DO₂ relationship therefore shares measured variables. This has been assumed to provide a source of potential linkage between VO₂ and DO₂ providing a false positive correlation, but there is a potentially more important factor which has been overlooked.

**The Effect of Data Standardization.** Pooled data obtained from a number of patients may provide an enormous source of error due to incorrect standardization. If the method of standardization, body surface area (BSA) or weight, over- or under-estimates the variation between patients, then an apparently dependent relationship will be formed. BSA or weight becomes a shared variable with a one way bias which will influence results when pooled patient data is analyzed. The effect of this can be assessed from available data. Carlile and Gray [17] found a significant correlation between VO₂ and DO₂ in their grouped data but stress that the overall state of DO₂ whether high, medium or low biased this result. Mohsenifar et al. [6] demonstrated that pooled data gave a significant positive correlation between VO₂ and DO₂ when standardized to body weight, but we have analyzed the data from their individual patients and in this case, only 5 of 10 patients show a significant
positive relationship. We do not think that any study which analyzes pooled data to produce a regression line can be interpreted as evidence for supply dependence. Data from individual patients must be considered separately.

The Effect of Shared Variables. Errors in measured variables (cardiac output, hemoglobin and saturations) may provide a source of linkage between VO₂ and DO₂ and produce an artificial correlation [18]. However, not all studies have found evidence of supply dependence using these measurements despite many of the patients having ARDS [19], suggesting that the contribution of linkage may not be that great. It is usually assumed that cardiac output, which can have an error of up to 15% when measured by thermodilution, contributes most to potential linkage, and it is suggested that these errors are best avoided by measuring VO₂ independently, by the difference between inspired and expired gases [18].

Three studies have investigated the VO₂/DO₂ relationship by the measurement of expired gases and all have failed to demonstrate a supply dependence, either using PEEP [17, 20] or blood transfusion [21] to vary DO₂. It is usually assumed that errors in cardiac output measurement account for the discrepancy and this may be the case if repeated measurements of an actual point are made when the measured results will vary around the actual value (Fig. 2). To produce linkage after a manipulation to change DO₂, however, a one way bias must be introduced into the measurements (Fig. 2).

Cardiac output bias may have influenced results in PEEP studies but other factors may also provide the measurement bias. Our interpretation of Ronco’s et al. [21] study, which compared the VO₂/DO₂ response in patients with ARDS when DO₂ was increased by blood transfusion, using both thermodilution and expired

Fig. 2. The effect on calculated variables of cardiac output error and bias, assuming that there is no positive relationship between VO₂ and DO₂. Points A±10% and B±10% show apparent supply dependence due to errors in cardiac output measurement of ±10%. This will be seen if repeated measurements are taken and the real values for VO₂ and DO₂ are at either A or B (lines of dotted arrows). Once delivery has been altered, supply dependence is only apparently seen if there is a bias in cardiac output measurement at the second data point, in this case C with a positive bias of +20% (solid arrow). If no consistent bias appears, the calculated point A will on average go to calculated point B without apparent supply dependence.
Is Oxygen Consumption an Important Clinical Target? 315

gases to measure VO$_2$, suggests that hemoglobin may have been an important factor. They showed an apparently dependent relationship when VO$_2$ was measured by thermodilution but not when measured by expired gases. However in their study, there was no consistent increase in cardiac output; 8 of 17 patients had a fall in cardiac output after blood transfusion. Cardiac output therefore does not appear to be the important factor as it is unlikely that transfusion would bias all subsequent cardiac output measurements upwards. Hemoglobin however increases in all patients at the second measurement point, and although the measurement of Hb is reliable, the calculation of DO$_2$ and VO$_2$ assumes that all the Hb is effective at carrying and delivering oxygen to the tissues at the same rate. This may not be the case for transfused blood [22], and we feel that an overestimate of 'functional' hemoglobin may have overestimated both DO$_2$ and VO$_2$ post-transfusion causing an apparent supply dependent pattern of oxygen transport when measured by thermodilution but not expired gases.

The available evidence supports the argument that random errors in values for shared measurements may cause an apparently dependent relationship between DO$_2$ and VO$_2$ in a static situation. If manipulations are used to increase oxygen delivery, a one way bias may be introduced that overestimates VO$_2$ in the second data set. This could be an overestimate of cardiac output, hemoglobin and arterial saturation, or an underestimate of the second mixed venous saturation. In practice, the effect of shared variables may be important but may have been overemphasized, because it requires the introduction of bias, not just random errors.

The Effect of Other Factors

Other factors affecting patients during their stay in ICU may influence the VO$_2$/DO$_2$ relationship. These factors may make it virtually impossible to interpret oxygen transport data.

The Use of Interventions Reducing DO$_2$. The first studies to find a supply dependence in patients with ARDS used PEEP as the method of alteration in DO$_2$ by its negative effect on cardiac output [1, 5]. DO$_2$ was therefore decreased in these patients during the study period. There are two criticisms of this approach. The first is that in the analysis of any intervention that decreases DO$_2$, it is essential to know the pre-intervention state of tissue oxygenation. If this is inadequate or only barely adequate, a reduction in DO$_2$ will be expected to reduce VO$_2$. Although Powers et al. [1] had an initially high DO$_2$, 4 of 11 of Danek's patients had DO$_2$ below 8 ml/min/kg [5], a level where even in normals, VO$_2$ is expected to fall as DO$_2$ decreases [23]. The second is that the institution of PEEP has considerable effects on the distribution of blood flow particularly to extra-thoracic organs [24] and this will have its own effects on total body VO$_2$.

Other interventions used to assess the VO$_2$/DO$_2$ relationship may have similar effects. Vasodilators can result in reductions of DO$_2$ and alterations in regional blood flow. Mohsenifar et al. [12] have used nitrate in cardiac failure patients and nifedipine in pulmonary hypertension patients [13]. In these studies, 50% and 34% of data points respectively show a fall in DO$_2$ and VO$_2$, all from a baseline of high
initial extraction ratios (>36%). If these data points are ignored, we estimate that only 2 of 8 patients with cardiac failure, and 4 of 11 patients with pulmonary hypertension show any evidence of supply dependence in these studies.

The Effect of Temperature. Temperature changes are known to affect metabolic rate and hence VO₂. It is usually assumed that increasing temperature causes an increased oxygen uptake. In critically ill patients however, the situation may be more complicated, and postoperative hemodynamic changes and rewarming can have various effects on oxygen transport. In patients undergoing open heart surgery, VO₂ increased postoperatively and then decreased [25]; this is probably due to shivering and has been seen in other postoperative patients [26]. In other critically ill patients, the relationship between central temperature and oxygen consumption may be more straightforward, showing a rise in VO₂ with temperature [27]. Few of the studies mentioned above record temperature, but the lack of a predictable relationship between VO₂ and temperature may mean that temperature changes accounted for large changes seen in VO₂ in individual patients.

The Effect of Sedation. We were impressed by changes that we observed in DO₂ and VO₂ in postoperative patients and wondered if these changes may have been misinterpreted as supply dependence particularly as many of these patients had a raised lactate, a supposed marker of tissue hypoxia and supply dependence. We studied the effects of changes in sedation on the VO₂/DO₂ relationship in 13 perioperative patients who had low maximum DO₂ (<500 ml/min/m²). Cardiac output was measured by the thermodilution method and DO₂ and VO₂ were calculated.

![Graph](image-url)  
**Fig. 3.** The VO₂/DO₂ relationships for 13 perioperative patients (top graph). Once VO₂ has been standardized for the effects of sedation (see text) the apparent dependent relationship is lost (bottom graph).
from this data. Sedation was assessed by the method of Ramsey et al. [28] on a simple bedside scoring system with scores varying from 1 to 6 where 1 is anxious and agitated, and 6 is unresponsive to painful stimuli. Data sets of DO$_2$, VO$_2$, lactate and sedation score were obtained pre-, intra- and postoperatively and were analyzed both as pooled data for all the patients and as individual patients, with linear regression analysis to assess relationships. Five of 13 patients received inotropic support with dopexamine hydrochloride. A total of 104 data sets showed significant negative correlation between VO$_2$ and sedation score ($r>0.7, p<0.001$) and all individual patients showed negative correlations between sedation score and VO$_2$; 7 of 13 were significant. All patients showed positive correlations between DO$_2$ and VO$_2$ and 6 of 13 were significant (Fig. 3). When VO$_2$ was standardized for the effects of sedation (by calculating an expected VO$_2$ for each sedation score from the regression of sedation score and VO$_2$ for each patient, and subtracting this from the measured oxygen consumption) no relation remained significant and the slopes of the regression lines were reduced towards zero (Fig. 3).

Previous studies have considered the possibility of other factors affecting oxygen transport. There are wide swings in metabolic rate in ICU patients and these variations in oxygen transport can mimic supply dependence both spontaneously [29] and in patients having physiotherapy [30]. Others have demonstrated that morphine decreases oxygen consumption in postoperative [26] and other critically ill patients [31]. Although these authors did not specifically measure sedation level, the variations that they observed may all have been due to changes in sedation level.

Very few studies on DO$_2$ and VO$_2$ record the sedation level of the patients studied. It is clear from our work that sedation may have been a major contributing factor to apparent supply dependence. The patient populations studied imply that sedation must have been used in all but 2 of the studies [12, 13], but only 3 of the remaining mention sedation at all and it is not possible to draw conclusions as to changes in sedation from their presented data [6, 15, 16]. The changes in sedation may have been quite great: Gilbert et al. [16] specifically mention that they only excluded patients with agitation, restlessness or seizures; 3 patients studied by Mohsenifar et al. [6] had to have pancuronium bromide; and 4 of the studies collected data on their patients over periods longer than 24 h [5-7] during which changes in sedation must have occurred.

**The Effect of Other Drugs.** It has been known for many years that catecholamines are potent stimuli for increasing metabolic rate in humans [32]. This is of major concern because many of the interventions used to increase DO$_2$ in critically ill patients involve the use of catecholamines, and dobutamine has been advocated as an agent to be used as part of an oxygen delivery challenge in the critically ill [14]. Our group has demonstrated, in our septic pig model, the large differences in VO$_2$ that result from different methods for increasing DO$_2$. 25 pigs (26-29 kg) were divided into 5 groups after 35 ml of caecal contents had been distributed throughout the peritoneum. In group 1, hetastarch was infused at 200 ml/h, and in group 2, hetastarch was infused sufficient to hold cardiac output constant. In the other 3 groups, cardiac output was increased by 25% by infusing hetastarch in group 3, dopexamine hydrochloride in group 4, or dobutamine hydrochloride in group 5.
The results (Fig. 4) show that while the DO$_2$ varied from 280 to 520 ml/min, there was little change in the VO$_2$ in the groups given colloid. In marked contrast, the group given dobutamine had VO$_2$ that was 50% greater despite similar DO$_2$. The group given dopexamine was midway between. In our pigs, VO$_2$ was divided into 3 groups depending on the treatment, not the DO$_2$.

Experimental evidence from humans has shown the effects of epinephrine, norepinephrine and dopamine in increasing oxygen consumption and resting energy expenditure. Cori and Buchwald [32] showed that epinephrine produced a 8-17% increase in VO$_2$ at 0.05 mcg/kg/min, and a 20-25% increase at 0.14 mcg/kg/min [33]. Norepinephrine has also been shown to increase VO$_2$ by 21% if infused at 0.13 to 0.31 mcg/kg/min [34]. Dopamine has recently been shown to increase VO$_2$ by as much as 33% at 5 mcg/kg/min, possibly by its effect on the release of epinephrine and norepinephrine [35], and dobutamine produces a dose related increase in VO$_2$ in stable patients having diagnostic cardiac catheterization [36].

These studies were performed on healthy or stable patients and the results may not apply to patients with severe cardiac failure or sepsis. VO$_2$ has been shown not to increase in patients with severe heart failure when given dobutamine [37], and Jardin et al. [38] has failed to show an increase in VO$_2$ following dobutamine infusion in septic patients. The discrepancy between the effects on healthy and ill patients may be due to the already elevated level of sympathetic stimulation in ill patients which may be reduced when blood flow is increased by dobutamine [39].

However, there are a number of studies that have considered the oxygen transport effects of dobutamine in patients with heart failure [14] and sepsis [14, 16] and have shown that VO$_2$ increases with dobutamine infusion. Gilbert et al. [16] even showed the effects of increasing DO$_2$ by different methods and, as we found in our animal model, dobutamine led to much greater increases in VO$_2$ than fluid or blood administration whether or not the patient had hyperlactemia and despite similar increases in DO$_2$. Vincent et al. [14] have reported that VO$_2$ only increases following dobutamine infusion in septic patients if the lactate is raised. From their data, if only patients with rises in DO$_2$ >75 ml/min/m$^2$ are analyzed, 12 of 14 of

![Fig. 4. The oxygen consumption characteristics of different methods of increasing oxygen delivery in septic pigs.](image-url)
the raised lactate group and 8 of 11 of the normal lactate group showed increased
VO\(_2\) as dobutamine was infused. This suggests that dobutamine itself might be
increasing the VO\(_2\), and the discriminating effect of a raised lactate may not be
great.

It is clear from our review of the available literature that if catecholamine infu­
sion results in a rise in VO\(_2\) it is interpreted as further evidence to support a supply
dependence of VO\(_2\) on DO\(_2\), and the few studies that do not report a rise in VO\(_2\)
following catecholamine infusion are held to demonstrate that catecholamines will
not \textit{per se} cause a rise in VO\(_2\) in ill patients. We have found far more evidence to
support an increase in VO\(_2\) when catecholamines are infused than to refute it.
To­
gether with the results from healthy people, this leads us to conclude that there is
no evidence to support the assertion that catecholamines do not increase VO\(_2\) in ill
patients \textit{per se}.

\textbf{The Effect of Fluids.} Various fluids have been used to increase DO\(_2\) in patients and
to assess the VO\(_2)/DO\(_2\) relationship. We are unable to find evidence that transfused
fluids cause increases in metabolic rate \textit{per se}, and so fluids might be considered a
more 'pure' way of increasing DO\(_2\). Fluids do not always cause increases in VO\(_2\),
particularly when given to patients without a raised lactate who it is suggested have
an adequate DO\(_2\) to meet demand [11, 16], suggesting that it is not the fluid itself
which increases VO\(_2\). When fluids lead to increases in DO\(_2\), they have a different
effect from other methods of changing DO\(_2\). While all the other methods cause
falls in the oxygen extraction ratio, fluids increase oxygen extraction ratio in most
studies. Oxygen extraction ratio and oxygen diffusing capacity into tissues in­
creased following mannitol infusion [9]. Hetastarch or albumin given to septic pa­
tients with a raised lactate caused the oxygen extraction ratio to rise [11], and mod­
ified fluid gelatin causes the same effect in a variety of critical illnesses [40]. Pen­
tastarch caused increases in oxygen extraction ratio when given to burned patients
with a raised lactate [41]. When fluid loading, blood transfusion and catecholam­
ines are compared in septic patients, the fluid therapy increased the oxygen extrac­
tion ratio and the other interventions decreased it (Fig. 5) [16]. However, if the
DO\(_2\) is low and the extraction ratio is high prior to fluid administration, even with
a raised lactate, fluids may not increase oxygen extraction further although there
are still increases in VO\(_2\) [10].

The effect of blood transfusion in critically ill patients is unclear. Blood transfu­
sion may increase VO\(_2\) [42] particularly when the lactate is raised (Fig. 5) [16], but

![Fig. 5. The effects of fluid, blood and dobutamine on changes in oxygen extrac­tion ratio in septic patients with normal and raised lactate. (From [16] with per­mission)](image)
other studies show no increase in VO₂ following blood transfusion [21, 22, 43]. These different findings may be related to the problems with the interpretation of data following blood transfusion that we have pointed out above.

Fluids increase VO₂ in many situations particularly when lactate is raised; this effect appears to be real as there is no evidence that the fluids increase VO₂ per se. Fluids also cause an increase in the oxygen extraction ratio possibly due to redistribution of flow and improvement of rheological characteristics of blood. Blood transfusion does not consistently increase VO₂; this may be due to a combination of varying oxygen transport effects of transfused blood and changing flow patterns in the organ capillary beds.

Conclusion

The basic defect in the development of MOF is tissue hypoxia. To increase VO₂ has been thought to imply that more tissues are metabolizing oxygen appropriately, yet the manipulation of DO₂ by the use of changes of ventilation, blood transfusion, catecholamines and other pharmacological agents makes changes in the VO₂ impossible to interpret. These difficulties are magnified when individual patients are treated out of the controlled environment of a formal study. We have shown that blood transfusion may apparently increase VO₂ but abnormal rheological and oxygen transport characteristics of transfused blood may fail to target the correct tissues. Catecholamines and other drugs may increase VO₂ but changes in blood flow [44], and an effect on the metabolic rate per se may both target tissues inappropriately and increase total oxygen requirement, giving a false impression, if treatment is continued, of supply dependence. The effects of sedation, temperature and other patient influences dramatically affect VO₂ and the VO₂/DO₂ relationship, and make data interpretation extremely difficult.

The effect of fluids however may offer evidence for a different approach to the manipulation of DO₂ in the clinical setting. In patients where an oxygen demand has arisen, and is manifest by a raised lactate, fluid therapy increases oxygen extraction implying organs are able to increase oxygen extraction to respond to the increased demand. This interpretation shows that local flow is more important than total DO₂. Increased organ blood flow may have prophylactic as well as treatment implications and may explain the results of studies showing benefit from an oxygen transport approach. Too much emphasis has been placed on VO₂ as an end point of treatment when the real end point of treatment should be an increase in tissue perfusion to both counteract a relative hypoxia at the time and to provide a reservoir of oxygen delivery from which a sudden increase in demand can be met.

We conclude that a change of emphasis from VO₂ to organ flow targeting is a more logical approach to the management of a patient at risk from MOF and suggest that the benefit demonstrated in studies using an oxygen delivery protocol may have been due to better organ blood flow rather than increased VO₂.
Is Oxygen Consumption an Important Clinical Target? 321

References

Comparing the information gained from routine blood gas analysis and from gastric tonometry for intramural pH. Lancet 1993; 341: 142-146
Comparison of clinical information gained from routine blood-gas analysis and from gastric tonometry for intramural pH

O. Boyd  C. J. Mackay  G. Lamb  J. M. Bland  R. M. Grounds  E. D. Bennett

The measurement of gastric intramucosal pH ($\text{pH}_i$) has been advocated to assist in decision-making for critically ill patients. To assess whether the information obtained from the measurement of $\text{pH}_i$ can be obtained from other measurements of metabolic acidosis, we studied 20 consecutive patients admitted to the intensive care unit.

A mean of eight (range two to fourteen) data sets per patient were obtained, comprising measurement of arterial pH, $\text{pO}_2$, $\text{pCO}_2$, and oxygen saturation, tonometer balloon fluid $\text{pCO}_2$, arterial pressures, and cardiac output. Bicarbonate concentration, base deficit or excess in blood and extracellular fluid, and $\text{pH}_i$ were calculated from these measurements. Relations between the variables and $\text{pH}_i$ were assessed by within-subject correlation comparisons. There were significant correlations ($r>0.6$, $p<0.001$) between markers of metabolic acidosis (base deficit in blood and extracellular fluid and bicarbonate concentration) and $\text{pH}_i$. A blood base deficit of $-4.65$ or less and an extracellular-fluid base deficit of $-6.13$ or less could estimate $\text{pH}_i$ below 7.32 (lower limit of normal range) with sensitivity of at least 77% and specificity of at least 96%. There was no patient in whom either $\text{pH}_i$ or blood base deficit consistently reflected acidosis when the other variable did not.

We conclude that the information that is obtained by gastric tonometry for $\text{pH}_i$ can be obtained more simply from measurements of metabolic acidosis; these variables can be calculated from routinely available blood-gas measurements.

Lancet 1993; 341:142-46.

Introduction

Measurements of gastric intramucosal pH ($\text{pH}_i$) are predictive of morbidity and mortality in a wide range of...
critically ill patients.1,4 Gastric pHH is measured simply by placing a balloon tonometer in the lumen of the stomach; from the pCO2 of the balloon fluid after a suitable equilibration period pHH can be calculated by a modified Henderson-Hasselbalch equation with the arterial bicarbonate concentration.2 The result of this calculation correlates well with directly measured pHH.7

Gutierrez and colleagues4 reported that mortality was lower among patients monitored and treated for falls in pHH below 7.32 than in those monitored only by conventional endpoints of resuscitation such as blood pressure and urine output. Fidjidian-Green8 has advocated use of pHH measurements to reduce the cost of treating critically ill patients. The importance of pHH measurement is thought to be related to its ability to reflect perfusion of the splanchnic vascular bed;10,11 the maintenance of adequate splanchnic perfusion seems to be important in the prevention of multiple organ dysfunction syndrome.12,13

We have observed, however, that pHH and other measures of metabolic acidosis, base excess or deficit and bicarbonate concentration, seem to be directly related and that they vary in and out of "normal" ranges at the same time. This prospective study investigated the association between pHH and other measures of metabolic acidosis in a critically ill population. We tried to find out the lowest limits of normal for markers of metabolic acidosis that correspond to the lower limit of normal for pHH.

Patients and methods

20 consecutive eligible patients were recruited during a 6-week period. Eligible patients were those who by our normal criteria were judged to need pulmonary artery catheterisation as part of their clinical management. Height and weight were recorded. As soon as was practicable after admission and initial resuscitation with fluid or inotropic support, a pulmonary artery catheter was placed by way of the subclavian or internal jugular vein, an arterial line was placed by way of a radial or femoral artery, and a tonometer was passed nasogastrically (Trip TGS catheter, Tonometries Inc, Bethesda, Maryland, USA). Collection of measurement sets was started as soon as correct placement of the pulmonary artery catheter and tonometer had been confirmed by radiography. Observations on each patient were made during a maximum of 48 h. Measurements were taken every 12 h, or more frequently if there was a change in treatment or in the patient's clinical condition. The patients were treated by the standard protocols of our intensive care unit including fluid volume replacement to maintain adequate cardiac preload and inotropic infusion (adrenaline or noradrenaline) to maintain systolic blood pressure above 110 mm Hg. Sodium bicarbonate infusions were not given.

Measurement sets consisted of tonometry measurement for pHH, selected gas analysis of arterial and mixed venous blood and measurement of whole blood lactate, and cardiorespiratory assessment. pHH was measured as instructed by the manufacturer; the silicone balloon of the tonometer was filled with 2.5 mL 0.9% saline after elimination of air bubbles. After 60 min for equilibration of pCO2 between the saline and the stomach lumen, an anaerobic sample of the last 1.5 mL saline from the tonometer was drawn at the same time as an arterial blood sample. The tonometer pCO2 and arterial bicarbonate (IL1312 Blood Gas Manager, Instrumentation Laboratory, Levington, USA), and the pHH was calculated by a modification of the Henderson-Hasselbalch equation:

\[ \text{pHH} = 6.1 + \log_{10} \left( \frac{\text{F} \times \text{tonometer saline pCO2}}{\text{bicarbonate concentration}} \right) \]

where F is a factor dependent on the equilibration time and supplied by the tonometer manufacturer. The blood gas analyser underwent quality control testing daily. All patients received ranitidine during the stay on the intensive care unit since this treatment increases the accuracy of measurements.14

Each sample of mixed venous/pulmonary arterial blood was taken by way of the distal pulmonary artery catheter, and the core body temperature was recorded from the pulmonary artery thermistor. Arterial samples were analysed for pHH, pO2, pCO2, oxygen saturation, and haemoglobin, and bicarbonate concentration and base deficit or excess in blood and extracellular fluid were calculated by standard formulae,15,16 that take into account the buffering effect of haemoglobin. It has been suggested that the extracellular fluid base deficit better represents tissue rather than blood acidosis.18 The mixed venous/pulmonary arterial sample was analysed for oxygen saturation (IL482 Co-oximeter, Instrumentation Laboratory) and whole-blood lactate.

### Table I—Demographic Details of Patients and Admission and 12 h pHH and Base Deficits

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>APACHE II</th>
<th>Outcome</th>
<th>pHH</th>
<th>ABb (mmol/L)*</th>
<th>pHH</th>
<th>ABb (mmol/L)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>F</td>
<td>30</td>
<td>Died</td>
<td>7.18</td>
<td>-11.33</td>
<td>7.24</td>
<td>-5.02</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>M</td>
<td>28</td>
<td>Died</td>
<td>7.18</td>
<td>-4.84</td>
<td>7.26</td>
<td>-2.79</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>F</td>
<td>20</td>
<td>Died</td>
<td>7.27</td>
<td>3.56</td>
<td>7.27</td>
<td>2.03</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>F</td>
<td>26</td>
<td>Died</td>
<td>7.00</td>
<td>-22.10</td>
<td>7.21</td>
<td>-8.91</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>M</td>
<td>41</td>
<td>Died</td>
<td>7.12</td>
<td>-11.70</td>
<td>7.28</td>
<td>-8.92</td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>M</td>
<td>17</td>
<td>Died</td>
<td>7.26</td>
<td>-5.43</td>
<td>7.30</td>
<td>-4.41</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>M</td>
<td>17</td>
<td>Died</td>
<td>7.13</td>
<td>-7.34</td>
<td>7.23</td>
<td>-7.20</td>
</tr>
<tr>
<td>8</td>
<td>61</td>
<td>F</td>
<td>15</td>
<td>Survived</td>
<td>7.47</td>
<td>11.30</td>
<td>7.53</td>
<td>15.33</td>
</tr>
<tr>
<td>9</td>
<td>49</td>
<td>F</td>
<td>13</td>
<td>Survived</td>
<td>7.47</td>
<td>-0.79</td>
<td>7.41</td>
<td>-1.49</td>
</tr>
<tr>
<td>10</td>
<td>62</td>
<td>M</td>
<td>10</td>
<td>Survived</td>
<td>7.39</td>
<td>0.06</td>
<td>7.32</td>
<td>3.12</td>
</tr>
<tr>
<td>11</td>
<td>71</td>
<td>M</td>
<td>28</td>
<td>Died</td>
<td>7.33</td>
<td>-2.19</td>
<td>7.14</td>
<td>-5.93</td>
</tr>
<tr>
<td>12</td>
<td>28</td>
<td>F</td>
<td>18</td>
<td>Survived</td>
<td>7.39</td>
<td>2.65</td>
<td>7.39</td>
<td>0.72</td>
</tr>
<tr>
<td>13</td>
<td>81</td>
<td>M</td>
<td>20</td>
<td>Died</td>
<td>6.68</td>
<td>-27.17</td>
<td>6.33</td>
<td>27.68</td>
</tr>
<tr>
<td>14</td>
<td>69</td>
<td>M</td>
<td>39</td>
<td>Died</td>
<td>6.85</td>
<td>-16.89</td>
<td>7.17</td>
<td>10.82</td>
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<tr>
<td>15</td>
<td>73</td>
<td>M</td>
<td>12</td>
<td>Survived</td>
<td>7.40</td>
<td>-1.91</td>
<td>7.41</td>
<td>-0.97</td>
</tr>
<tr>
<td>16</td>
<td>67</td>
<td>M</td>
<td>19</td>
<td>Died</td>
<td>7.36</td>
<td>-1.99</td>
<td>7.36</td>
<td>-1.15</td>
</tr>
<tr>
<td>17</td>
<td>62</td>
<td>M</td>
<td>11</td>
<td>Survived</td>
<td>7.35</td>
<td>-2.51</td>
<td>7.27</td>
<td>-4.74</td>
</tr>
<tr>
<td>18</td>
<td>54</td>
<td>M</td>
<td>13</td>
<td>Survived</td>
<td>7.40</td>
<td>-2.08</td>
<td>7.31</td>
<td>-3.62</td>
</tr>
<tr>
<td>19</td>
<td>62</td>
<td>M</td>
<td>21</td>
<td>Died</td>
<td>6.85</td>
<td>22.28</td>
<td>6.90</td>
<td>-23.54</td>
</tr>
<tr>
<td>20</td>
<td>73</td>
<td>M</td>
<td>30</td>
<td>Died</td>
<td>7.19</td>
<td>-10.50</td>
<td>7.23</td>
<td>-6.89</td>
</tr>
</tbody>
</table>

*Base deficit (negative) or excess (positive) in blood.

**Table II—Regression Statistics for Within-Subject Comparisons Between pHH and Gasometric Data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>pO2</td>
<td>154</td>
<td>-0.12</td>
<td>0.2</td>
</tr>
<tr>
<td>pCO2</td>
<td>155</td>
<td>-0.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pH</td>
<td>159</td>
<td>0.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bicarbonate concentration</td>
<td>159</td>
<td>0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Base deficit in blood</td>
<td>158</td>
<td>0.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Base deficit in extracellular fluid</td>
<td>159</td>
<td>0.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arterial oxygen saturation</td>
<td>159</td>
<td>0.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Venous oxygen saturation</td>
<td>152</td>
<td>0.02</td>
<td>0.9</td>
</tr>
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</table>
Scattergrams and within-subject correlations of blood and extracellular base deficits/excesses with pH.

The aim of this study was to assess relations between pH, and the cardiorespiratory variables recorded were arterial and pulmonary arterial pressure, right atrial pressure, pulmonary arterial occlusion pressure, cardiac output (measured by thermodilution), and cardiac index (calculated from body-surface area derived from a standard nomogram of height and weight). Systemic and pulmonary vascular resistance and oxygen delivery and consumption were calculated from standard formulae.

The significance of differences in pH, and blood base deficit or excess between survivors and non-survivors at hospital discharge was tested at admission and 12 h by Student’s t test. A clinically important abnormal value of pH, was taken as below 7.32, which is the mean minus two standard deviations in healthy subjects receiving H2-receptor blockade and has been regarded as abnormally low previously. Lower limits of normal ranges for other variables were calculated from the regression line of pH, against other variables with pH, = 7.32. The sensitivity and specificity of metabolic variables predicting pH, could be calculated; a true positive was taken as pH, below 7.32 (an indication for further intervention in the clinical setting) and a true negative as pH, of 7.32 or higher (an indication for no further intervention in the clinical setting).

### Results

Details of the 20 patients are given in table I. We obtained a mean of eight data sets per patient (range two to fourteen), which gives more than 7000 data points.

Within-subject regressions of arterial pH, base deficit/excess in blood and extracellular fluid, and bicarbonate concentration with pH, were significant (table II). The figure shows scattergrams for base deficit in blood and extracellular fluid and bicarbonate concentration with pH, in a mean of eight data sets per patient (range two to fourteen), which gives more than 7000 data points.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>158</td>
<td>0.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>157</td>
<td>-0.08</td>
<td>0.3</td>
</tr>
<tr>
<td>Diastolic</td>
<td>157</td>
<td>-0.16</td>
<td>0.06</td>
</tr>
<tr>
<td>Pulmonary artery pressure</td>
<td>153</td>
<td>-0.02</td>
<td>0.6</td>
</tr>
<tr>
<td>Pulmonary artery occlusion pressure</td>
<td>146</td>
<td>-0.12</td>
<td>0.2</td>
</tr>
<tr>
<td>Pulmonary artery pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>149</td>
<td>-0.25</td>
<td>0.003</td>
</tr>
<tr>
<td>Diastolic</td>
<td>149</td>
<td>-0.22</td>
<td>0.01</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>141</td>
<td>0.00</td>
<td>1.0</td>
</tr>
<tr>
<td>Vascular resistance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>133</td>
<td>-0.09</td>
<td>0.3</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>131</td>
<td>-0.03</td>
<td>0.8</td>
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<tr>
<td>Oxygen</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Delivery</td>
<td>141</td>
<td>0.03</td>
<td>0.8</td>
</tr>
<tr>
<td>Consumption</td>
<td>141</td>
<td>0.02</td>
<td>0.8</td>
</tr>
<tr>
<td>Blood lactate</td>
<td>126</td>
<td>-0.36</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Table III—Regression Statistics for Within-Subject Comparisons between pH, and Cardiorespiratory Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood base deficit</td>
<td>160</td>
<td>0.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pH</td>
<td>160</td>
<td>0.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>160</td>
<td>0.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Extracellular fluid base deficit</td>
<td>160</td>
<td>0.78</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Table IV—Lower Limits of Gasometric Variables* and Sensitivity, Specificity, and Predictive Value for an Abnormally Low pH, Value (<7.32)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Calculated lower limit (mmol/L)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Predictability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood base deficit</td>
<td>-6.65</td>
<td>78.3</td>
<td>96.6</td>
<td>98.1</td>
</tr>
<tr>
<td>pH</td>
<td>7.45</td>
<td>98.1</td>
<td>54.7</td>
<td>67.8</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>18.00</td>
<td>61.6</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table V—pH, and Blood Base Deficit (ΔB) in Survivors and Non-Survivors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Non-survivors</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.25 (0.02)</td>
</tr>
<tr>
<td>ΔB (mmol/L)</td>
<td>-0.47 (0.36)</td>
</tr>
<tr>
<td>Admission</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.1 (0.05)</td>
</tr>
<tr>
<td>ΔB (mmol/L)</td>
<td>-0.73 (0.25)</td>
</tr>
<tr>
<td>12 h</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.23 (0.06)</td>
</tr>
<tr>
<td>ΔB (mmol/L)</td>
<td>-0.78 (1.94)</td>
</tr>
</tbody>
</table>

*From regression lines with pH, when pH, is 7.32.

Variables were calculated within the subject. The method used was multiple regression with subject as a class variable. The within-subject correlation coefficient was calculated from the sum of squares for pH, and residual, the sign being found from the sign of the regression coefficient for pH, in the multiple regression with subject as a class variable.
Both pH$_i$ and base deficit in blood on admission and at 12 h differed significantly between patients who died and those who survived (table V).

**Discussion**

The routine measurement of metabolic acidosis available from a conventional blood-gas analyser gives the same clinical information as the measurement of pH$_i$ obtained by gastric tonometry. Metabolic acidosis is reflected by changes in blood and extracellular fluid base deficits and in bicarbonate concentrations and these variables are significantly correlated with pH$_i$ throughout the range of acid-base conditions that our patients represented. Our reason for seeking out such a correlation is that gastric tonometry is more expensive and time-consuming than routine blood-gas analysis, from which these variables are readily available. In addition, to enable the collection of accurate pH$_i$ data, patients have to be treated with H$_2$ receptor agonists and such treatment may have substantial risks in critically ill patients.

There is little published work on the predictive value of blood base deficit measurement or of its use in the clinical setting. In studies of blunt abdominal trauma, base deficit in blood was a good predictor of mortality. This variable is also a good indicator of the need for further investigation of abdominal injury caused by blunt trauma, when values of $-3$ mmol/L or $-6$ mmol/L are taken as a strong indication for diagnostic laparotomy. Blood base deficit can accurately reflect the haemodynamic and tissue perfusion changes associated with haemorrhagic shock in pigs; the value fell to $-3.7$ mmol/L in shocked animals. The estimated lower level of a normal blood base deficit in our patients was $-4.6$ mmol/L, which is compatible with clinical information as the measurement of pH$_i$ obtained by gastric tonometry. The information that is obtained by gastric tonometry for measurement of pH$_i$ can be obtained more simply from measurement of base deficit in blood or extracellular fluid. Larger studies are needed to assess the predictive value of base deficit measurements and their role as a target for resuscitation.

**REFERENCES**


Effects of insertion depth and use of the sidearm of the introducer sheath of pulmonary artery catheters in cardiac output measurement

Owen Boyd, MRCP; C. John Mackay, FRCA; Philip Newman, FRCA; E. David Bennett, FRCP; R. Michael Grounds, MD, FFARCS

Objective: To investigate the effects of various insertion depths and sidearm functions of the introducer sheath of pulmonary artery flotation catheters on cardiac output measurement.

Design: Prospective, randomized, crossover study.

Setting: A general intensive care unit.

Patients: Ten patients who had a pulmonary artery flotation catheter placed in the right internal jugular vein as part of their clinical management.

Interventions: Cardiac output was measured at three insertion depths of the pulmonary artery catheter, each with a different rate of flow into the introducer sheath.

Measurements and Main Results: Significant differences of up to 23% occurred in the measurement of cardiac output under the various conditions. Cardiac output measurement is greater, the closer the injection port lies to the introducer sheath and the more open the introducer sheath sidearm.

Conclusions: All users of pulmonary artery catheters should be alert to this problem. For reliable measurements of cardiac output by thermodilution, the cold saline injection port of the pulmonary artery catheter must be downstream of the introducer sheath, and the introducer sidearm must be closed. (Crit Care Med 1994; 22:1132-1135)

Key Words: catheterization, Swan-Ganz; cardiac output; thermodilution; pulmonary artery; intensive care; monitoring, physiologic; critical illness; heart

Since their development 22 yrs ago (1), pulmonary artery flotation catheters have become standard equipment for the monitoring of critically ill patients. Frequently, the information gained from measurements derived from using the pulmonary artery catheter is used to direct therapy; clinical studies (2–6) have demonstrated reductions in morbidity and mortality rates when these measurements are used. If the values obtained from pulmonary artery catheters are to be used in this manner, the information obtained must be reliable and reproducible, particularly if the measured cardiac output is used to derive other parameters, when errors may be magnified.

We have observed in a number of patients that, during measurement of cardiac output by the thermodilution method, there was return of injectate up the sidearm of the pulmonary artery catheter introducer sheath. We hypothesized that the return of injectate may have been caused by the injectate port of the pulmonary artery catheter lying within the introducer sheath (Fig. 1); as cold fluid was injected, some of the fluid passed incorrectly up the introducer sheath in a retrograde fashion. We expected that this phenomenon would cause the over estimation of cardiac output, because cardiac output is computed as the ratio of the amount of indicator injected divided by the time integral of temperature change. If indicator is lost into the sheath, the integrated temperature change is less, and, in turn, computed cardiac output is correspondingly larger. This study was designed to investigate the potential effect of return of injectate up the introducer sidearm on the measurement of cardiac output.

MATERIALS AND METHODS

Ten patients who had placement of a pulmonary artery catheter via the right internal jugular vein as part of normal clinical management were studied. Patients were only included if, before the study period, cardiovascular measurements were stable for at least half an hour without change in any necessary inotropic medication. Only patients who were mechanically ventilated were studied. Institutional Ethics Committee approval was given for the study, and informed consent was obtained from the patients or their representatives.
All patients had a pulmonary artery catheter (Swan-Ganz catheter, 93A-131-7.5F, Baxter Healthcare, Irvine, CA) inserted into the right internal jugular vein using a standard introducer sheath (Percutaneous sheath introducer, AK-09801, 8.5F; Arrow International, Reading, PA). The cold saline injection port is sited 30 cm from the tip of the pulmonary artery catheter, and the introducer sheath is 15 cm long. The position of the pulmonary artery catheter was checked by radiograph, and the insertion depth of the pulmonary artery catheter was recorded when a pulmonary artery occlusion trace was first obtained. A 100-mL bag of saline (0.9% sodium chloride intravenous infusion BP, Baxter Healthcare, Norfolk, UK) was connected to the sidearm of the introducer sheath with a standard fluid administration set (Codan B86, Codan, Wokingham, Berkshire, UK), and, with the patient lying supine, the drip chamber was elevated 150 cm above the patient's midaxillary line. The roller clamp was sited 30 cm below the drip chamber. Cardiac output was measured using the thermodilution technique. Randomly, 5-mL injections of cold (8°C to 16°C) 5% dextrose were injected manually (7) throughout the respiratory cycle (8, 9) using an injection system (CO-Set+ closed injectate delivery system, 93-600; Baxter Healthcare). Cardiac output was calculated using a computer (Supermon 7210; Kontron Instruments, Watford, Herts, UK); the calibration constant was obtained from the manufacturer of the pulmonary artery catheter.

Cardiac output was measured at three different insertion depths for the pulmonary artery catheter, 40, 45, and 50 cm. At 45 cm, the injection port is at the tip of the introducer sheath. At each insertion depth, the sidearm of the introducer sheath was allowed to function in three different ways to give different resistances to any injectate backflow. With the roller clamp closed, a maximum resistance to backflow of injectate fluid up the sidearm is provided. With the roller clamp fully open, and the saline run into the patient to equilibrate at the level of the central venous pressure, there is a minimum degree of resistance to injectate backflow. With the roller clamp allowing only 20 drops/min of saline, a medium degree of resistance to injectate backflow is created. The order of the nine experimental conditions was randomly assigned.

Four cardiac output measurements were made at each insertion depth and at each sidearm function. All injection curves were inspected to exclude curves that were irregular (10). One investigator injected the cold dextrose and another, blinded to the insertion depth and sidearm function, recorded all cardiac output measurements. Cardiac output measurements were made until three were separated by <0.5 L/min, and the mean of these three measurements was then taken.

The results for cardiac output at different insertion depths with the same sidearm function, and for different sidearm functions at the same insertion depth, were compared by repeated-measures analysis of variance. Scheffe's F-test was then used to compare specific differences. A $p < .05$ was considered statistically significant.

RESULTS

Results of the ten patients are shown in Table 1. Significant differences occurred in cardiac output measured under the various conditions (Table 2 and Fig. 2). Consistently higher cardiac output
measurements were obtained at a 40-cm insertion depth compared with either a 45-cm or a 50-cm insertion. This effect was seen at all three different sidearm functions, but only reached significance when the sidearm was open. Cardiac output measurements were higher when the sidearm was open than when the sidearm was closed or running at 20 drops/min. This effect occurred at all insertion depths and reached significance when compared with a closed sidearm at 40 cm and both of the other sidearm functions at 50-cm insertion. Figure 2 shows the differences in the measured cardiac output as a percentage of cardiac output measured at a 50-cm insertion with a closed sidearm. Cardiac output measurements were higher at shorter insertion depths and when the sidearm of the introducer sheath was more open.

**DISCUSSION**

This study presents two unrecognized errors in cardiac output estimation using the thermodilution method. Significant differences occur in the value of cardiac output obtained when a pulmonary artery catheter is inserted to different depths through an introducer sheath. We have also shown that the measured cardiac output is different depending on the function of the sidearm of the introducer sheath at the time of the cardiac output measurement. Our initial observation of return of injectate up the sidearm of the introducer sheath probably explains these findings, although further investigation is required to confirm this explanation. Before the study, we were able to observe return of the injectate up the sidearm of the introducer sheath when blood was infused and when the sidearm was open. When a cardiac output measurement was performed, the column of blood was pushed back toward the blood bag by a column of clear fluid from the injection syringe. During the study, a similar phenomenon was observed with backfilling of the drip chamber of the fluid administration set when a thermodilution injection was performed. Variations in the amount of fluid injected in each bolus can cause large variations in the measured cardiac output; a 0.5-mL error in a 5-mL injectate will cause a 10% error in cardiac output measurement (11). When the injectate port of the pulmonary artery catheter lies within the introducer sheath (Fig. 1), some injectate goes the wrong way, producing a smaller injectate volume and an over-estimation of cardiac output. When the sidearm of the introducer is open, more injectate is able to flow the wrong way, and therefore, higher cardiac output measurements are obtained when the introducer sidearm is fully open. Surprisingly, higher cardiac output measurements were obtained when the sidearm was fully open, even when the pulmonary artery catheter was inserted to 50 cm, which suggests that some backflow must have occurred even at this distance of the injection port from the tip of the introducer sheath.

**Table 1.** Details of the patients studied

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Age (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>160</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>165</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>175</td>
<td>76</td>
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<td>4</td>
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<td>5</td>
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<tr>
<td>6</td>
<td>160</td>
<td>43</td>
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<td>7</td>
<td>160</td>
<td>40</td>
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<tr>
<td>8</td>
<td>150</td>
<td>55</td>
</tr>
<tr>
<td>9</td>
<td>160</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>150</td>
<td>65</td>
</tr>
</tbody>
</table>

**Table 2.** Cardiac output (L/min) measured under the different experimental conditions (mean ± se); significant differences are indicated by the following symbols: *, §, #, and ¶

<table>
<thead>
<tr>
<th>Sidearm Function</th>
<th>50-cm Insertion</th>
<th>45-cm Insertion</th>
<th>40-cm Insertion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closed</td>
<td>4.93 ± 1.24</td>
<td>5.09 ± 1.13</td>
<td>5.42 ± 1.24</td>
</tr>
<tr>
<td>20 drops/min</td>
<td>5.05 ± 0.95</td>
<td>5.21 ± 1.00</td>
<td>5.53 ± 1.18</td>
</tr>
<tr>
<td>Open</td>
<td>5.25 ± 0.99*§</td>
<td>5.26 ± 0.91</td>
<td>5.96 ± 1.20*¶</td>
</tr>
</tbody>
</table>

*Closed sidearm/same insertion depth; §20 drops/min at same depth; #45-cm insertion/same sidearm function; ¶50-cm insertion/ same sidearm function.

**Figure 2.** Mean percentage difference in measured cardiac output for varying insertion depths and sidearm function of the pulmonary artery catheter, compared with cardiac output measured by thermodilution when the pulmonary artery catheter is inserted to 50 cm and the introducer sidearm is closed.
Patients who were included in our study were below average in height and weight, which tends to confirm the expectation that these effects are more likely to be seen in smaller patients. We were, however, unable to find any specific correlations to either height or weight. In an informal survey undertaken in our intensive care unit over a 3-month period, we found that ~30% of patients obtained a satisfactory pulmonary artery occlusion trace at an insertion depth of <50 cm, and therefore, the errors we have defined may be common. To make our study as clinically relevant as possible, we chose to duplicate the routine used in many intensive care units to measure cardiac output; injections were made randomly through the respiratory cycle, and the mean of results separated by <0.5 L/min were taken as the final result. We would expect other methods, such as timing the injection to the respiratory cycle or taking results separated by a certain percentage of the expected cardiac output, to give results similar to those findings of our study.

The findings of this study are important. It has been shown that a change in sidearm function led to changes in cardiac output measurement (12), but the magnitude of the changes has never been investigated. Reproducible measurement of cardiac output by thermodilution requires accurate measurement of the blood and injectate temperatures (13) and accurate delivery of the injectate into the right atrium (14) in the correct volume (11), as well as avoidance of the errors highlighted by the current study.

Increasingly, results derived from cardiac output measurements are used as specific goals of therapy, and these goals have been shown to reduce mortality and morbidity rates in a variety of critically ill patients (2–6). The absolute nature of therapeutic goals, as opposed to the requirements of a specific percentage change in the values, means that errors of up to 20%, as found in our study, may lead to inappropriate treatment. In the clinical situation, cardiac output is recorded intermittently over a period of some hours during which time infusions down the sidearm of the introducer sheath are likely to vary. Therefore, even changes observed in a patient from a baseline value that had been previously obtained may be misleading.

To avoid the errors shown by this study, the injection port of the pulmonary artery catheter must lie distal to the introducer sheath. If necessary, this positioning can be achieved by withdrawing the introducer sheath while maintaining it within the central vein. This catheter placement can also be achieved by using a vein more distal to the heart as the insertion site, so that the catheter can be advanced further before wedging is achieved. Manufacturers might also provide a choice of catheters with injection ports at different distances from the catheter tip. In addition, the introducer sidearm must be closed before performing a thermodilution cardiac output.

In summary, we have identified two new, potentially important errors in cardiac output measurement by thermodilution. Related to the depth of insertion of the pulmonary artery catheter and the function of the introducer sidearm, differences of up to 23% in measured cardiac output were seen. Cardiac output measurements are greater the closer the injection port lies to the introducer sheath and the more open the introducer sheath sidearm. These variations may lead to inappropriate treatment. We recommend that all users of pulmonary artery catheters be alert to this problem and close the introducer sidearm, where appropriate, while ensuring that the injection port lies downstream of the introducer sheath.

REFERENCES

The cardiovascular changes associated with equipotent anaesthesia with either propofol or isoflurane

Particular emphasis on right ventricular function

O. Boyd1, L. J. Murdoch2, C. J. Mackay2, E. D. Bennett1 and R. M. Grounds2

The General Intensive Care, Departments of Medicine1 and Anaesthesia2, St George's Hospital, London, UK

The differences in effects of anaesthetic agents on right ventricular function have not been studied. We have developed a cross-over study design to compare the effects of propofol and isoflurane on cardiac and specifically right ventricular function. Ten patients were anaesthetised with equivalent MAC of isoflurane to MIR of propofol. After measurements had been taken on the randomly assigned first agent the patients were crossed over to the other agent and measurements were repeated. Cardiac function was assessed using a pulmonary artery catheter with a fast response thermistor. There were no differences in heart rate or blood pressure between the two agents suggesting that equivalent anaesthetic doses had been given. There were significantly ($P<0.05$) higher cardiac output (4.0 to 4.5 l·min$^{-1}$), right ventricular ejection fraction (35.1 to 39.4%), stroke volume (35.4 to 39.6 ml) and right ventricular end-diastolic volume index (102 to 110 ml·m$^{-2}$·l$^{-1}$) with propofol compared to isoflurane. We conclude that propofol results in improved right ventricular performance compared to isoflurane. We have also shown that anaesthetic agents can be compared using a cross-over study design, and have demonstrated that MAC of isoflurane and MIR of propofol can be directly compared. We suggest that propofol may be a more suitable agent than isoflurane for anaesthesia in patients who may already have impaired right ventricular function and in whom maintaining high cardiac output may be beneficial.

Received 22 January, accepted for publication 8 July 1993

Key words: Anaesthesia, general; cardiac output; human; inhalation; intravenous; isoflurane; minimum alveolar concentration (MAC); minimum infusion rate (MIR); propofol; right ventricular function; vascular surgery.

Anaesthetic agents are known to have negatively inotropic effects on cardiac function (1–3) but their specific comparative effects on right ventricular function have not been studied. Differences in effects on right ventricular function may be important when choosing an anaesthetic technique, particularly in aged patients or those with pre-existing cardiac or respiratory disease. The importance of maintaining high cardiac output during the peri-operative period has recently been shown to reduce mortality and morbidity in these patients (4–6).

Comparing the cardiovascular effects of different anaesthetic techniques is, however, difficult due to large variations in the results for different patients (7). We have, therefore, developed a within patient cross-over study design to allow meaningful comparison of the cardiovascular effects of different anaesthetic agents. Using this, we have compared the cardiovascular effects of propofol and isoflurane with particular emphasis on right ventricular function.

PATIENTS AND METHODS

Patient selection and pre-operative management

Informed consent for participation in the study was obtained from ten consecutive patients who were booked to have peripheral vascular reconstructive procedures. Height and weight were recorded for calculation of body surface area. The study had previously been approved by the hospital medical ethics committee. As is usual in our unit, the patients were admitted pre-operatively to the Intensive Care Unit and a radial arterial line was placed, under local anaesthesia, for blood pressure measurement. A pulmonary arterial catheter (Baxter/Edwards 93A-434H-7.5F) was placed with local anaesthesia via the right internal jugular vein. The PA catheter had a fast response thermistor and, when connected to an appropriate cardiac output computer (Baxter/Edwards REF-1), could be used to calculate not only cardiac output and stroke volume, but also parameters of right ventricular function. The right ventricular parameters recorded were:
right ventricular end-diastolic volume (RVEDV), right ventricular end-systolic volume (RVESV) and right ventricular ejection fraction (RVEF). Catheter position was checked by chest x-ray and pressure transduction confirmed that the injection port was situated 2–3 cm proximal to the tricuspid valve and that there was no significant tricuspid regurgitation.

Anesthesia and experimental procedures

The patients were transferred to theatre without premedication and anaesthesia was induced with intravenous thiopentone, vecuronium and alfentanil. Thiopentone was given to a steep dose (2.5–3.8 mg·kg⁻¹). Vecuronium was given as a bolus dose of 100 µg·kg⁻¹ and then as bolus doses of 50 µg·kg⁻¹ to maintain paralysis throughout the operation. Alfentanil was given as an initial bolus dose of 100 µg·kg⁻¹ and continued throughout the operation as an infusion of 1 µg·kg⁻¹ per min.

Following induction and intubation of the trachea, artificial ventilation using an air/oxygen mixture, with a fresh inspired oxygen concentration of 46% and tidal volume of 10 ml·kg⁻¹ was commenced. Anaesthesia was maintained with either propofol or isoflurane. All patients were to receive both agents one after the other, but the order that the agents were given was randomly assigned and the agents were crossed over during the surgery.

Isoflurane was given at a dose of 0.5 to 1 minimal alveolar concentration (MAC) by vaporiser, which had been previously calibrated, and the levels were continuously measured in inspired and expired gases (Datex Capnomac). A steady state of isoflurane was confirmed by identical concentrations of isoflurane in inspired and expired gases, and this concentration was then maintained for at least 15 min prior to any measurements being obtained. If it was given as the first agent the isoflurane dose was adjusted within the range 0.5–1.0 MAC until satisfactory anaesthesia was achieved, this dose was then used as maintenance. If given as the second agent the dose was increased until the MAC was equivalent to the propofol MIR dose (see below).

Propofol was infused using an Ohmeda 9000 infusion pump (8). The rate of infusion was controlled using a Pison II computer which varied the rate of infusion to allow predicted steady state plasma concentrations of propofol. The computer prediction of plasma concentration of propofol is based on a three compartment kinetic model for the drug taking into account the patient's age and weight; the accuracy of the prediction has previously been well described (9). The plasma concentration was related to the minimal infusion rate (MIR) of propofol and the dose was adjusted within the range 0.5 to 1.0 MIR until satisfactory anaesthesia was achieved, if it was given as the first agent; or the dose was increased until the MIR was equivalent to the isoflurane MAC dose (see above) if it was given as the second agent.

In this way all patients received both agents during the course of the anaesthesia for surgery. Measurements of cardiovascular parameters were only made when a steady state was achieved. Once the measurements had been made the second agent was slowly substituted for the first to maintain anaesthesia, and the first agent was discontinued. A suitable washout time allowed the first agent to be eliminated and a steady state of the second agent was then achieved as described above. This cross-over technique took a minimum of 1.5 h to perform.

Throughout the study anaesthesia was judged to be satisfactory on the basis of an aggregate of clinical signs used daily to monitor and control the depth of anaesthesia (10). The patients had to have a heart rate less than 15% above control and a systolic blood pressure less than 15% above control, as well as no evidence of sweating or tears. The first agent was adjusted in the range 0.5–1.0 MAC/MIR to achieve this result.

In the first period of anaesthesia hetastarch solution (Hespan, DuPont UK, Ltd) was infused to maintain systolic arterial pressure in the range 100–120 mmHg and the right atrial pressure (RAP) at this time was recorded. This RAP became the target for fluid management thereafter, with hetastarch solution being used. Blood products were not transfused until after the second set of measurements had been recorded. Continuous ECG and pressure recordings were performed during the operation (Datex Cardiocap, Helsinki, Finland).

When an appropriate MAC or MIR had been achieved and the patient was considered stable for at least 15 min by the observation of sympathetic responses, heart rate and blood pressure, as discussed above, the following parameters were recorded: dose of isoflurane or propofol, heart rate, systolic, diastolic and mean arterial pressure, systolic, diastolic and mean pulmonary artery pressure, right atrial pressure, pulmonary artery occlusion pressure, cardiac output, stroke volume, right ventricular ejection fraction, right ventricular end-diastolic volume, right ventricular end-systolic volume, right and left ventricular stroke work, arterial saturation, end-tidal CO₂. After these measurements had been obtained the patient was maintained with the same anaesthetic for at least a further 5 min to ensure that there was no change in any of the parameters during the period that data was recorded. The operator of the cardiac output computer was blinded to the anaesthetic technique. Appropriate parameters were indexed to body surface area.

Statistical analysis

Results are presented as mean ± s.e. for each anaesthetic agent. As has been suggested for the analysis of two-period cross-over clinical trials, the data was compared by t-test to assess both treatment differences and the importance of a period effect (11). Significance was taken as P<0.05.

RESULTS

Ten consecutive patients having vascular reconstructive surgery were studied. Their demographic details are shown in Table 1 and operative details in Table 2. No patients had to be withdrawn from the study and full measurement sets were obtained on all patients. There were no untoward side-effects of either type of anaesthesia, in particular there were no dysrhythmias.

All patients could be satisfactorily anaesthetised according to our criteria during anaesthesia with the first agent. After crossover to the second agent, which was set to be given at the same numerical value of MAC or MIR as the first, all patients remained satisfactorily anaesthetised. There were no significant differences in heart rate, systolic, diastolic and mean arterial pressure, systolic, diastolic and mean pulmonary artery pressure, right atrial pressure, pulmonary artery occlusion pressure, arterial oxygen saturation or end-tidal CO₂ for the two agents (Table 3).

There were, however, significant differences in cardiac output, cardiac index and stroke volume and the parameters of right ventricular function: RVEF, RVEDV and RVESV during anaesthesia with the two agents (Table 4). The changes in cardiac index and right ventricular ejection fraction for the individual patients are shown in Fig. 1 and 2, only one patient showed a fall in cardiac index and right ventricular
### Table 1
Details of the patients.

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>ASA</th>
<th>Comcomitant disease process</th>
<th>Pre-operative cardiovascular drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>62</td>
<td>III</td>
<td>Peripheral vascular disease</td>
<td>captopril</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>51</td>
<td>III</td>
<td>Peripheral vascular disease, hypertension</td>
<td>nifedipine</td>
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<tr>
<td>3</td>
<td>58</td>
<td>49.5</td>
<td>III</td>
<td>Peripheral vascular disease</td>
<td>none</td>
</tr>
<tr>
<td>4</td>
<td>77</td>
<td>70</td>
<td>III</td>
<td>Peripheral vascular disease, previous myocardial infarction, hypertension</td>
<td>frusemide, amiloride</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>F</td>
<td>50</td>
<td>Peripheral vascular disease, diabetes, previous cerebral vascular accident</td>
<td>frusemide, amiloride</td>
</tr>
<tr>
<td>6</td>
<td>83</td>
<td>M</td>
<td>58</td>
<td>Peripheral vascular disease</td>
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</tr>
<tr>
<td>7</td>
<td>36</td>
<td>M</td>
<td>70</td>
<td>Bentham's disease</td>
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</tr>
<tr>
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<td>56</td>
<td>M</td>
<td>74</td>
<td>Peripheral vascular disease</td>
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</tr>
<tr>
<td>9</td>
<td>62</td>
<td>M</td>
<td>60</td>
<td>Peripheral vascular disease, diabetes, hypertension</td>
<td>none</td>
</tr>
<tr>
<td>10</td>
<td>83</td>
<td>M</td>
<td>79</td>
<td>Peripheral vascular disease</td>
<td>none</td>
</tr>
</tbody>
</table>

### Table 2
Details of the operations*.

<table>
<thead>
<tr>
<th>Operation</th>
<th>Operation time (hr)</th>
<th>First agent</th>
<th>MIR of propofol</th>
<th>MAC of isoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Ext Iliac A. to Peroneal A. PTFE graft, Vein patch x 2</td>
<td>6.5</td>
<td>Isoflurane</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>2 Exploration of Femoral A. aneurysm with vein patch</td>
<td>2.5</td>
<td>Propofol</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>3 Ext Iliac A. to Peroneal A. PTFE graft, Vein patch x 2</td>
<td>4.5</td>
<td>Propofol</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>4 Sup Femoral A. to Peroneal A. RSV graft</td>
<td>5.0</td>
<td>Propofol</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>5 Sup Femoral A. to Peroneal A. RSV graft</td>
<td>4.0</td>
<td>Isoflurane</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>6 Common Femoral A. to ant Tibial A. PTFE graft</td>
<td>5.0</td>
<td>Isoflurane</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>7 Exploration of post Tibial A. distal graft not possible</td>
<td>2.0</td>
<td>Propofol</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>8 Aorto-bifemoral graft to Sup Femoral A. PTFE graft</td>
<td>3.5</td>
<td>Isoflurane</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>9 Femoral A. to ant Tibial A. RSV graft</td>
<td>6.0</td>
<td>Isoflurane</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>10 Femoral A. to low Poplitical A. PTFE graft with vein patch</td>
<td>3.5</td>
<td>Propofol</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* Abbreviations used: Ext = external, Int = internal, Sup = superficial, Ant = anterior, Post = posterior, A = artery, RSV = reversed saphenous vein. PTFE = polytetrafluoroethylene.

Ejection fraction while anaesthetised with propofol. Analysis of the influence of whether propofol or isoflurane may have caused a period effect (11) by being given first showed no evidence that this affected the results.

### DISCUSSION
Our study has demonstrated that at equivalent anaesthetic doses, propofol anaesthesia results in higher cardiac index, stroke volume index and right ventricular ejection fraction than isoflurane. Propofol also leads to higher right ventricular end-diastolic volume index compared to isoflurane. Propofol has previously been shown to influence the right ventricular pressure-volume relationship reflecting a negative effect on right ventricular function compared to the awake state (12), and propofol has been shown in a recent presentation to significantly increase cardiac index and to increase right ventricular end-diastolic volume but without change in right ventricular ejection fraction (13). It is known also that inhalational agents cause a dose-related reduction in cardiac output (14). There are, however, no previously published results on the effects of isoflurane or other inhalational anaesthetics on right ventricular function, and comparisons between anaesthetic agents, particularly those between an intravenous and an inhalational agent, have not been made.

The mechanisms which lead to the different effects of propofol and isoflurane are, however, unclear. Our data show that at identical right ventricular filling pressures propofol anaesthesia results in greater right ventricular end-diastolic volume, showing an increase in diastolic compliance with propofol. Propofol is known to cause relaxation of isolated arteries and veins (15, 16) and our study shows that the same effect seems to occur in the right ventricle. The greater stroke volume and right ventricular ejection fraction seen with propofol might be as a result of greater ventricular wall stretch, as the end-diastolic volume is greater, or of a less negatively inotropic action than isoflurane, or...
Table 3
No significant differences are seen in routine haemodynamic parameters between the periods of propofol and isoflurane anaesthesia.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Propofol (n = 10)</th>
<th>Isoflurane (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right atrial pressure (mmHg)</td>
<td>8.4 ± 0.8</td>
<td>8.4 ± 0.8</td>
</tr>
<tr>
<td>Pulse rate (bpm)</td>
<td>68.2 ± 4.0</td>
<td>67.9 ± 4.2</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>117.7 ± 6.8</td>
<td>106.9 ± 8.7</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>57.8 ± 2.5</td>
<td>55.1 ± 3.2</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>79.6 ± 4.1</td>
<td>73.6 ± 4.8</td>
</tr>
<tr>
<td>Systolic pulmonary artery pressure (mmHg)</td>
<td>32.3 ± 2.8</td>
<td>31.6 ± 3.2</td>
</tr>
<tr>
<td>Diastolic pulmonary artery pressure (mmHg)</td>
<td>14.9 ± 1.7</td>
<td>15.2 ± 2.0</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mmHg)</td>
<td>22.3 ± 1.8</td>
<td>22.2 ± 2.2</td>
</tr>
<tr>
<td>Pulmonary artery occlusion pressure (mmHg)</td>
<td>11.4 ± 1.7</td>
<td>11.6 ± 1.5</td>
</tr>
<tr>
<td>Systemic vascular resistance index (dyne. sec·cm⁻¹·m⁻²)</td>
<td>2214 ± 203</td>
<td>2279 ± 264</td>
</tr>
<tr>
<td>Pulmonary vascular resistance index (dyne. sec·cm⁻¹·m⁻²)</td>
<td>343 ± 36</td>
<td>373 ± 52</td>
</tr>
<tr>
<td>Fractional inspired oxygen concentration (%)</td>
<td>46.4 ± 2.0</td>
<td>46.1 ± 2.0</td>
</tr>
<tr>
<td>Arterial oxygen saturation (%)</td>
<td>98.7 ± 0.3</td>
<td>98.6 ± 0.5</td>
</tr>
<tr>
<td>End tidal CO₂ concentration (%)</td>
<td>3.9 ± 0.12</td>
<td>3.9 ± 0.10</td>
</tr>
</tbody>
</table>

Table 4
Significant differences in cardiac function and particularly right ventricular function in the periods of propofol and isoflurane anaesthesia.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Propofol (n = 10)</th>
<th>Isoflurane (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output (l·min⁻¹)</td>
<td>4.5 ± 0.49**</td>
<td>4.0 ± 0.36</td>
</tr>
<tr>
<td>Cardiac index (l·min⁻¹·m⁻²)</td>
<td>2.7 ± 0.20**</td>
<td>2.4 ± 0.16</td>
</tr>
<tr>
<td>Stroke volume index (ml·m⁻²)</td>
<td>39.6 ± 2.2**</td>
<td>35.4 ± 2.1</td>
</tr>
<tr>
<td>Right ventricular ejection fraction (%)</td>
<td>39.4 ± 3.2*</td>
<td>35.1 ± 3.2</td>
</tr>
<tr>
<td>End diastolic volume index (ml·m⁻²)</td>
<td>110 ± 10.1**</td>
<td>102 ± 4</td>
</tr>
<tr>
<td>End systolic volume index (ml·m⁻²)</td>
<td>70.6 ± 10.9</td>
<td>67.0 ± 10.8</td>
</tr>
</tbody>
</table>

both. Although no significant difference in pulmonary or systemic vascular resistance was seen in our study, the slightly lower values seen with propofol than with isoflurane may have contributed to the higher stroke volume. It is not possible from the data in our study to draw specific conclusions about diastolic function of the left ventricle under propofol or isoflurane anaesthesia.

The comparison of the effect of propofol and isoflurane in our study relies on the assumption that equivalent anaesthetic doses of propofol and isoflurane were given and the other factors remained constant. Assessing the equivalent anaesthetic dose of a volatile and an intravenous agent is difficult and there are no universally accepted criteria. In our study we set a number of clinical criteria that had to be met for anaesthesia to be judged satisfactory. These criteria were adapted from previous authors (10, 17), and are commonly used in daily clinical anaesthetic practice. Although such clinical criteria have many limitations...
they represent a practical solution for assessing anaesthesia, and have been shown to give as much information as more complicated measurements of the depth of anaesthesia (17). Neither heart rate nor recorded pressures were significantly different with the different anaesthetics demonstrating that equivalent anaesthetic doses were indeed given. Other investigators have suggested that MAC and MIR are comparable (18), indeed that was the reason for defining MIR in the first place (19). We are not aware of previously documented evidence to show that fractions or multiples of MAC and MIR are equivalent, although intuitively they should be. We have shown that by the criteria defined in our study for measurement of depth and effect of anaesthesia the patients were similarly anaesthetised for equivalent fractions of MAC and MIR. As well as confirming that patients were anaesthetised to a similar depth in both limbs of our crossover study, or data further suggest that anaesthetic agents at equivalent fractions of MAC and MIR can be directly compared.

The cross over design of our study does not seem to have been used previously in anaesthetic research; a long and generally haemodynamically stable operation is required, and one in which it can be considered ethical to perform invasive monitoring. We chose to study patients having reconstructive peripheral vascular surgery as these operations take a long time, characteristically 2 to 3 h, during which there is minimal cardiovascular disturbance from the surgery itself. The patients are elderly and have proven or suspected coronary artery disease and limitation of myocardial and/or respiratory function and are therefore the type of patient where invasive monitoring and maintaining an elevated cardiac output has been shown to reduce both mortality and morbidity (8–6).

Fluid loading can clearly affect cardiac index and ventricular function (20), and fall in cardiac preload might be the mechanism of reduction in cardiac output following anaesthesia with propofol in man (2, 3, 21), although not all studies have found this effect to be as important (22). We therefore titrated fluids to a fixed RAP as we were interested in looking at cardiac effects and not the effects of changes in right ventricular filling pressures. We chose RAP as opposed to PCWP because we were investigating right ventricular function and were therefore concerned that the right-sided filling pressure should remain constant allowing other parameters, such as end-diastolic volume, to change as a result of varying drug treatment. Furthermore in clinical anaesthesia RAP is more commonly and easily measured than either PCWP, and our results might therefore be of more widespread relevance. In this study we also have excluded the effects that changes in other pharmacological agents may have on right ventricular function. We did not give nitrous oxide which may have cardiac effects itself and might potentiate any effects of propofol (2, 22), and analgesia was provided by alfentanil infusion which has been found not to increase the negative inotropic effects of anaesthetic agents (23).

In our study we have directly compared the cardiovascular and right ventricular effects of the propofol and isoflurane. We have shown, in a cross over within patient study, that for equivalent degrees of anaesthesia cardiovascular function is better maintained with propofol than isoflurane. We have also shown that multiples of MAC and MIR are comparable in the patients studied.

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Division of Vascular Surgery, St George's Hospital, London, UK for allowing us to study their patients and The Medical Statisticians, The Department of Public Health Medicine, St George's Hospital Medical School, London, UK for statistical advice.

REFERENCES

12. Martin C, Saux P, Albanese J, Eon B, Goudin F. Right ventricu-


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### 10.12 Abbreviations used in the text

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>Cardiac Index</td>
</tr>
<tr>
<td>DO$_2$I</td>
<td>Oxygen delivery</td>
</tr>
<tr>
<td>VO$_2$I</td>
<td>Oxygen consumption</td>
</tr>
<tr>
<td>pHi</td>
<td>Intramucosal gastric pH</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>MODS</td>
<td>Multiple organ dysfunction syndrome</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>SV</td>
<td>Stroke Volume</td>
</tr>
<tr>
<td>PA</td>
<td>Pulmonary Artery</td>
</tr>
<tr>
<td>CVP</td>
<td>Central Venous Pressure</td>
</tr>
<tr>
<td>PAOP</td>
<td>Pulmonary Artery Occlusion Pressure</td>
</tr>
<tr>
<td>SVR</td>
<td>Systemic Vascular Resistance</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anesthesiology</td>
</tr>
<tr>
<td>MOF</td>
<td>Multiple Organ Failure</td>
</tr>
<tr>
<td>SIRS</td>
<td>Systemic Inflammatory Response Syndrome</td>
</tr>
<tr>
<td>APACHE</td>
<td>Acute Physiology and Chronic Health Evaluation</td>
</tr>
<tr>
<td>POSSUM</td>
<td>Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>NF</td>
<td>Nuclear Factor</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumour Necrosis Factor</td>
</tr>
<tr>
<td>FT&lt;sub&gt;c&lt;/sub&gt;</td>
<td>Corrected Flow Time</td>
</tr>
<tr>
<td>P&lt;sub&gt;T&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Tissue Oxygen</td>
</tr>
<tr>
<td>P&lt;sub&gt;te&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Cutaneous Tissue Oxygen</td>
</tr>
<tr>
<td>P&lt;sub&gt;T&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Tissue Carbon Dioxide</td>
</tr>
<tr>
<td>pgCO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>pCO&lt;sub&gt;2&lt;/sub&gt; gap, Mucosal – arterial pCO&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>CO</td>
<td>Cardiac output</td>
</tr>
<tr>
<td>CaO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Arterial Oxygen Content</td>
</tr>
<tr>
<td>BSA</td>
<td>Body Surface Area</td>
</tr>
</tbody>
</table>
CvO\(_2\) - Venous Oxygen Content  
SaO\(_2\) - Arterial Oxygen Saturation  
SvO\(_2\) - Mixed Venous (Pulmonary Artery) Oxygen Saturation  
Hb - Haemoglobin  
PaO\(_2\) - Partial Pressure of Arterial Oxygen  
ScvO\(_2\) - Central Venous (Superior Vena Cava) Oxygen Saturation  
ARDS - Adult Respiratory Distress Syndrome  
NIRS - Near Infra-Red Spectroscopy  
TEB - Transthoracic Electrical Bioimpedance

10.13 Acknowledgments

During the three and a half years of the research my supervisors Dr David Bennett and Dr Michael Grounds gave invaluable encouragement and advice and were a constant spur to improve the methods and presentation of the work. Various other colleagues have contributed to some of the studies and their role is mentioned in the individual papers. All patient studies received approval from the Ethics Committee at St George’s Hospital, London, where the studies were conducted and patients gave informed consent as appropriate. During much of the time that the research was being undertaken I was sponsored by a grant from Fisons (UK) plc.
11. References


72. Kirkpatrick, C.J., et al., *The role of the microcirculation in multiple organ
dysfunction syndrome: a review and perspective.* Virchows Archiv, 1996. 427:
p. 461-476.
73. Nuytinck, H.K., et al., *Whole body inflammation in trauma patients: an autopsy
74. Granger, D.N., *Role of xanthine oxidase and granulocytes in ischemia-
75. Shoemaker, W.C., P.L. Appel, and H.B. Kram, *Role of oxygen debt in the
development of organ failure, sepsis and death in high risk surgical patients.*
76. Liu, P., et al., *Role of endogenous nitric oxide in TNF-alpha and IL-1beta
77. Wanner, G.A., et al., *Differential effect of anti-TNF-alpha antibody on
proinflammatory cytokine release by Kupffer cells following liver ischemia and
78. Donnahoo, K.K., et al., *Early renal ischemia, with or without reperfusion,
activates NFkappaB and increases TNF-alpha bioactivity in the kidney.* J Urol,
79. Yoshidome, H., et al., *Interleukin-10 inhibits pulmonary NF-kappaB activation
80. Welborn, M.B., et al., *The relationship between visceral ischemia,
proinflammatory cytokines, and organ injury in patients undergoing
7.
81. Bown, M.J., et al., *Cytokines and inflammatory pathways in the pathogenesis of
multiple organ failure following abdominal aortic aneurysm repair.* Eur J Vasc
82. Bown, M.J., et al., *Cytokine gene polymorphisms and the inflammatory
92.

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