Non-invasive Cardio-haemodynamic
Assessment in Adult Emergency Department
Patients with Sepsis

Thesis submitted for degree of
Doctor of Medicine at the University of Leicester

by

Christiane Vorwerk
Department of Cardiovascular Sciences
University of Leicester

February 2011
ABSTRACT

Title: Non-invasive cardio-haemodynamic assessment in adult Emergency Department patients with sepsis.

Author: Christiane Vorwerk

Objective:
To explore the potential benefit of non-invasive cardio-haemodynamic variables in the management of sepsis in the Emergency Department (ED) by measuring their changes with normal treatment and their relationship to outcome.

Methods:
Study 1: Prospective cohort study of a convenience sample of adult ED patients with uncomplicated sepsis. Cardio-haemodynamic parameters were obtained using a Thoracic Electrical Bioimpedance (TEB) device. Study 2: Prospective cohort study of a convenience sample of adult ED patients with severe sepsis / septic shock. Cardio-haemodynamic parameters were obtained using a TEB device, transcutaneous Doppler ultrasound and Near-Infrared Spectroscopy. Measurements for both studies were taken on ED arrival, ED departure and after 24 hours, whilst patients received normal treatment. All patients were followed up for 30 days.

Results:
50 patients were enrolled in study 1 and 73 patients in study 2. Septic patients had a significantly higher cardiac output and significantly lower stroke volume and systemic vascular resistance than non-septic ED controls. After 24 hours of normal treatment cardio-haemodynamic parameters of patients with uncomplicated sepsis and survivors from severe sepsis / septic shock began to normalise. In addition, patients with severe sepsis/septic shock had abnormal tissue oxygen saturation on ED arrival, which, in survivors normalised with treatment.

Conclusion:
This is the first description of cardio-haemodynamic parameters in septic patients at their entry to hospital (ED). Septic patients have initially abnormal haemodynamics and the ability to normalise haemodynamics and tissue oxygen saturation is associated with good outcome. This thesis has identified a number of parameters, which warrant validation to define their role as diagnostic or co-diagnostic biomarkers for sepsis and sepsis outcome.
ACKNOWLEDGEMENTS

I wish to express my sincerest gratitude to Professor Tim Coats, Professor of Emergency Medicine, University of Leicester, for his encouragement and skilful supervision of my work. His extensive discussions concerning my work made my MD experience both productive and stimulating.

In addition, I wish to thank Professor Bryan Williams, Professor of Medicine, University of Leicester, for his comments on my thesis.

I would like to express my thanks to the College of Emergency Medicine for supporting my MD work with a research grant.

I am grateful to the nursing and medical staff in the Emergency Department of the Leicester Royal Infirmary for their support, particularly during the recruitment phase.

I also wish to express my gratitude to Sarah Sutton, Clinical Librarian, Leicester Royal Infirmary, for her unstinting assistance with obtaining countless numbers of papers relevant to my thesis.

I wish to thank Suzanne Rafelt, Medical Statistician, for her assistance with the sample size calculations and Janet Harris for her help with the financial aspects of this research project.

Lastly, and most importantly I wish to express my sincere gratitude to Antony, my husband, and Hannah, our daughter. If it were not for their unconditional support and encouragement, this work would have been so much more difficult to complete.
Dedicated to my little girl,

Hannah.
CONTRIBUTORSHIP

I conceived the idea for the MD project, conducted the literature review, designed the studies, prepared Ethics applications and attended the Ethics Committee meetings; managed the research projects, undertook the recruitment, data acquisition, data analysis, interpretation of findings and wrote the thesis.

Professor Tim Coats supervised the MD project from the preliminary to the final stage, provided advice on study design and Ethics application, attended Ethics Committee meetings, provided guidance on the structure of the thesis and reviewed and constructively commented on the thesis.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>ii</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>iii</td>
</tr>
<tr>
<td>CONTRIBUTORSHIP</td>
<td>v</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>vi</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>xiii</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>xvi</td>
</tr>
<tr>
<td>LIST OF EQUATIONS</td>
<td>xviii</td>
</tr>
<tr>
<td>ABBREVIATIONS AND ACRONYMS</td>
<td>xix</td>
</tr>
<tr>
<td>GLOSSARY OF TERMS</td>
<td>xxii</td>
</tr>
<tr>
<td>1  INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>1.1 Opening Remarks</td>
<td>1</td>
</tr>
<tr>
<td>1.2 Epidemiology of sepsis</td>
<td>4</td>
</tr>
<tr>
<td>1.3 Standards of care for patients with sepsis</td>
<td>6</td>
</tr>
<tr>
<td>1.3.1 Improving care for septic patients</td>
<td>6</td>
</tr>
<tr>
<td>1.3.2 Sepsis bundles</td>
<td>10</td>
</tr>
<tr>
<td>1.4 Pathophysiological concept of sepsis</td>
<td>14</td>
</tr>
<tr>
<td>1.5 Sepsis and the cardiovascular system</td>
<td>15</td>
</tr>
<tr>
<td>1.5.1 Cardiovascular Physiology</td>
<td>15</td>
</tr>
<tr>
<td>1.5.2 Cardiovascular involvement in sepsis</td>
<td>19</td>
</tr>
<tr>
<td>1.6 Non-invasive cardio-haemodynamic monitoring</td>
<td>22</td>
</tr>
</tbody>
</table>
2 METHODOLOGY .............................................................................................. 46

2.1 Research Setting ......................................................................................... 46

2.2 Study 1 – Assessment of cardio-haemodynamic parameters in adult
Emergency Department patients with uncomplicated sepsis ......................... 47

2.2.1 Study design and population ..................................................................... 47

2.2.2 Study 1 – Objective 1  Comparison of TEB cardio-haemodynamic
parameters between septic and non-septic ED patients ............................ 51

2.2.3 Study 1 – Objective 2  Change of TEB cardio-haemodynamic
parameters in septic patients during normal treatment in the ED ........ 52

2.2.4 Study 1 – Objective 3  Change of TEB cardio-haemodynamic
parameters in septic ED patients after a 24-hour period of treatment ... 53

2.2.5 Study 1 – Objective 4  Relationship between changes in TEB
cardio-haemodynamic parameters and changes in conventional
MAP and HR in septic patients ......................................................................... 53

2.3 Study 2 – Assessment of cardio-haemodynamic parameters and tissue
oxygen saturation in adult Emergency Department patients with severe
sepsis or septic shock ....................................................................................... 54

2.3.1 Study design and population ..................................................................... 54
2.3.2 Study 2 – Objective 1  Comparison of cardio-haemodynamic parameters in ED patients with severe sepsis/septic shock and non-septic ED patients ................................................................. 60

2.3.3 Study 2 – Objective 2  Change of cardio-haemodynamic parameters with normal treatment during the stay in the ED and after 24 hours ..... 61

2.3.4 Study 2 – Objective 3  Relationship between cardio-haemodynamic parameters in patients with severe sepsis/septic shock and outcome ... 62

2.3.5 Study 2 – Objective 4  Relationship between TEB cardio-haemodynamic parameters and conventional heart rate and mean blood pressure ................................................................. 63

2.3.6 Study 2 – Objective 5  Comparison of simultaneous TEB and transcutaneous Doppler ultrasound cardio-haemodynamic measurements ................................................................. 64

2.3.7 Study 2 – Objective 6  Determining tissue oxygen saturation in patients with severe sepsis or septic shock; its change with normal treatment and relationship to outcome ........................................ 65

2.4 Data acquisition using non-invasive modalities ............................................. 66

2.4.1 Thoracic Electrical Bioimpedance (TEB) .................................................. 66

2.4.2 Transcutaneous Doppler Ultrasound ...................................................... 70

2.4.3 NIRS tissue oxygen saturation ($StO_2$) ................................................. 73

2.5 Ethics & Consent .................................................................................. 75

2.5.1 Ethical approval ............................................................................. 75

2.5.2 Consent procedure ......................................................................... 75

2.5.3 Adverse events monitoring .............................................................. 77

2.5.4 Data protection .............................................................................. 77
3 RESULTS ............................................................................................................. 79

3.1 STUDY 1 – Assessment of cardio-haemodynamic parameters in adult
Emergency Department patients with uncomplicated sepsis ................. 79

3.1.1 General ............................................................................................................. 79

3.1.2 Study 1 – Results – Objective 1 Comparison of TEB cardio-
haemodynamic parameters between septic and non-septic
ED patients ........................................................................................................ 81

3.1.3 Study 1 – Results – Objective 2 Change of TEB cardio-
haemodynamic parameters in septic patients with normal treatment
in the ED ........................................................................................................... 85

3.1.4 Study 1 – Results – Objective 3 Change of TEB cardio-
haemodynamic parameters in septic ED patients after a 24-hour
period of treatment .................................................................................... 87

3.1.5 Study 1 – Results – Objective 4 Relationship between changes
in TEB parameters and changes in MAP and HR in patients with
uncomplicated sepsis ................................................................................... 90

3.2 STUDY 2 – Assessment of cardio-haemodynamic parameters and
tissue oxygen saturation in adult ED patients with severe sepsis or
septic shock .................................................................................................... 93

3.2.1 General ............................................................................................................. 93

3.2.2 Study 2 – Results – Objective 1 Comparison of cardio-
haemodynamic parameters in Emergency Department patients with
severe sepsis or septic shock and non-septic ED patients ................. 98

3.2.3 Study 2 – Results – Objective 2 Change of cardio-haemodynamic
parameters in severe sepsis / septic shock patients with normal
treatment in the ED and after 24 hours ................................................ 103
3.2.4  Study 2 – Results – Objective 3  
Comparison of cardio-haemodynamic parameters in survivors and non-survivors from severe sepsis or septic shock

3.2.5  Study 2 – Results – Objective 4  
Relationship between TEB cardio-haemodynamic and conventional parameters

3.2.6  Study 2 – Results – Objective 5  
Comparison of simultaneous TEB and Doppler ultrasound cardio-haemodynamic measurements

3.2.7  Study 2 – Results – Objective 6  
Assessment of tissue oxygen saturation in severely septic ED patients; its change with normal treatment and relationship to outcome

4  DISCUSSION

4.1  To determine whether patients with sepsis have abnormal cardio-haemodynamic parameters on arrival in the ED compared with normal controls

4.2  To determine whether abnormal cardio-haemodynamic parameters normalise with treatment

4.2.1  Change of cardio-haemodynamic parameters in septic ED patients with normal treatment in the ED

4.2.2  Change of cardio-haemodynamic parameters in septic ED patients after 24 hours of normal treatment

4.3  To determine whether the degree of initial abnormality is related to outcome

4.3.1  Comparison of initial cardio-haemodynamic parameters in survivors and non-survivors from severe sepsis / septic shock

4.3.2  Comparison of initial tissue oxygen saturation (StO₂) in survivors and non-survivors
4.4 To determine whether normalisation of cardio-haemodynamic parameters with treatment is related to outcome ................................................ 164

4.4.1 Comparison of cardio-haemodynamic parameters following normal treatment in survivors and non-survivors from severe sepsis or septic shock ................................................................. 164

4.4.2 Comparison of change in tissue oxygen saturation following normal treatment in survivors and non-survivors ................................. 167

4.5 To determine which non-invasive monitoring modality is most strongly related to outcome ........................................................................ 170

5 CONCLUSIONS ................................................................................................ 174

5.1 Research findings .............................................................. ............................................................ 174

5.2 Limitations ....................................................................................................................... 180

5.2 The next stage ......................................................................................................................... 182

6 REFERENCES ...................................................................................................................... 184

APPENDICES .................................................................................................................... 212

Appendix 1. Applying research methodology in the acute setting ............... 212

Appendix 2. Patient Entry Form .......................................................... ........................................ 215

Appendix 3. TEB parameters measured in this thesis ..................................................... 216

Appendix 4. Doppler parameters measured in this thesis ............................................. 217

Appendix 5. Ethics approval – Study 1 .......................................................... ........................................ 218

Appendix 6. R&D approval – Study 1 ..................................................................................... 220

Appendix 7. Ethics approval – Study 2 ..................................................................................... 222

Appendix 8. R&D approval – Study 2 ..................................................................................... 225
Appendix 9.  Verbal Prompts................................................................. 227
Appendix 10.  Summary Information Leaflet .................................... 228
Appendix 11.  Patient Information Leaflet (study group) ..................... 229
Appendix 12.  Consultee Information leaflet ..................................... 231
Appendix 13.  Patient Information Leaflet (control group) .................... 233
Appendix 14.  Consent Form – Study 2 ............................................. 235
Appendix 15.  MD related / derived publications /presentations ............. 236
<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Protocol for Early Goal-Directed Therapy</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>Sepsis Resuscitation Bundle</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>Sepsis Six</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>Determinants of stroke volume</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>Transmitted and sensing current pathway</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>ECG and impedance waveforms</td>
<td>26</td>
</tr>
<tr>
<td>7</td>
<td>Electrode configuration</td>
<td>31</td>
</tr>
<tr>
<td>8</td>
<td>Principle of tissue oxygenation measurement</td>
<td>42</td>
</tr>
<tr>
<td>9</td>
<td>Niccomo™ monitor</td>
<td>67</td>
</tr>
<tr>
<td>10</td>
<td>Sensor and electrode positioning</td>
<td>68</td>
</tr>
<tr>
<td>11</td>
<td>USCOM interface and transducer</td>
<td>70</td>
</tr>
<tr>
<td>12</td>
<td>Transducer placement at the suprasternal notch (aortic window)</td>
<td>71</td>
</tr>
<tr>
<td>13</td>
<td>Transducer placement left sternal edge (pulmonary window)</td>
<td>71</td>
</tr>
<tr>
<td>14</td>
<td>Example of optimal aortic valve Doppler profil</td>
<td>72</td>
</tr>
<tr>
<td>15</td>
<td>InSpectra™ tissue oxygenation monitor(^{136})</td>
<td>73</td>
</tr>
<tr>
<td>16</td>
<td>Sensor position on thenar eminence(^{127})</td>
<td>74</td>
</tr>
<tr>
<td>17</td>
<td>Flow diagram of study population</td>
<td>80</td>
</tr>
<tr>
<td>18</td>
<td>ROC curves for cardiac index, stroke index and systemic vascular resistance (ED arrival)</td>
<td>84</td>
</tr>
<tr>
<td>19</td>
<td>Comparison of cardiac output, stroke volume and systemic vascular resistance in septic patients on ED arrival, ED departure, at 24 hour with non-septic controls</td>
<td>89</td>
</tr>
<tr>
<td>20</td>
<td>Relationship between changes in cardio-haemodynamic and conventional parameters in septic patients with 24 hours of normal treatment</td>
<td>92</td>
</tr>
<tr>
<td>21</td>
<td>Flow diagram of study population</td>
<td>94</td>
</tr>
</tbody>
</table>
Figure 22. Number of deaths in relation to length of survival since arrival in the ED ................................................................. 97

Figure 23. Probability of survival from sepsis with organ dysfunction over time .... 97

Figure 24. ROC curves for stroke index, stroke volume, systemic vascular resistance and thoracic fluid content (ED arrival) ...................... 102

Figure 25. Differences in cardiac output, stroke volume and thoracic fluid content in severely septic patients between measurement taken on ED arrival, departure and at 24 hour follow up; compared with control ............... 108

Figure 26. Patterns of cardio-haemodynamic parameters of survivors and non-survivors ........................................................................................................ 119

Figure 27. Receiver operating characteristics curve for cardiac output (ED arrival) ........................................................................................................ 121

Figure 28. Receiver operating characteristics curves for LVET and ETR (ED departure) ........................................................................................................ 122

Figure 29. ROC curves for stroke volume, stroke index, heart rate and left ventricular ejection time (at 24 hours) ......................................................... 123

Figure 30. Patterns of cardio-haemodynamic and conventional parameters in patients with severe sepsis or septic shock ........................................ 130

Figure 31. Chronological patterns of TEB and USCOM parameters .................. 133

Figure 32. Relationship between paired TEB and USCOM cardiac output, stroke volume and heart rate measurements presented as Scatter and Bland-Altman plots .................................................................................. 135

Figure 33. Changes in StO$_2$ in early and late non-survivors and survivors with short and long hospital stay ................................................................. 138

Figure 34. Changes in StO$_2$ and SpO$_2$ in survivors and non-survivors during the first 24 hours .................................................................................... 140

Figure 35. Relationship between StO$_2$ and SpO$_2$ on arrival and departure from the ED ........................................................................................................ 141
Figure 36. Physiological derangements in septic patients on ED arrival compared to controls........................................................................................................ 144

Figure 37. Physiological parameters after 24 hours of treatment compared to controls ................................................................................................................. 155

Figure 38. Physiological state of survivors and non-survivors on ED arrival compared to controls................................................................. 159

Figure 39. Physiological state of survivors and non-survivors after 24 hours of treatment compared to controls................................................................. 165
LIST OF TABLES

Table 1. Correlation between TEB and PAC-TD .......................................................... 29
Table 2. Characteristics of septic and control ED patients ........................................... 81
Table 3. Routine physiological parameters on arrival in ED .................................... 82
Table 4. TEB parameters of septic and non-septic (control) patients on arrival in the ED ..................................................................................................... 83
Table 5. ROC derived values predictive of sepsis ...................................................... 84
Table 6. TEB measurements on arrival and departure from the ED ......................... 86
Table 7. TEB measurements of septic patients on ED arrival and at 24 hour follow up ..................................................................................................... 88
Table 8. Pearson's correlation coefficients for relative changes in TEB cardio- haemodynamic and conventional variables .................................................... 91
Table 9. Characteristics of study participants ............................................................ 95
Table 10. Physiological and biological parameter on arrival in ED ............................ 96
Table 11. Characteristics of study and control group .................................................. 98
Table 12. TEB parameters in severe sepsis/septic shock on ED arrival compared to control .................................................................................................. 99
Table 13. TEB parameters in severe sepsis/shock at 24 follow up compared to controls ................................................................................................. 100
Table 14. ROC derived values predictive of severe sepsis on ED arrival ................. 101
Table 15. TEB measurements of severely septic patients on ED arrival and departure ......................................................................................................... 105
Table 16. TEB measurements in severely septic patients on ED arrival and at 24 hour follow up ..................................................................................... 107
Table 17. Doppler measurements on ED arrival and departure ............................... 109
Table 18. Doppler measurements on Ed arrival and at 24 hour follow up ............... 110
Table 19. Baseline characteristics of survivors and non-survivors .......................... 111
Table 20. Conventional parameters on arrival in the Emergency Department ........... 112
Table 21. TEB measurements of survivors and non-survivors on ED arrival............. 114
Table 22. TEB measurements of survivors and non-survivors on ED departure ....... 115
Table 23. TEB measurements of survivors and non-survivors at 24 hour follow-up ................................................................. 116
Table 24. Area under the ROC curve for TEB parameters ..................................... 120
Table 25. ROC derived values predictive of survival at 24 hours .............................. 124
Table 26. Doppler measurements of survivors and non-survivors on ED arrival .... 125
Table 27. Doppler measurements of survivors and non-survivors on ED departure 126
Table 28. Doppler measurements of survivors and non-survivors at 24 hours ..... 127
Table 29. AUROC values for transcutaneous Doppler parameters ......................... 128
Table 30. Pearson's correlation coefficients for cardio-haemodynamic and conventional variables ......................................................... 131
Table 31. Pearson's correlation coefficients ........................................................... 134
Table 32. Tissue oxygen saturation in survivors and non-survivors from severe sepsis / septic shock ......................................................... 137
Table 33. Area under the ROC curve values for StO₂ and SpO₂ on arrival and departure from the ED ................................................................. 141
Table 34. Pearson's correlation coefficients for StO₂ and haemodynamic variables 142
# LIST OF EQUATIONS

<table>
<thead>
<tr>
<th>Equation</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Oxygen delivery</td>
<td>15</td>
</tr>
<tr>
<td>2.</td>
<td>Cardiac output</td>
<td>15</td>
</tr>
<tr>
<td>3.</td>
<td>Systemic vascular resistance</td>
<td>18</td>
</tr>
<tr>
<td>4.</td>
<td>Ohm’s law</td>
<td>23</td>
</tr>
<tr>
<td>5.</td>
<td>Impedance (1)</td>
<td>23</td>
</tr>
<tr>
<td>6.</td>
<td>Volume of cylinder</td>
<td>24</td>
</tr>
<tr>
<td>7.</td>
<td>Impedance (2)</td>
<td>24</td>
</tr>
<tr>
<td>8.</td>
<td>Impedance (Thorax)</td>
<td>25</td>
</tr>
<tr>
<td>9.</td>
<td>Stroke volume</td>
<td>27</td>
</tr>
<tr>
<td>10.</td>
<td>Doppler shift of frequency</td>
<td>34</td>
</tr>
<tr>
<td>11.</td>
<td>Volume equation</td>
<td>36</td>
</tr>
<tr>
<td>12.</td>
<td>Stroke volume</td>
<td>36</td>
</tr>
<tr>
<td>13.</td>
<td>Outflow tract area</td>
<td>36</td>
</tr>
</tbody>
</table>
# ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% CI</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>AUROC</td>
<td>Area under the ROC curve</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CaO\textsubscript{2}</td>
<td>Arterial oxygen content</td>
</tr>
<tr>
<td>CI</td>
<td>Cardiac index</td>
</tr>
<tr>
<td>CO</td>
<td>Cardiac output</td>
</tr>
<tr>
<td>CVE</td>
<td>Cerebral vascular event</td>
</tr>
<tr>
<td>CVP</td>
<td>Central venous pressure</td>
</tr>
<tr>
<td>DO\textsubscript{2}</td>
<td>Oxygen delivery</td>
</tr>
<tr>
<td>DPB</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency Department</td>
</tr>
<tr>
<td>EDV</td>
<td>End-diastolic volume</td>
</tr>
<tr>
<td>EGD\textsubscript{T}</td>
<td>Early goal directed therapy</td>
</tr>
<tr>
<td>ESV</td>
<td>End-systolic volume</td>
</tr>
<tr>
<td>ET%</td>
<td>Ejection time percentage</td>
</tr>
<tr>
<td>ETR</td>
<td>Ejection time ratio</td>
</tr>
<tr>
<td>FT</td>
<td>Flow time</td>
</tr>
<tr>
<td>GCS</td>
<td>Glasgow Coma Score</td>
</tr>
<tr>
<td>GI</td>
<td>Gastro-intestinal</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>ICG</td>
<td>Impedance Cardiography</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>ISS</td>
<td>Injury Severity Score</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>LCW</td>
<td>Left cardiac work</td>
</tr>
<tr>
<td>LCWI</td>
<td>Left cardiac work index</td>
</tr>
<tr>
<td>LR-</td>
<td>Negative likelihood ratio</td>
</tr>
<tr>
<td>LR+</td>
<td>Positive likelihood ratio</td>
</tr>
<tr>
<td>LVEDP</td>
<td>Left ventricular end-diastolic pressure</td>
</tr>
<tr>
<td>LVEDV</td>
<td>Left ventricular end-diastolic volume</td>
</tr>
<tr>
<td>LVESV</td>
<td>Left ventricular end-systolic volume</td>
</tr>
<tr>
<td>LVET</td>
<td>Left ventricular ejection time</td>
</tr>
<tr>
<td>LVSWI</td>
<td>Left ventricular stroke work index</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
</tr>
<tr>
<td>MD</td>
<td>Minute distance</td>
</tr>
<tr>
<td>MEDS</td>
<td>Mortality in Emergency Department Sepsis</td>
</tr>
<tr>
<td>MPG</td>
<td>Mean pressure gradient</td>
</tr>
<tr>
<td>NIRS</td>
<td>Near infrared spectroscopy</td>
</tr>
<tr>
<td>NNT</td>
<td>Numbers needed to treat</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>OT</td>
<td>Outflow tract</td>
</tr>
<tr>
<td>PAC-TD</td>
<td>Pulmonary artery catheter thermodilution</td>
</tr>
<tr>
<td>PE</td>
<td>Pulmonary embolus</td>
</tr>
<tr>
<td>PEP</td>
<td>Pre-ejection period</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>QI</td>
<td>Quality indicator</td>
</tr>
<tr>
<td>REC</td>
<td>Research &amp; Ethics Committee</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver operating characteristics</td>
</tr>
<tr>
<td>RR</td>
<td>Respiratory rate</td>
</tr>
<tr>
<td>RVEDP</td>
<td>Right ventricular end-diastolic pressure</td>
</tr>
</tbody>
</table>
ScvO2  Central venous oxygen saturation
SD    Standard deviation
SI    Stroke index
SIRS  Systemic inflammatory response syndrome
SPB   Systolic blood pressure
SpO2  Pulse oximetry oxygen saturation
SSC   Surviving Sepsis Campaign
StO2  Tissue oxygen saturation
SV    Stroke volume
SvO2  Mixed venous oxygen saturation
SVR   Systemic vascular resistance
SVRI  Systemic vascular resistance index
SVV   Stroke volume variation
TEB   Thoracic Electrical Bioimpedance
TFC   Thoracic fluid content
UO    Urine output
USCOM Ultrasonic Cardiac Output Monitor
VO2   Oxygen consumption
VP    Velocity peak
VTI   Velocity time integral
WCC   White cell count
# GLOSSARY OF TERMS

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bias</td>
<td>Reflects a systematic error in the methods or conduct of the study.</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>Cardiac output related to body surface area.</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>Amount of blood pumped by the left ventricle per minute.</td>
</tr>
<tr>
<td>Conductivity</td>
<td>Measure of a tissue’s (material’s) ability to conduct an electric current.</td>
</tr>
<tr>
<td>Confidence Interval (95%)</td>
<td>A range of values around a point estimate that have a 95% probability of including the true value.</td>
</tr>
<tr>
<td>Confounding</td>
<td>Describes an error in the interpretation of findings.</td>
</tr>
<tr>
<td>Correlation Coefficient</td>
<td>Measure of strength of the linear relationship between two variables.</td>
</tr>
<tr>
<td>Cryptic Shock</td>
<td>State of shock with raised lactate and deceptively normal blood pressure.</td>
</tr>
<tr>
<td>Ejection time percentage</td>
<td>Percentage of cycle duration occupied by systolic ejection [aortic valve (AV) opening to closure divided by AV opening to opening x 100].</td>
</tr>
<tr>
<td>Ejection time ratio</td>
<td>Ratio of mechanical systole to heart rate.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Flow time</strong></td>
<td>Equals systolic ejection time.</td>
</tr>
<tr>
<td><strong>Gap analysis</strong></td>
<td>Business resource assessment tool enabling a company to compare its actual with its potential performance.</td>
</tr>
<tr>
<td><strong>Generalisability</strong></td>
<td>Describes the extent to which research findings derived in one setting can be applied to other settings.</td>
</tr>
<tr>
<td><strong>Impedance</strong></td>
<td>Resistance that a system offers to an alternating electrical current.</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>Number of new cases of a disease occurring in a population during a defined time.</td>
</tr>
<tr>
<td><strong>Left cardiac work</strong></td>
<td>Amount of work the left ventricle has to perform per minute to pump blood.</td>
</tr>
<tr>
<td><strong>Left cardiac work index</strong></td>
<td>Left cardiac work related to body surface area.</td>
</tr>
<tr>
<td><strong>Left ventricular ejection time</strong></td>
<td>Time interval between opening and closing of aortic valve (mechanical systole).</td>
</tr>
<tr>
<td><strong>Left ventricular ejection time</strong></td>
<td>Time interval from opening to closing of the aortic valve.</td>
</tr>
<tr>
<td><strong>Likelihood ratio</strong></td>
<td>The probability of a test result being seen in a patient with the disease relative to it being seen in an unaffected patient.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Mean pressure gradient</td>
<td>Presents the pressure gradient across the scanned heart valve.</td>
</tr>
<tr>
<td>Minute distance</td>
<td>The distance a blood cell travels in metres per minute.</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>Proportion of patients with a negative test result who genuinely do not have the disease.</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>Proportion of patients with a positive test who genuinely have the disease.</td>
</tr>
<tr>
<td>Pre-ejection period</td>
<td>Time interval from the onset of electrical stimulation of the ventricle to the opening of the aortic valve (electrical systole).</td>
</tr>
<tr>
<td>Prevalence</td>
<td>Total number of cases of the disease in a population at a given time.</td>
</tr>
<tr>
<td>Relative risk</td>
<td>Risk of an event relative to exposure</td>
</tr>
<tr>
<td></td>
<td>$RR = \frac{\text{Exposure group event rate}}{\text{Non-exposure group event rate}}$</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Proportion of patients with the disease who are correctly identified by the diagnostic test.</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Systemic inflammatory response syndrome triggered by an infection.</td>
</tr>
<tr>
<td>Septic Shock</td>
<td>Sepsis with evidence of organ dysfunction.</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>Proportion of patients without the disease who are correctly identified by the diagnostic test.</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Stroke index</strong></td>
<td>Stroke volume related to body surface area.</td>
</tr>
<tr>
<td><strong>Stroke Volume</strong></td>
<td>Define as the amount of blood ejected from the ventricle during one cardiac contraction.</td>
</tr>
<tr>
<td><strong>Stroke volume variation</strong></td>
<td>Percentage change of stroke volume between a group of beats.</td>
</tr>
<tr>
<td><strong>Systemic vascular resistance</strong></td>
<td>Resistance to the flow in the arterial system.</td>
</tr>
<tr>
<td><strong>Thoracic fluid content</strong></td>
<td>Represents the conductivity of the entire thorax and is an indicator of chest fluid status.</td>
</tr>
<tr>
<td><strong>Velocity Peak</strong></td>
<td>Peak velocity of the measured Doppler profile measured in m/s.</td>
</tr>
<tr>
<td><strong>Velocity time integral</strong></td>
<td>The distance (in cm) a single reflector travels per cycle.</td>
</tr>
</tbody>
</table>
1 INTRODUCTION

1.1 Opening Remarks

Sepsis is a major cause of morbidity and mortality worldwide and remains an ongoing challenge in medicine. Its incidence is steadily rising. Until 1992 there was no clear definition for sepsis and terms such as sepsis, septicaemia, septic syndrome or bacteraemia were used interchangeably.

In 1992 the American College of Chest Physicians and the Society of Critical Care Medicine consensus conference committee defined sepsis as a systemic inflammatory response syndrome (SIRS) triggered by an infection, leading to inadequate tissue oxygenation and organ perfusion. SIRS is manifested by two or more of the following conditions: temperature >38°C or < 36°C, heart rate of > 90 beats per minute, respiratory rate of > 20 breaths per minute or white cell counts of > 12.0 × 10⁹/l or < 4.0 × 10⁹/l. Sepsis associated with dysfunction of one or more organs was defined as severe sepsis. Septic shock is a subset of severe sepsis. It is described as persistent sepsis-induced arterial hypotension (systolic blood pressure < 90 mmHg) with or without tissue hypoperfusion, characterised by lactic acidosis, oliguria or acute alteration in mental status, despite adequate intravenous fluid resuscitation (20mls/kg).

Sepsis is not a distinct disease but a complex dynamic syndrome that forms a continuum of clinical and pathophysiological severity with definable stages along this continuum that adversely affect patient’s outcome. These critical stages are termed severe sepsis and septic shock and are associated with increased mortality.
It took nearly a decade for the sepsis definition to be applied in day-to-day clinical practice. Even though awareness of sepsis has improved, early recognition and instigation of appropriate treatment at the patient’s bedside is still inadequate. Unfortunately, it is not uncommon that the dynamic process of sepsis remains unrecognised until severe sepsis or septic shock has developed.

In 2001 Rivers and colleagues published a randomised controlled trial demonstrating that mortality from sepsis can be significantly reduced if goal-driven resuscitation is commenced as early as in the Emergency Department. This concept is called early-goal-directed therapy (EGDT). It aims to achieve a balance between systemic oxygen delivery and oxygen demands, preventing global tissue hypoxia with subsequent organ failure. EGDT aims for pre-defined endpoints of central venous pressure (CVP), mean arterial pressure (MAP), urine output (UO) and central venous oxygen saturation (ScvO₂). Measurements of the CVP and ScvO₂ require the placement of a central venous catheter whilst arterial catheterisation is required for continuous MAP readings. Both procedures are not without risk to the patient and require time and expertise. This may be a drawback for its wider implementation in the UK Emergency Department which has a heavy work load and often overstretched resources.

The main difference between successful and futile goal-directed resuscitation in sepsis appears to be the time at which therapy had been commenced rather than the chosen resuscitation endpoint. There is evidence to suggest that early initiation of haemodynamic optimisation with frequent reassessments, rather than achieving an invasive resuscitation endpoint, such as central venous oxygen saturation, improves clinical outcome from severe sepsis or septic shock. This raises an interesting question as to whether early goal directed therapy, using carefully chosen non-invasive
endpoints, would result in a similar outcome as demonstrated by Rivers and co-workers.

Non-invasive haemodynamic monitoring is safe, quick and feasible even in settings with limited resources. It has the potential to provide the clinician with essential information to guide goal-directed haemodynamic optimisation at the patient’s bedside.

Over the last two decades a number of non-invasive methods assessing cardiovascular function or tissue oxygenation in critically ill patients have been explored, mainly as research tools.

There are three methods of non-invasive haemodynamic monitoring that have shown promising initial results in critically ill patients. These are Thoracic Electrical Bioimpedance (TEB), transcutaneous Doppler ultrasound and near-infrared spectroscopy (NIRS). However, it is not known whether any of these technologies might be useful in the early management of septic patients.
1.2 Epidemiology of sepsis

Data on the incidence of severe sepsis and septic shock is fragmented and incomplete. Over the last 5 decades there has been a reported decreasing incidence in gram-negative sepsis with gram positive and fungal pathogens being on the rise.\textsuperscript{10, 11} The overall incidence of sepsis continues to climb and is currently believed to be 3 per 1,000 population with an expected annually increase of 1.5 %.\textsuperscript{11, 12}

The major contributing factor for the rising incidence in the developed world is the aging population. The elderly (age $\geq 65$ years) account for more than half of adult patients with severe sepsis and septic shock, and one third of these are nursing home residents.\textsuperscript{12-14}

Unsurprisingly, there has been a steady increase in the number of intensive care unit (ICU) admissions due to severe sepsis or septic shock, with ICU admissions being associated with a 46\% in-hospital mortality.\textsuperscript{14, 15} Increase in multi-resistant strains, high-risk patients undergoing major surgery and the wider use of immunosuppressive therapy are likely to be contributing factors. ICU patients with septic shock were usually older, had a higher proportion of co-morbidities and had undergone recent surgery. They were found to have a 4-fold higher mortality than non-septic ICU patients.\textsuperscript{14}

Not only are intensive care units faced with an increased number of septic patients; there is a growing pressure on Emergency Care Units to diagnose and manage sepsis. A recent survey in the United States highlighted that, contrary to previous belief, sepsis is far more likely to be community-acquired and that two thirds of patients with severe sepsis come through the Emergency Department.\textsuperscript{13}
The death toll from sepsis remains unacceptably high. About 20 years ago an estimated 1,400 people died each day worldwide from sepsis.\textsuperscript{1} This figure is likely to underestimate the magnitude of this public health burden owing to low diagnostic rates and the difficulty to track sepsis in many countries, since death is often attributed to the primary cause, such as pneumonia or cancer. A recent study from the U.S. reported more than 1 Million deaths from sepsis during a 7-year period, equating to approximately 400 sepsis related deaths per day in the U.S. alone.\textsuperscript{16}

In comparison to other acute conditions such as myocardial infarction (MI) the mortality associated with sepsis has changed only slightly over the last decades. Severe sepsis is still associated with a mortality rate as high as 28.7 to 49.7\%, similar to the in-hospital mortality seen in acute MI in the 1960’s, before the implementation of successive life-saving treatments.\textsuperscript{3, 10, 12, 17, 18}

The last decade saw the beginning of the decline in sepsis mortality as a result of improved diagnostic and therapeutic strategies.\textsuperscript{10, 17, 19} Despite such progress, sepsis mortality remains unacceptably high. Likely reasons for this finding are the change in patient demographics with increasing number of elderly and high risk patients as well as an increase in antibiotic-resistant cases and the overall rising incidence of sepsis.
1.3 Standards of care for patients with sepsis

1.3.1 Improving care for septic patients

The discovery of Penicillin by Sir Alexander Fleming in 1928 set a benchmark in the management of sepsis saving millions of lives. It marks the beginning of modern antibiotics. Even today, prompt and adequate antibiotic therapy combined with supportive therapy remains the mainstay of sepsis management.

The introduction of antibiotics into common clinical practice after World War II led to a significant decline in death from sepsis. In the 1950s the concept of the Intensive Care Unit (ICU) was introduced into the health care system, providing care to critically ill or injured patients. Unfortunately this had little effect on the outcome from sepsis. It was not until the end of the twentieth century when a number of landmark clinical trials introduced new or newly applied concepts of sepsis managements, that there was a further decrease in mortality.

The PROWESS study demonstrated in 2001 a 6.1% absolute reduction in mortality (NNT=16) in patients with severe sepsis treated with Drotrecogin alfa (recombinant human activated protein C). Drotrecogin alfa, subsequently approved for the treatment of patients with severe sepsis, was found to be futile in patients with less severe disease but effective in septic patients with three or more organs failing.

In the same year Rivers, et al. published a randomised controlled trial with compelling evidence that ‘Early goal-directed therapy’ (EGDT) significantly reduced the mortality in patients with severe sepsis or septic shock (absolute risk reduction 16%). EGDT is a concept that aims to prevent global tissue hypoxia with subsequent organ failure by
establishing a balance between systemic oxygen delivery and oxygen demands. It is a protocol-driven early intervention method that uses pre-defined values of central venous pressure (CVP), mean arterial pressure (MAP), urine output (UO) and central venous oxygen saturation (ScvO₂) as endpoints for resuscitation (Figure 1). EGDT uses CVP as a marker of intravascular filling and ScvO₂ as a surrogate marker for cardiac index, a parameter often referred to as measure for haemodynamic therapy.⁴,⁵

![Diagram](image-url)

**Figure 1. Protocol for Early Goal-Directed Therapy⁴**

Rivers *et al.*³ demonstrated that only six patients need to be treated following the EGDT protocol in order to save one life (NNT=6). An external validation of the EGDT
protocol using a ‘before and after study’ design found it to be similarly effective (NNT=11). Though these figures are impressive, there remains scepticism about the magnitude of the effect amongst the wider medical community. The Rivers et al. study is open to criticism. Not only does this single centre study lack generalisability but it also raises concerns about bias, given the unacceptable high mortality rate in the cohort receiving standard sepsis management. Nevertheless, Rivers et al. deserve credit for their efforts to reduce mortality from sepsis by emphasising the importance of commencing effective sepsis management as early as possible.

Traditionally sepsis has been viewed as an ‘intensive care unit’ disease. However, it is now recognised that sepsis is a disease that demands critical care management at the earliest opportunity to improve outcome. For this to happen it would require greater awareness of sepsis and early clinical recognition by medical and nursing staff as well as the ability to instigate appropriate treatment in a timely manner. Furthermore, effective collaboration between ‘in-house’ specialities, particularly between emergency medicine and intensive care, is a key to facilitate improved sepsis management and outcome.

To raise international awareness of the challenges associated with sepsis, the Surviving Sepsis Campaign (SSC), an international collaboration of health experts, was formed less than a decade ago. In 2004 the SSC committee published consensus guidelines for the management of severe sepsis providing guidance to the clinicians caring for septic patients. These guidelines were extensively revised using the ‘Grades of Recommendation, Assessment, Development and Evaluation’ (GRADE) system which allows a structured assessment of the quality of evidence and of the strength of the recommendation. Whilst in 2004 the SSC guidance was primarily focused on
the management of septic patients in intensive care units, the new guidelines allude to the fact that greater improvement would be achieved by better sepsis management in non-ICU settings.\textsuperscript{26, 27}

The SSC was committed to a 25\% relative reduction in mortality from severe sepsis by 2009.\textsuperscript{28} This was to be achieved by changing clinical behaviour through the implementation of consensus guidelines known as ‘sepsis bundles’. There were two bundles, the sepsis resuscitation bundle, which includes EGDT, and the sepsis management bundle.\textsuperscript{29} The goal was, for these bundles to be implemented in all hospitals caring for the acutely ill to ensure consistent and evidence based management of patients with severe sepsis.

As expected, there were limitations to the widespread reliable implementation of the sepsis bundles, particularly, as initiation of invasive EGDT depends on local critical care facilities and expertise. However, if it would be possible for less invasive optimal endpoints to be substituted for CVP and ScvO\textsubscript{2} then compliance with the sepsis resuscitation bundle may markedly improve.
1.3.2 Sepsis bundles

The concept of care bundles, which is not unique to sepsis, originated from an extensive review of critical care literature aiming to identify interventions that improve patient outcomes. A ‘care bundle’ is a group of several evidence based interventions which when applied in combination are expected to enhance clinical outcome. It is well known that the highest survival rate from a cardiac arrest can only be achieved when all components of the cardiac resuscitation bundle are applied as rapidly as possible. For a care bundle to be effective, the delivery of each element must be achievable in terms of resources, must be measurable, must be based on sound evidence and must not be a source of major controversy.

The two sepsis bundles were created by the SSC as performance improvement tools. The ‘sepsis resuscitation bundle’, designed to be completed within six hours of identifying severe sepsis or septic shock, is most relevant to Emergency Care. This bundle is composed of a number of tasks which are essential to the care of patient with severe sepsis. These are measurement of serum lactate, obtaining blood cultures before administration of appropriate antibiotics, intravenous fluids and commencement of EGDT if indicated (Figure 2). It can be argued that early administration of appropriate antibiotics is one of the most important elements of this care bundle, as it has been shown to greatly reduce mortality. The SSC advocated that in severe sepsis or septic shock antibiotics should be given within one hour for patients in the ED. A recommendation which was recently reported to be strongly associated with improved outcome.
The goals set out in the ‘sepsis management bundle’ are centred around the ICU management. They include administration of steroids, drotrecogin alfa (recombinant human activated protein C), glucose control and adequate inspiratory plateau pressures for ventilated patients. Completion of all tasks, if clinically indicated, must be accomplished within 24 hours of identifying severe sepsis or septic shock.

### SEPSIS RESUSCITATION BUNDLE

1. Measure serum lactate
2. Obtain blood cultures prior to antibiotic administration
3. Administer broad-spectrum antibiotic, within 3 hrs of ED admission and within 1 hour of non-ED admission
4. In the event of hypotension and/or a serum lactate > 4 mmol/L
   a) Deliver an initial minimum of 20 ml/kg of crystalloid or an equivalent
   b) Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) > 65 mm Hg
5. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4mmol/L
   c) Achieve a central venous pressure (CVP) of ≥ 8 mm Hg
   d) Achieve a central venous oxygen saturation (ScvO₂) ≥ 70 % or mixed venous oxygen saturation (SvO₂) ≥ 65 %

**Figure 2.  Sepsis Resuscitation Bundle**

Successful implementation of the sepsis resuscitation bundle into clinical practice presents a greater challenge. Whilst well established severe sepsis and septic shock are commonly encountered in intensive care units, identifying and treating the disease at its early stage is still challenging for medical staff. A recent UK study highlighted the effect of non-compliance with the sepsis resuscitation bundle on mortality in patients...
with severe sepsis, demonstrating a two-fold increase in mortality in the non-compliant group (ARR 26%, NNT=4).\textsuperscript{4} Is this an effect of poor compliance with a new guideline or is it lack of early identification of ‘eligible’ patients? As with any newly implemented clinical guideline, there are teething problems, many of which can be overcome by raising awareness, involving front line staff, setting up work-shops or creating networks to share experiences. These issues were extensively addressed through the international sepsis awareness programme led by the SSC. However, despite these efforts there was still only an up to three-fold improvement in compliance with sepsis bundle management and this was from a very low baseline.\textsuperscript{34, 35}

A gap analysis performed in UK hospitals has shown that despite best efforts there are deficits in implementing the sepsis resuscitation bundle. To address this problem, ‘Survive Sepsis UK’ initiated the implementation of the so called ‘Sepsis Six’, six simple tasks which can be applied rapidly and easily by non-ICU staff in the ED or on the wards within the first hour of identifying severe sepsis (Figure 3).\textsuperscript{36}

\begin{itemize}
  \item Give 100\% oxygen
  \item Take blood cultures
  \item Give IV antibiotics
  \item Start IV fluid resuscitation
  \item Check haemoglobin and lactate
  \item Place and monitor urinary catheter
\end{itemize}

\textbf{Figure 3. Sepsis Six}
Compliance might be better using this more simplified approach. However, what these sepsis management strategies fail to address is the importance of early identifications of sepsis, since patients, who are not identified will not receive the SSC recommended treatment. Given the fact that there is no specific test or distinguishing feature for sepsis as there is e.g. myocardial infarct or stroke the early recognition of sepsis is difficult. Thus, one of the key issues to improve outcome from sepsis lies with the early identification of sepsis.
1.4 Pathophysiological concept of sepsis

Sepsis is the result of complex interactions of the host’s inflammatory, immune and coagulation responses to the infecting microorganism. Initiation of the host’s defence mechanisms results in activation of neutrophils and release of numerous inflammatory mediators. The circulating mediators cause direct or indirect tissue injury leading to increased vascular permeability, vasodilatation and activation of the coagulation cascade. This results in redistribution and loss of circulatory blood volume due to fluid shift from the intravascular into the extravascular space. To compensate for these changes and to maintain oxygen supply to the tissues the RR and HR will increase. It is only at this stage that physiological deterioration manifests itself clinically. These physiological changes are an attempt to improve the oxygen content of the circulating blood and cardiac output. Whilst there may be a temporary improvement, these measures will not be able to sustain the tissues’ oxygen demands for long.

As the disease process progresses hypotension, oliguria, tissue oedema and acute confusion will occur, indicating clinical decompensation. At this advanced stage of severe sepsis organ dysfunctions may be profound and irreversible, contributing to high morbidity and mortality. It has been shown that, once multiple organ dysfunction has occurred, instigation of goal-driven haemodynamic optimisation in an Intensive Care Unit does not significantly alter the patient’s outcome.

Whilst the traditional vital signs, such as heart rate, blood pressure, respiratory rate or oxygen saturation, as well as vital signs based scoring systems are of help in recognising clinical deterioration, the timing and magnitude of their derangement is not a true reflection of the underlying pathophysiological changes.
1.5 Sepsis and the cardiovascular system

1.5.1 Cardiovascular Physiology

The primary goal of the cardiovascular system is the delivery of adequate oxygen to the tissues in order to meet their metabolic demands. This is done by establishing a balance between oxygen consumption and oxygen delivery. Oxygen delivery (DO\textsubscript{2}) is defined as the amount of oxygen made available to the body during one minute. It is equal to cardiac output multiplied by arterial oxygen content (CaO\textsubscript{2}) (Equation 1).\textsuperscript{38}

\[
DO_2 = CO \times CaO_2
\]

Equation 1. Oxygen delivery

In situations where there is an increasing oxygen demand by the tissues, this is usually met by an increase in cardiac output. Clearly, cardiac output plays a pivotal role in delivering oxygen to the tissues.

1.5.1.1 Regulation of cardiac output

Cardiac output (CO) is the amount of blood ejected by the heart during a one minute period and is imperative for maintaining blood pressure and oxygen delivery. Cardiac output is defined as heart rate (HR) multiplied by stroke volume (SV) (Equation 2) and if related to body surface area is referred to as cardiac index. It is measured in litres per minute, with the normal adult range being 4.0-8.0 l/min.\textsuperscript{39}

\[
CO = HR \times SV
\]

Equation 2. Cardiac output
Although CO is determined by HR and SV, changes in HR will produce a greater effect on changes in CO, since HR may increase by up to 200% under physiological extremes, such as exercise, compared to an up to 50% increase in SV. As HR increases CO will increase until a critical point is reached when any further increase in HR will result in a fall in CO. This is due to a HR related decrease in ventricular filling time leading to a reduction in end-diastolic volume (EDV) and therefore SV.

Heart rate is controlled by sympathetic and parasympathetic nervous system activity at the sino-atrial node whilst SV is regulated by three mechanisms; (1) preload, (2) afterload and (3) inotropy. The determinants of SV are depicted in Figure 4.

![Figure 4. Determinants of stroke volume](image)
(1) **Preload** is defined as the initial stretching of cardiac myocytes prior to contraction. Changes in preload alter EDV which has a positive effect on SV, thus an increase in preload will increase SV. Preload is predominantly affected by the central venous pressure (CVP) but there are a number of other factors, such as heart rate (HR), ventricular compliance (VC), atrial contractility (AC) and inflow or outflow obstruction (FO), that have an effect on preload.\(^{40}\)

(2) **Afterload** can be described as the pressure against which the heart must contract in order to eject blood into the aorta. The two main factors affecting afterload are mean arterial pressure (MAP) and systemic vascular resistance (SVR). An increase in MAP or SVR will lead to an increase in afterload. This again will increase end-systolic volume (ESV) and thus decrease SV.

(3) **Inotropy** is often referred to as contractility. There are a number of factors influencing inotropy, the most important of which are activation of sympathetic (SN) or parasympathetic nerves (PN) as well as exogenous catecholamines (exC).\(^{40}\)Whilst catecholamines have a positive inotropic effect, acetylcholine released via parasympathetic nerve stimulation decreases inotropy.\(^{40}\)

A further factor influencing the stroke volume is the Frank-Starling mechanism, which describes the relationship between stretching of cardiac myocytes, as a result of increased diastolic filling, and contractility.\(^{40}\) It states that within certain limits an increase in preload will result in improved contractility producing a greater stroke volume and thus cardiac output.
1.5.1.2 Regulation of systemic vascular resistance

Systemic vascular resistance is defined as the resistance to blood flow offered by the systemic circulation. The major determinant of SVR is the vascular tone of small arteries and arterioles, the so called ‘resistance vessels’, although changes in blood viscosity also have an effect. An increase in vascular tone will lead to an increase in SVR. The vascular tone is generated by smooth muscle contraction within the wall of the vessel. A number of extrinsic and intrinsic factors, such as sympathetic nerves and endothelin-1, promote smooth muscle activation and vasoconstriction, whilst others, such as adenosine and endothelium-derived relaxing factor (nitric oxide), promote smooth muscle relaxation and vasodilatation.\(^\text{40}\)

Systemic vascular resistance can be derived from cardiac output (CO), mean arterial pressure (MAP) and central venous pressure (CVP) (Equation 3). It is measured in units of dyne·sec/cm\(^5\), with a normal range for adult of 1000 to 1500 dyne · sec/cm\(^5\).\(^\text{39}\)

\[
SVR = \frac{MAP - CVP}{CO}
\]

Equation 3. Systemic vascular resistance
1.5.2 Cardiovascular involvement in sepsis

The cardiovascular impairment in sepsis is complex and multifaceted. More than a century ago it was documented that septic illness affects the cardiovascular system and that the degree of disturbance is associated with the severity of the disease.\textsuperscript{41} The traditional cardiovascular dysfunction seen in sepsis and septic shock was first described in 1951 by Waisbren.\textsuperscript{42} He observed two distinct clinical stages of septic shock, the first being the hyperdynamic or high CO state characterized by fever, full bounding pulses, flushing and warm dry skin. The second being the hypodynamic state characterized by a thready pulse, oliguria, cold and clammy skin was thought to have a decreased CO. The traditional view was that patients with sepsis present initially in the hyperdynamic state and then either recover or progress to the pre-terminal hypodynamic shock state with decreased CO and elevated SVR.\textsuperscript{43} Contrary to traditional beliefs Wilson et al. demonstrated in 1965 that septic shock is characterised by increased CO and decreased SVR, which is different from cardiogenic and haemorrhagic shock.\textsuperscript{44}

1.5.2.1 Cardiac response

In an attempt to meet the body’s increased oxygen requirements in sepsis the CO rises. This is achieved primarily by an increase in HR and to some extent by an increase in SV. It was initially thought that as septic shock deteriorates CO would decline and this was believed to be due to myocardial depression.\textsuperscript{43} Myocardial depression in sepsis was thought to be associated with globally impaired myocardial perfusion causing myocardial ischaemia. This hypothesis was refuted by a number of studies demonstrating that the cause of myocardial dysfunction is not reduced coronary
perfusion but the effect of a circulating myocardial depressant factor. The concept of a circulating myocardial depressant factor was first postulated by Wiggers' more than 60 years ago. The existence of a myocardial depressant substance was first demonstrated in 1985 by Parrillo et al. They found that by exposing in-vitro cardiac myocytes to a serum taken from a severely septic patient myocyte depression could be generated. Subsequently a number of circulating substances, such as cytokines, leucotrienes, nitric oxide and prostanoids, have been proposed to be linked to myocardial dysfunction in severe sepsis and septic shock. Of these cytokine mediators such as tumour necrosis factor - alpha (TNF-α) and interleukin - 1 beta (IL-1β) are considered to play a key role in the depression of myocardial contractility in sepsis.

It has been shown that myocardial depression occurs within the first days of septic shock, characterised by dilatation of the left ventricle and a decrease in left ventricular ejection fraction. These changes were found to be transient in survivors. Interestingly, despite myocardial depression the cardiac output of septic patients is usually normal or elevated, possibly a result of the low SVR obscuring the concomitant myocardial dysfunction.

Normal cardiac output is seen under normal physiological conditions while situations of physiological extremes, such as sepsis, demand an increase in cardiac output to meet increased metabolic requirements. It has been shown that inability to adequately augment CO in critical illness is associated with poor outcome. Also, a persistently low CO in patients with septic shock, despite aggressive resuscitation, was found to increase mortality.
1.5.2.2  Peripheral circulation in sepsis

In sepsis there is typically a reduction in SVR as a result of vasodilatation of the small arteries and arterioles due to loss of sympathetic tone.\textsuperscript{56} The peripheral vasodilatation is caused by a number of circulating mediators, such as nitric oxide and cytokines, and results in well-perfused warm skin as seen in the early phase of sepsis.\textsuperscript{57}

At the later phase of severe sepsis or septic shock the progressing vasodilatation leads to blood pooling and microcirculation failure with maldistribution of blood flow and capillary leak, resulting in relative hypovolaemia and clinical hypotension. As sepsis progresses the peripheral vessels become refractory to vasopressor agents resulting in an even lower SVR and progressive hypotension.\textsuperscript{58}
1.6 Non-invasive cardio-haemodynamic monitoring

Three non-invasive haemodynamic technologies have shown initial promising results in critically ill or injured patients. Two of these, Thoracic Electrical Bioimpedance and transcutaneous Doppler ultrasound, measure a variety of cardio-haemodynamic parameters, the third technology, near-infrared spectroscopy, measures tissue oxygen saturation. A detailed description of these three technologies is presented below.

1.6.1 Thoracic Electrical Bioimpedance

Thoracic electrical bioimpedance (TEB) also called impedance cardiography (ICG) is the study of cardiac functions determined from measurements of the electrical impedance of the thorax.\(^5\) It is a non-invasive method of determining cardiac output, which allows continuous real-time assessment with no risk to the patient. It is immediately available, easy to use and cost-effective.

The first attempts to study the volume changes of the heart by placing the human body between two electrodes in an electrical circuit were described more than 100 years ago.\(^6\) However, it was not until 1940 when Nyboer et al. set the keystone for the use of electrical bioimpedance to measure cardiac function.\(^7\) TEB, as a method to measure cardiovascular performance, gained increasing popularity in the 1960s when the original TEB system, the Minnesota impedance cardiograph, was developed for the National Aeronautics and Space Administration (NASA).\(^8\) Since then TEB technology has undergone numerous transformations.
1.6.1.1  **Electrophysiological Principles**

Thoracic Electrical Bioimpedance is the electrical resistance of the thorax to a high-frequency and very-low amplitude alternating current (AC).

The fundamental principle behind electrical bioimpedance is based on Ohm’s law. It states that impedance to current flow ($Z$) is equal to the voltage drop ($E$) between the two ends of the electrical circuit divided by the electrical current ($I$) (Equation 4).

$$Z = \frac{E}{I}$$

**Equation 4.** Ohm’s law

Therefore, if the electrical current ($I$) remains constant, changes in impedance ($Z$) to flow are equal to changes in voltage drop ($E$) across the circuit. Furthermore, impedance ($Z$) is dependent on the resistivity ($\rho$), length ($L$) and cross sectional area ($A$) of the conductor (Equation 5).\(^{59}\)

$$Z = \rho \times \frac{L}{A}$$

**Equation 5.** Impedance (1)

The conductor referred to is the thorax which, for simplicity, can be modelled as a cylinder.\(^{59}\) Since the volume ($V$) of a cylinder is equal to the product of the cross-sectional area ($A$) and length ($L$), changes in impedance ($Z$) are related to changes in the volume ($V$) of the conductor (Equation 6).
\[ V = A \times L \]

Equation 6. Volume of cylinder

Therefore, equation 5 changes to:

\[ Z = \rho \times \frac{L^2}{V} \]

Equation 7. Impedance (2)

If a current is applied to a conductor it will seek the path of lowest resistivity. The thorax, an electrically inhomogeneous conductor, is primarily composed of tissues with a high resistivity (R), such as bone, fat, muscle air filled spaces and to a lesser extent of blood, which has the lowest resistivity in the human body (whole blood 130 \( \Omega/cm \), plasma 63 \( \Omega/cm \)).\textsuperscript{64, 65} Thus, when a constant alternating current is applied to the thorax it will primarily travel up the great vessels and any changes of impedance over time within the thorax will be related to dynamic changes of blood volume in the aorta and vena cava (Figure 5).\textsuperscript{64, 65}
The overall impedance of the thorax is composed of base impedance ($Z_0$), respiration impedance ($Z_R$) and haemodynamic impedance ($Z_H$) and has an average value of 25\,\Omega (Equation 8).\textsuperscript{64}

$$Z(t) = Z_0 + Z_R(t)Z_H(t)$$

Equation 8. Impedance (Thorax)

$Z_0$, indicative of chest fluid volume, does not change suddenly with time, whereas $Z_R$ and $Z_H$ show variations during the cardiac cycle. The change in impedance induced by respiration is approximately 1\,\Omega, which is as much as ten times higher than the blood
flow induced change in impedance (0.1 to 0.2Ω). These changes are reflected in the impedance waveform (Delta Z) (Figure 6).

In order to overcome variability in impedance over time caused by respiration the first derivative of delta Z (dZ/dt) was introduced. This was a great advantage since, by applying this method, it has been shown that nearly all changes in thoracic impedance over time are due to blood volume and velocity changes in the thoracic aorta alone. The maximum deflection of the first derivative of delta Z is proportional to the peak flow in the ascending aorta.

![Figure 6. ECG and impedance waveforms](image)

**Figure 6.** ECG and impedance waveforms
The $dZ/dt$ waveform reflects a number of physiological actions and allows measurement of various parameters.$^{69}$ PEP, the pre-ejection period, is measured from ventricular depolarisation (Q-point) to the aortic valve opening (B-point). The left ventricular ejection time (LVET) is measured from the opening of the aortic valve (B-point) to valve closure (‘X’-point). The C-point reflects the maximal systolic flow $(dZ/dt)_{\text{max}}$. The Y-point represents closure of the pulmonary valve and the O-point indicates mitral valve opening.

Assuming that SV is proportional to the maximal systolic flow and the duration of the left ventricular ejection phase (LVET) it can be calculated using the following formula (Equation 9)$^{63,67,69}$:

$$SV = V_{EPT} \times \frac{(dZ/dt)_{\text{max}}}{Z_0} \times LVET$$

Equation 9. Stroke volume

This Bernstein/Scramek formula operates on the assumption that the thorax is geometrically modelled as a truncated cone which allows a better estimation of the electrically participating thoracic volume compared to the mere cylinder model used in previous formulas.$^{70}$ $V_{EPT}$, the volume of electrically participating thoracic tissue, is a personal constant and is determined by the patient’s height, weight and gender.$^{67}$

Cardiac output and cardiac index can be calculated by using the stroke volume derived from the first derivative of the impedance waveform.
Additional information can be gained from the base impedance \(Z_0\) which, not affected by the cardiac cycle, is an indicator of chest fluid volume. The reciprocal of \(Z_0\) is termed thoracic fluid content (TFC), a parameter that can be used to assess changes in intravascular and extravascular thoracic fluid.\(^71\)

### 1.6.1.2 Validation

There are currently more than 200 TEB validation studies published. TEB has been evaluated in different clinical settings in a wide range of populations. Since there is no true ‘gold standard’ to measure cardiac output, different reference methods have been used to validate thoracic electrical bioimpedance measurements.\(^{64, 72, 73}\) The majority of studies were validated against the pulmonary artery catheter thermodilution (PAC-TD) method which is widely accepted as the ‘clinical gold standard’. Other reference techniques used were the Fick method, dye-dilution and echocardiography. Each reference technique lacks absolute accuracy and reproducibility in measuring the ‘true’ cardiac output, making agreement between two methods likely to be imperfect.\(^{63, 74-77}\)

Furthermore, the validation studies differed considerably in their applied TEB methodology. This involved the use of different electrode configurations, values for resistivity of blood, differently modelled thoracic volume and different equations for calculating cardiac output.\(^{66, 67, 73, 78}\) Also, the subjects studied varied greatly from healthy to critically ill patients. It may therefore not come as a surprise that the validation studies reached conflicting conclusions.
A large meta-analysis including 112 studies yielded an overall correlation coefficient \( r^2 \) of 0.67 (95% CI 0.64-0.71) which is similar to the cumulative correlation coefficient \( r^2 = 0.66 \) found in a previous meta-analysis and in a recent literature review.\(^{64, 73, 79}\)

Interestingly, TEB cardiac output correlated less well with PAC-TD in ICU patients compared to non-ICU patients \( (r^2 = 0.64 \text{ versus } r^2 = 0.77) \). This is likely to be the result of the technical challenge to achieve correct electrode positioning due to dressings or CVP-lines.\(^{79}\)

When reviewing validation studies in critically ill patients, utilising the same electrode configurations and SV equation as used in my research study, a satisfactory correlation between TEB and PAC-TD cardiac output measurements was found (Table 1).

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Reference Method</th>
<th>Patient group</th>
<th>( r^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoemaker (2006)(^{80})</td>
<td>PAC-TD</td>
<td>Trauma</td>
<td>0.84</td>
</tr>
<tr>
<td>Van De Water (2003)(^{63})</td>
<td>PAC-TD</td>
<td>Critically ill surgical</td>
<td>0.66</td>
</tr>
<tr>
<td>Shoemaker (1998)(^{81})</td>
<td>PAC-TD</td>
<td>Trauma, critically ill medical and surgical</td>
<td>0.73</td>
</tr>
<tr>
<td>Shoemaker (1994)(^{82})</td>
<td>PAC-TD</td>
<td>Critically ill</td>
<td>0.74</td>
</tr>
<tr>
<td>Shoemaker (1988)(^{83})</td>
<td>PAC-TD</td>
<td>Critically ill surgical</td>
<td>0.69</td>
</tr>
<tr>
<td>Appel (1986)(^{84})</td>
<td>PAC-TD</td>
<td>Critically ill surgical</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Although there was not always a strong correlation \( (r^2 < 0.8) \) in cardiac output measurements between TEB and the PAC-TD method, TEB derived CO changes were
shown to closely follow changes in CO measured by thermodilution. Furthermore, when comparing the intra-method variability of TEB cardiac output and PAC-TD cardiac output measurements TEB demonstrated better intra-patient reproducibility than thermodilution.

Overall, when compared with the PAC-TD, TEB can be regarded as a reliable method to measure cardiac output, having demonstrated clinically acceptable accuracy and reproducibility. From a pragmatic point of view, it is probably even more important whether TEB is able to measure parameters and track dynamic changes that are related to a disease process or patient outcome.

1.6.1.3 Practical application

There are currently a number of thoracic electrical bioimpedance or impedance cardiography devices in use. The two current market leaders are the Niccomo™ Monitor (Medis. Medizinische Messtechnik GmbH) and the BioZ ®monitor (Cardio Dynamics). Both devices display, in real-time, non-invasive cardio-haemodynamic data. They require four dual pre-gelled sensor patches, two of which are placed at the root of the patient’s neck and two at the lateral aspect of the lower thorax (Figure 7). The outer electrodes (blue and orange) are used to transmit a constant alternating measurement current of high frequency (85kHz) and low amplitude (1mA). With this type of current the tissues are not excitable, minimising the risk of any physiological effect. The inner electrodes (purple and green), placed inside the current path are used to receive the ECG signal, thus the heart rate and the thoracic impedance signal.
Figure 7. Electrode configuration
1.6.1.4 Clinical applications

TEB monitoring has been investigated in a wide range of clinical conditions and settings. It has demonstrated a potential to assist diagnostic and therapeutic management of acutely and chronically ill patients. Its current use however, remains that of a research tool, for example:

Emergency Department

- Diagnostic tool to aid differentiation of acute dyspnoea\textsuperscript{86-89}
- Haemodynamic assessment of critically ill patients\textsuperscript{80, 90}
- Outcome prediction in critically ill emergency patients\textsuperscript{91}
- Clinical decision-making tool\textsuperscript{92}

In-patient

- Management of acute heart failure\textsuperscript{93}

Out-patient

- To predict clinical deterioration and response to treatment in patients with heart failure\textsuperscript{68, 94-96}
- To guide therapy in patients with hypertension\textsuperscript{97-99}
- Monitoring tool in haemodialysis to prevent significant hemodynamic instability\textsuperscript{100}
- Assessment aid in preeclampsia\textsuperscript{101}
1.6.2 Transcutaneous Doppler ultrasound

The first description of the principle of modern Doppler ultrasound is attributed to Christian Doppler, an Austrian scientist. In 1843 he postulated that certain properties of light waves emitted from the stars depend on the relative motion of either the emitting source or the observer. More than 100 years passed before the Doppler Effect became of practical relevance to medicine.

In medicine the Doppler concept was first employed to detect movements of the heart. Subsequently, Satomura, a Japanese scientist, discovered that by transmitting a continuous ultrasonic beam through the skin surface it is possible to determine the character of blood flow within the blood vessel. In the early 1960s transcutaneous Doppler ultrasound was gaining increasing popularity particularly as invasive cardiovascular assessment methods were rather time consuming and not without risks to the patient. The fact that Doppler ultrasound compared favourably with invasive circulatory methods when measuring relative flow values, set the foundation for the development of Doppler ultrasound as an attractive assessment tool.

There are two main types of Doppler ultrasound systems, the continuous wave (CW) and pulse wave (PW) Doppler. They differ in their operating features and in the information they provide. The CW Doppler, as the name suggests, continuously transmits and receives ultrasound waves. Its main advantage is the ability to measure high blood flow velocities, thus providing information on haemodynamics. Its disadvantage is the lack of imaging capability thus providing no anatomical information about the examined structure. The PW Doppler uses a transducer that alternates between transmission and reception of ultrasound waves. The main
advantages of the PW Doppler is its ability to provide information on selected small segments along the ultrasonic beam as well as carrying out imaging alternatively with the Doppler.\textsuperscript{107}

Currently transcutaneous Doppler ultrasound is used for the assessment of a wider spectrum of circulatory disorders, such as peripheral artery disease, acute venous thrombosis, cardiac valvular disease, and also for the evaluation of myocardial function.\textsuperscript{105}

1.6.2.1 \textit{How does it work}

Doppler ultrasound is based on the principle that the frequency of sound waves reflected from a moving object changes with the direction of motion in relation to the emitting source. This change in frequency is called the Doppler shift. The relationship between the Doppler shift of frequency ($F_d$) and the movement of a single object ($V$) can be expressed in the following equation (Equation 10):

$$F_d = \frac{2F_e \times V \times \cos \theta}{c}$$

\textbf{Equation 10. Doppler shift of frequency}

If the frequency of the emitting sound ($F_e$), the angle of the directed beam ($\theta$) and the speed of sound through the tissues ($c$) are kept constant then the Doppler shift is directly proportional to the velocity of the moving object. Doppler shift of frequency ($F_d$) is highly dependent on the angle of the beam ($\theta$). If the direction of the beam is
perpendicular to the blood flow, the Doppler signal is very poor with velocity measurements close to zero, whereas alignment of the ultrasound waves with the direction of blood flow gives the most accurate Doppler signal.

A Doppler ultrasound system consists of three elements, an emitter, a receiver and electronics. The emitting and receiver transducers are usually combined into one handheld Doppler probe. The emitter produces an ultrasound beam which passes through the tissues and is reflected from moving red blood cells. Cells moving towards the transducer will create waves of higher frequency than those moving away from the transducer. The reflected waves are detected by the receiving transducer. The difference in frequency between the emitted and received ultrasound waves is analysed by the system’s electronics and transformed into blood flow data.

There are three main factors that affect the Doppler signal these are air, bone and fat. Air, whether between transducer and skin or within the tissues, prevents any transmission of ultrasound waves and reflects the entire beam back to the transducer. Bony tissue absorbs the ultrasound waves completely, whereas adipose tissues absorb a proportion leading to a weakened Doppler signal.

1.6.2.2 Assessing cardio-haemodynamic function

The use of transcutaneous Doppler ultrasound as an ‘Ultrasonic cardiac output monitor’ (USCOM) to assess cardio-haemodynamic function is a recent addition to its array of applications. CW Doppler ultrasound (frequency > 20,000 Hz) is applied to determine blood flow across the aortic or pulmonary outflow tract. This is done by measuring the distance that blood has travelled through the outflow tract in one heart
beat, which is referred to as the velocity time integral (vti). If the area of the outflow tract (OTa) is known then stroke volume (SV) can be calculated by applying the basic volume equation (Equation 11).

\[
\text{volume} = \text{area} \times \text{height}
\]

Equation 11. Volume equation

Applying this formula to the blood flow through the outflow tract leads to the stroke volume equation (Equation 12):

\[
SV = OTa \times vti
\]

Equation 12. Stroke volume

For the area across the aortic or pulmonary outflow tract (OT) to be calculated the OT diameter needs to be known (Equation 13).

\[
OTa = \pi r^2 = \pi \times (D/2)^2
\]

Equation 13. Outflow tract area

In adults and children the OT diameter has been shown to correlate linearly with body height.\textsuperscript{109} Thus the OT diameter can be estimated using anthropometric normograms.
1.6.2.3 Validation

The ultrasonic cardiac output monitor (USCOM) was introduced into clinical use in 2001. Since then it has been evaluated in different clinical settings in adult and paediatric populations. The pulmonary artery catheter thermodilution (PAC-TD) method was the most commonly used reference technique. Although PAC-TD is considered to be the ‘clinical gold standard’ for assessing cardiac output it has to be remembered that it does not measure the ‘true’ cardiac output.76, 77 Thus comparing any novel method with the ‘old’ standard requires careful interpretation.

A recently published review article attempted to compare the USCOM technique with currently used methods of measuring cardiac output, in particular with the PAC-TD.110 This review included 16 studies, all of which had small numbers of patients. The studies were heterogeneous in design and population which precluded a meta-analysis. A number of the studies demonstrated a good correlation ($r^2 = 0.76$) between USCOM derived CO measurements and PAC-TD values, whilst others found poor agreement between the two methods.111-115

Further evidence has since emerged indicating acceptable agreement between USCOM and PAC-TD values in adult intensive care patients.116-119 It has also been shown that USCOM is well suited to track intra-patient changes in CO over time.118

The lack of agreement between the two methods seen in some studies may have been a result of suboptimal Doppler flow signals due to intra-thoracic air in ventilated patients and inadequate beam alignment with the direction of the blood flow, which may have been caused by a lack of training.110
Given the current evidence the USCOM can be regarded as a feasible method for measuring cardio-haemodynamic parameters at the patient’s bedside by a trained operator assessing non-ventilated patients.

1.6.2.4 Clinical Applications

The USCOM has been used in a range of clinical settings. It has been considered to be a feasible method to assess cardiac output and CO changes with treatment at the patient’s bedside. It has been primarily used as a research tool in intensive care and to a limited extent in emergency medicine and paediatrics.111, 113, 115, 117, 119-124
1.6.3 Near Infrared Spectroscopy

The use of near infrared spectroscopy (NIRS) as a non-invasive method to measure oxygenation in human tissues was pioneered by Jöbsis in 1977. He noticed that biological tissues were transparent to the near infrared region of the electromagnetic spectrum, allowing sufficient photon transmission through the tissues to determine changes in oxyhaemoglobin and deoxyhaemoglobin.\textsuperscript{125} In the 1990s NIRS gained increasing popularity in plastic and reconstructive surgery as a method of monitoring regional tissue oxygen saturation following flap surgery.\textsuperscript{126,127} The ability of NIRS to provide non-invasive information about local tissue oxygenation coupled with the development of a more sophisticated technology opened up a much wider clinical spectrum which focused on monitoring tissue oxygen as a marker of tissue hypoperfusion in critically ill and major trauma patients.\textsuperscript{128-131}

1.6.3.1 Tissue oxygenation monitoring

Adequate tissue oxygen levels, essential for cell survival, rely on efficient oxygen delivery (DO\textsubscript{2}) and oxygen consumption (VO\textsubscript{2}) by the tissue. Oxygen delivery is a function of cardiac output (CO) and arterial oxygen content (CaO\textsubscript{2}). It is influenced by several factors: i) the oxygen content of the inspired gas mixture, ii) oxygen diffusion across the lung-blood barrier, iii) oxygen carrying capacity of the blood, iv) the body’s capability to transport blood to the tissues and v) oxygen diffusion across the blood-tissue interface.

Impaired tissue oxygenation as a result of inadequate oxygen delivery to meet the tissues’ demands is a feature of septic shock. Resuscitation efforts in sepsis
management aim to improve tissue oxygenation and to prevent prolonged global hypoxia. Assessing DO$_2$ or VO$_2$ in a clinical environment is cumbersome. Even invasive methods measuring mixed venous (SvO$_2$) or central venous oxygen saturation (ScvO$_2$) provide only a limited insight into oxygen utilisation in tissues. Furthermore, these systemic parameters of oxygenation may be normal despite significant regional hypoxia.$^{132}$

Early correction of hypoxia, preventing a cascade of cellular and organ dysfunction, was found to significantly improve survival in patients with severe sepsis and septic shock.$^3$ A recent meta-analysis concluded that optimisation of tissue oxygenation in critically ill patients by optimising oxygen delivery reduces mortality.$^{133}$ This meta-analysis also highlighted that only early maximisation of oxygen delivery is associated with improved survival.$^5, 6, 134$ Paramount to all of this is however, the early detection of tissue hypoxia in sepsis, as delay in identification would defer strategies to optimise tissue oxygenation.

The central venous oxygen saturation (ScvO$_2$) is commonly used to gain information about the tissue oxygenation, although a thorough validation of how well it reflects oxygen delivery is lacking. Furthermore, ScvO$_2$ measurements require invasive monitoring which restricts its application to critical care units. Less cumbersome methods such as laser-Doppler flowmetry or orthogonal polarization spectral imaging are difficult to use at the patient’s bedside. For a tissue oxygenation assessment method to be accepted into routine acute clinical care it would have to be non-invasive, whilst being rapid and easy to apply. The near infrared spectroscopy (NIRS) monitoring device (described below) seems to fit these criteria. Such a device would
provide the clinician at the bedside with instant information about the patient’s tissue oxygenation.

### 1.6.3.2 How does it work

Near infrared spectroscopy (NIRS) is a non-invasive technology which is based on the spectrophotometric principles that relates the absorbance of light of a certain wavelength to the presence of a particular structure or chemical. The fundamental principle behind NIRS is Beer’s law. It states that the amount of light absorbed by a coloured substance is proportional to the concentration of the substance in solution.

NIRS uses the near infrared region of the electromagnetic spectrum, which is differently absorbed by oxygenated and deoxygenated haemoglobin. A sensor placed onto the skin scatters the near infrared light through the tissues below to a depth of up to 14 mm, where it is absorbed by haemoglobin. The amount of light absorbed varies with the level of oxygenation. A photodetector which is placed in close proximity to the sensor (15mm) is used to detect the light that has not been absorbed (Figure 8). The incoming signal from the photodetector is analysed using the well described absorption spectra of oxygenated and deoxygenated haemoglobin to calculate the tissue oxygen saturation (StO₂).
1.6.3.3 How does StO$_2$ differ from SpO$_2$

StO$_2$ and SpO$_2$ (pulse oximetry oxygen saturation) are both non-invasive measures of oxygenation which can be easily obtained at the patient’s bedside. They rely on the different light absorption characteristics of oxygenated and deoxygenated haemoglobin. Their main difference lies in where oxygenation is measured. Whilst pulse oximetry SpO$_2$ measures arterial oxygen saturation, StO$_2$ measures arterial and venous oxygen saturation and gives therefore a better reflection of oxygen delivery and consumption within the tissue. Pulse oximetry SpO$_2$ is often referred to as a surrogate marker of systemic or global oxygen saturation whereas StO$_2$ is considered to be a measure of local oxygen saturation within the microcirculation. Therefore changes in StO$_2$ are more closely related to changes in the patient’s tissue perfusion status, as opposed to SpO$_2$ which is a reflection of blood oxygenation and tends to
change once pulmonary or cardiac function are compromised. Additionally, SpO₂ readings require a pulsatile signal generated by the arterial blood flow.¹³⁶, ¹³⁸

1.6.3.4 Validation

There is no accepted ‘gold standard’ against which to validate StO₂ measurements. However, there are a number of very small studies which compared StO₂ against invasive ScvO₂ values. ScvO₂ is a commonly used target for haemodynamic optimisation. A study conducted in an ICU setting demonstrated significant correlation ($r^2=0.79$) between the two methods.¹³⁹ This finding was confirmed by a study amongst critically ill ED patients ($r^2=0.74$).¹⁴⁰

1.6.3.5 Clinical application

Tissue oxygen saturation (StO₂) monitoring has been used as a research tool to assess microvascular dysfunction in critically ill patients suffering from major trauma, different types of shock, sepsis, heart failure; patients with compartment syndrome and those undergoing cardiac or reconstructive surgery.¹²⁸-¹³¹, ¹⁴¹-¹⁴⁴ This monitoring modality has not been introduced into routine clinical practice. Data about the distribution of StO₂ values in healthy adults is limited. A study amongst healthy volunteers (n=707) found a thenar StO₂ of 87± 6% (mean ±SD).¹³¹ In major trauma patients a StO₂ <75% in the first hour upon arrival in the ED was associated with multi-organ failure.¹²⁸
1.7 Summary of Introduction

Several key aspects emerge from this introduction. Sepsis remains a major health care burden associated with a rising incidence and high mortality. The introduction of new sepsis management strategies has resulted in only small improvements. These strategies rely upon invasive monitoring to tailor treatment to predefined resuscitation targets. Such an approach is neither feasible nor practical in many EDs worldwide. Since early intervention in sepsis has shown to improve outcome, monitored goal directed therapy needs to start as soon as possible. However, for monitoring modalities to be applied as the patient reaches the hospital, they have to be safe, quick and easy to use. A number of non-invasive technologies have been developed and validated in different clinical settings and of these, three have shown promising results in critically ill patients. These are TEB, transcutaneous Doppler ultrasound and NIRS tissue oxygen saturation. However, the usefulness of any of these modalities in the early management of sepsis is not known.
1.8 **General aims of this project**

The overall aim of this thesis is to explore the potential benefit of different methods of non-invasive monitoring in the management of sepsis and severe sepsis / septic shock in the Emergency Department.

To justify a future therapeutic trial it would need to be shown that:

1. Patients with sepsis have abnormal cardio-haemodynamic parameters on arrival in the ED.
2. The abnormal cardio-haemodynamic parameters change towards normal with treatment.
3. The degree of initial abnormality is related to outcome (mortality).
4. Normalisation of cardio-haemodynamic parameters with treatment is related to outcome.

It would also be necessary to show:

5. Which non-invasive monitoring modality is most strongly related to outcome?
2 METHODOLOGY

2.1 Research Setting

This research project consists of two separate prospective studies amongst Emergency Department patients with differing severities of sepsis. The main body of research was carried out in the ED of the Leicester Royal Infirmary (LRI), a large urban teaching hospital. The follow up took place on hospital wards of the LRI, including the Intensive Care Unit, and the Leicester General Hospital (LGH). (A personal account of setting up and carrying out research in emergency care can be found in Appendix 1).

The LRI and the LGH are two of the three hospitals that form the University Hospitals of Leicester NHS Trust. All three hospitals receive acute patients but the LRI is the only hospital in Leicestershire that has an Emergency Department catering for a mixed urban and rural population. The ED at the LRI sees 400 patients per day on average, a quarter of which are children. It is the busiest single site ED in the UK and amongst the busiest EDs in Europe. The recruitment for the first study ‘Assessment of cardio-haemodynamic parameters in adult Emergency Department patients with uncomplicated sepsis’ took place between August and November 2007.

Data for the second study ‘Assessment of cardio-haemodynamic parameters and tissue oxygen saturation in adult Emergency Department patients with severe sepsis or septic shock’ was collected during two three-month periods between July 2008 and April 2009.
2.2 Study 1 – Assessment of cardio-haemodynamic parameters in adult Emergency Department patients with uncomplicated sepsis

2.2.1 Study design and population

2.2.1.1 Study objectives

Primary objectives

1) To assess TEB cardio-haemodynamic parameters in septic patients and how they compare to non-septic ED patients.

2) To assess the change in TEB cardio-haemodynamic parameters in septic patients during normal management in the ED.

Secondary objectives

3) To assess the change in TEB cardio-haemodynamic parameters in septic patients after a 24 hour-period of treatment.

4) To determine the relationship between changes in TEB cardio-haemodynamic parameters and changes in conventional variables (mean arterial pressure and heart rate) in septic patients.
2.2.1.2   Design and selection of patients

This was a prospective observational cohort study amongst adult patients presenting to the Emergency Department at the Leicester Royal Infirmary with the clinical diagnosis of sepsis. Recruitment took place whenever the researcher (myself) was available which was usually daily between 0800 and 2000 hours. Potential participants were identified through the computerised Emergency Department database (EDIS) upon their arrival in the ED. Patients who met the inclusion criteria (see below) were approached by the researcher and the study was explained to them. Non-invasive cardio-haemodynamic monitoring using TEB was commenced as soon as possible. Informed consent was obtained from the patient as soon as clinically appropriate. Cardio-haemodynamic parameters were measured continuously throughout the patient’s stay in the ED whilst they received normal therapy for sepsis. A further 10 minute measurement was obtained on the ward 24 hours after the initial TEB assessment. All readings were stored electronically and were not available to the treating clinician.

The age and gender matched controls were recruited amongst non-septic Emergency Department patients from the ‘Minor’ treatment area. They were only eligible for participation if their injury severity score was less than one (ISS ≤ 1) and their pain score assessment confirmed no or mild discomfort. This was to minimise any injury provoked cardiovascular changes that have been previously reported. The control group underwent only one 10 minute TEB measurement.
**Study population**

- **Study group**

  **Inclusion criteria:**

  1. Age over 16 years
  2. Clinical evidence of infection and two or more SIRS (Systemic inflammatory response syndrome) criteria:
      - Temperature $> 38^\circ$C or $< 36^\circ$C
      - Heart rate $> 90$/min
      - Respiratory rate $> 20$ breaths/min
      - WCC $> 12.0 \times 10^9$/l or $< 4.0 \times 10^9$/l

  **Exclusion criteria:**

  1. Need for immediate ventilatory support or surgery
  2. Hypotension (systolic BP $< 90$ mm Hg)
  3. Lactic acidosis (blood lactate $\geq 4$ mmol/l)
  4. Administration $> 500$ ml of intravenous fluid
  5. Pregnancy

- **Control group**

  **Inclusion criteria:**

  1. Age over 16 years (age-matched)
  2. No evidence / suspicion of infection
  3. Injury Severity Score (ISS) $\leq 1$
  4. No or mild discomfort (using validated pain score for assessment)

  **Exclusion criteria:**

  1. As for study group
  2. Presence of any SIRS criteria
2.2.1.3 Data acquisition

Patients’ eligible for participation were connected to the Thoracic Electrical Bioimpedance (TEB) monitor in order to commence cardio-haemodynamic measurements as soon as possible. A detailed description of data acquisition and the TEB monitor can be found in section 2.4.

2.2.1.4 Sample size calculation

From preliminary work amongst critically ill patients in the Emergency Department of the Leicester Royal Infirmary I discovered a standard deviation (SD) of 2.0 for TEB cardiac output. Assuming a power of 90% and an alpha of 0.05% with a SD of 2.0 to detect a minimum clinically significant difference of 2.0 in cardiac output (based on unpublished data) between septic patients and the control group, 44 patients would be required. Allowing for a 10% attrition rate would increase the sample size to 49 patients. To allow for equal numbers to be recruited in each group the sample size had to increase to 50. This sample size would have sufficient power to detect a clinically significant difference in change of cardiac output after intravenous fluid administration in the Emergency Department (paired data).
2.2.2 Study 1 – Objective 1

Comparison of TEB cardio-haemodynamic parameters between septic and non-septic ED patients

The first primary aim of this research project was to assess whether there exists a clinically significant difference in cardiac output measured using TEB between septic and non-septic ED patients. The detailed study methodology has been described in section 2.2.1.

Cardio-haemodynamic parameters of the study group patients taken on arrival in ED were compared with the measurements obtained from the age and gender matched control group. For each patient the median of the best 100 readings, as indicated by quality of signal, obtained within the first 10 minutes of recording were used for analysis. Comparison was made using the overall mean value of each parameter of the study and control group.
2.2.3 Study 1 – Objective 2

Change of TEB cardio-haemodynamic parameters in septic patients during normal treatment in the ED

The same patients and data as described for the study group in section 2.2.1 were used. The study’s sample size of 50 patients (section 2.2.1.4) gave sufficient power to detect a clinically significant difference in change of cardiac output, as paired data was used. Cardio-haemodynamic parameters taken on arrival and departure from the ED were compared. For the analysis the median of the best 100 measurements obtained for each patient within the first and last 10 minutes of recording in the ED were used. Comparison was made using the overall mean value of each parameter in the study group on arrival and departure from the ED.
2.2.4 Study 1 – Objective 3

Change of TEB cardio-haemodynamic parameters in septic ED patients after a 24-hour period of treatment

Again, the same study group patients as described in section 2.2.1 were used. Cardio-haemodynamic parameters taken on arrival in the ED were compared with the measurements obtained after 24 hours of normal treatment. For the analysis the median of the best 100 measurements obtained for each patient within the first 10 minutes on arrival in the ED and during the 10 minute follow-up recording were used. Comparison was made using the overall mean value of each parameter in the study group on arrival in the ED and at 24 hours.

2.2.5 Study 1 – Objective 4

Relationship between changes in TEB cardio-haemodynamic parameters and changes in conventional MAP and HR in septic patients

A secondary aim of this study was to assess how changes in TEB cardio-haemodynamic data in septic ED patients compare with changes in conventional parameters such as heart rate and blood pressure. Comparisons were made using data taken on ED arrival, ED departure and at 24 hour follow up. The patients’ data as described in section 2.2.3 and 2.2.4 was used.
2.3 Study 2 – Assessment of cardio-haemodynamic parameters and tissue oxygen saturation in adult Emergency Department patients with severe sepsis or septic shock

2.3.1 Study design and population

2.3.1.1 Study objectives

Primary objectives

1) To determine cardio-haemodynamic parameters in patients with severe sepsis / septic shock and how they compare to non-septic ED patients.

2) To assess the change in cardio-haemodynamic parameters in patients with severe sepsis / septic shock during normal management in the Emergency Department and after a 24 hour-period of treatment.

Secondary objectives

3) To determine the relationship between cardio-haemodynamic parameters in patients with severe sepsis / septic shock and outcome (length of survival / in-hospital mortality)

4) To assess the relationship between cardio-haemodynamic parameters and conventional variables (mean arterial pressure and heart rate) in severely septic patients
5) To compare simultaneous pairs of TEB and Doppler ultrasound cardiac output/index and stroke volume estimations in patients with severe sepsis/septic shock.

6) To assess the change in tissue oxygen saturation in patients with severe sepsis/septic shock before and after standard ED resuscitation; and to obtain initial data on the relationship between tissue oxygen saturation and clinical outcome.

2.3.1.2 Design and selection of patients

This was a prospective observational cohort study amongst adult patients (sixteen years or older) presenting to the Emergency Department at the Leicester Royal Infirmary with the clinical diagnosis of sepsis and evidence of organ dysfunction. Sepsis was defined according to the criteria of the International Sepsis Definitions Conference and organ dysfunction as one or more of the following: systolic blood pressure less than 90 mmHg, venous lactate equal or greater than 4mmol/l, reduced level of consciousness. Venous lactate (Roche OMNI S, Roche Diagnostics Ltd) is available in the LRI Emergency Department as part of the routine near-patient blood tests analysis using the blood gas analyser.

Recruitment took place whenever the researcher (myself) was available which was usually daily between 0800 and 2000 hours. Senior nursing and medical staff in the ED were aware of the study and familiar with the inclusion criteria. Potential participants were identified through the computerised ED database (EDIS) upon their arrival in the Emergency Department and through the clinical staff, who were
encouraged to contact the researcher if any of their patients fulfilled the inclusion criteria. Potential candidates were screened for eligibility by the researcher, who was not involved in the clinical management of the patient. Patients eligible for participation were approached by the researcher and had the study explained to them. Non-invasive cardio-haemodynamic monitoring using TEB, tissue oxygen saturation (StO$_2$) and transcutaneous Doppler ultrasound was commenced as soon as possible. Informed consent was obtained as soon as clinically appropriate. Cardio-haemodynamic parameters were measured throughout the patient’s stay in the Emergency Department whilst they received normal therapy. A further 10 minute measurement was obtained on the ward 24 hours after the initial cardio-haemodynamic assessment. All readings were stored electronically and were not available to the treating clinician.

The age and gender matched controls were recruited amongst non-septic Emergency Department patients from the ‘Minor’ treatment area. They were only eligible for participation if their injury severity score was less than one (ISS ≤ 1) and their pain score assessment confirmed no or mild discomfort. This was to minimise any injury provoked cardiovascular changes that have been previously reported.$^{146}$ The control group underwent only one 10 minute TEB measurement.
Study population

• Study group

    Inclusion criteria:  1. Age over 16 years

    2. Severe sepsis or septic shock (all 3 of the following)
        a. Clinical evidence of infection
        b. Two or more indicators of SIRS
            • Temperature > 38°C or < 36°C
            • Heart rate > 90/min
            • Respiratory rate > 20 breaths/min
            • WCC > 12.0 ×10⁹/l or < 4.0 ×10⁹/l
        c. Evidence of organ dysfunction
            (any of the following):
            • Lactate ≥ 4mmol/l
            • Systolic BP < 90mmHg
            • GCS <15

    Exclusion criteria:  1. Need for immediate ventilatory support or surgery

    2. Presence of an acute cerebral event, acute coronary syndrome, acute pulmonary oedema, status asthmaticus, active gastrointestinal bleed, trauma

    3. Known metastatic cancer

    4. Pregnancy

• Control group

    The same inclusion and exclusion criteria as used for the first study were applied (see section 2.2.1.2).
2.3.1.3 **Data acquisition**

Patients eligible for participation were immediately commenced upon cardio-haemodynamic monitoring. The three applied non-invasive modalities (TEB, Doppler ultrasound, NIRS tissue oxygen saturation) and the process of data acquisition are described in detail in section 2.4.

2.3.1.4 **Sample size calculation**

*For Objective 1*

From preliminary work amongst critically ill patients in our Emergency Department I found a standard deviation (SD) of 0.34 (for cardiac index). Assuming 80% power and alpha=0.05 with SD of 0.34 to detect a minimum clinically significant difference of 0.3 l/min/m² in cardiac index (based on published data ⁸¹, ⁹¹) between patients with severe sepsis and the control group, 50 patients were required in total (25 in each group), including a 10% attrition rate.

*For Objective 2*

This sample size would have had sufficient power to detect a clinically significant difference in change of cardiac index (0.3 l/min/m²) after treatment in ED and after 24 hours (paired data).

*For Objective 3*

As approximately 30% of septic patients were not expected to survive this would have given an approximately 1:2 ratio of non-survivors to survivors in the severe sepsis group. Assuming that out of 48 patients with severe sepsis/septic shock 16 would not
survive but 32 would, this would have provided a 80\% power to detect a significant difference of 0.3 in cardiac index between survivors and non-survivors (SD 0.34, alpha=0.05). Therefore, 48 patients (54 allowing for 10\% withdrawal rate) with severe sepsis were required to be recruited.

**Overall**

Thus for the study to be adequately powered to detect clinically significant differences in cardiac index (for primary and secondary outcomes) I had to recruit a minimum of 73 patients (48 with severe sepsis / septic shock and 25 controls). Using all 73 patients for the primary endpoint would have provided me with greater than 90\% power to detect a difference of 0.3 in cardiac index between the severe sepsis group and the controls.
2.3.2 Study 2 – Objective 1

Comparison of cardio-haemodynamic parameters in ED patients with severe sepsis/septic shock and non-septic ED patients

The first primary question for this research project to answer was, whether there exists a clinically significant difference in cardiac index measured using TEB between ED patients with severe sepsis / septic shock and non-septic ED patients. The detailed methodology has been described in section 2.3.1.

TEB cardio - haemodynamic parameters of severely septic patients taken on arrival in the ED were compared with the snap-shot measurements obtained from the age and gender matched control group. For each patient the median of the best 100 readings, as shown by the quality indicator, obtained within the first 10 minutes of recording was calculated and used to compute the mean value for each cardio-haemodynamic parameter.
2.3.3 Study 2 – Objective 2

Change of cardio-haemodynamic parameters with normal treatment during the stay in the ED and after 24 hours

The other primary aim of study 2 was to assess the change in cardio-haemodynamic parameters of patients with severe sepsis / septic shock with treatment. The same patients and data as described for the study group in section 2.3.1 was used. Comparisons were made between cardio-haemodynamic parameters recorded on arrival and departure from the ED and after 24 hours of normal treatment. For TEB parameters the median of the best 100 measurements, as indicated by quality signal, obtained for each patient within the first and last 10 minutes of recording in the ED and during the 10 minute follow-up were used. During each assessment point a minimum of two transcutaneous Doppler measurements were carried out in close succession within 10 minutes. The reading with the best Doppler flow characteristics was used for analysis. Comparison was made using the overall mean value of each parameter from the study group on ED arrival and departure.
2.3.4 Study 2 – Objective 3

Relationship between cardio-haemodynamic parameters in patients with severe sepsis/septic shock and outcome

A secondary aim of this research project was to determine the relationship between cardio-haemodynamic parameters, 30 days in-hospital mortality and length of survival. The same patients and data as described for the study group in section 2.3.1 were used.

TEB and Doppler cardio-haemodynamic parameters of survivors and non-survivors taken on ED arrival, ED departure and at 24 hours were compared. For TEB parameters the median of the best 100 measurements, as revealed by the quality indicator, obtained for each patient within the first and last 10 minutes of recording in the ED and during the 10 minute follow up were used. For Doppler parameters the reading with the best flow characteristics obtained at each assessment point was used for analysis.
2.3.5 Study 2 – Objective 4

Relationship between TEB cardio-haemodynamic parameters and conventional heart rate and mean blood pressure

Another secondary aim of study 2 was to assess the relationship between cardio-haemodynamic parameters in ED patients with severe sepsis / septic shock and conventional parameters such as heart rate and blood pressure. The same patients and data as described for the study group in section 2.3.1 were used. Comparisons were made using data taken on ED arrival, ED departure and at 24 hour follow up.
2.3.6 Study 2 – Objective 5

Comparison of simultaneous TEB and transcutaneous Doppler ultrasound cardio-haemodynamic measurements

The aim was to compare simultaneous pairs of TEB and Doppler measurements obtained at the three assessment points and to assess correlation and agreement between them. The same patients and data as described for the study group in section 2.3.1 were used. For TEB parameters the median of the best 100 measurements, as revealed by the quality indicator, obtained for each patient within the first and last 10 minutes of recording in the ED and during the 10 minute follow up were used. For Doppler parameters the reading with the best flow characteristics obtained at each assessment point was used for analysis.
2.3.7 Study 2 – Objective 6

Determining tissue oxygen saturation in patients with severe sepsis or septic shock; its change with normal treatment and relationship to outcome

The final objective of study 2 was to determine tissue oxygen saturation (StO$_2$) in severely septic patients, how it changes with treatment and its correlation with pulse oximetry and cardio-haemodynamic parameters. This technology is at an early stage of development, thus no formal sample size calculation could be performed. Part of this final objective was also to explore the relationship between tissue oxygen saturation and in-hospital mortality.

The same patients and data as described for the study group in section 2.3.1 were used. Tissue oxygen saturation was continuously recorded in the ED and followed up with a 10 minute measurement after 24 hours of treatment. For the purpose of analysis the median value obtained during the first and last five minutes of recording in the ED and during the follow up period was calculated for each patient.
2.4 Data acquisition using non-invasive modalities

Demographic data including anthropometric measures, past cardiovascular history and current drug history were documented for all recruited patients using a ‘Patient Entry Form’ (Appendix 2). Heart rate, respiratory rate, systolic and diastolic blood pressure, oxygen saturation (Propaq® CS monitor Welch Allyn Ltd), temperature and need for supplemental oxygen were obtained from the initial nurse assessment on patient’s arrival in the ED.

2.4.1 Thoracic Electrical Bioimpedance (TEB)

**TEB monitor**

The Niccomo™ monitor (Medis Medizinische Messtechnik GmbH) was used to measure and calculate TEB cardio-haemodynamic parameters of all patients (Figure 9). Its inbuilt technology converts measured changes of thoracic impedance, which are the result of blood entering and leaving the aorta, into cardio-haemodynamic parameters (as described in section 1.6.1). The types of measured and calculated parameters are described in appendix 3. All recorded data was stored anonymously within the Niccomo™ and exported onto a computer for analysis.
Figure 9. Niccomo™ monitor

TEB data acquisition

The Niccomo™ monitor required the placement of four disposable pre-gelled dual sensor patches on the patient’s thorax and neck. Prior to attaching the sensor patches, the patients skin was inspected to ensure it was not broken and then gently cleaned with an alcohol wipe (Uhs Alcotip Swab) and allowed to dry. In the meantime the patient’s study number, height, weight, gender and age were entered into the Niccomo™ monitor.

The sensors were connected to colour coded electrode cables and then attached to the patient according to the manufacturer’s instruction (Figure 10). The two neck sensors were placed opposite each other at the base of the neck in line with the earlobe. The thoracic sensors were positioned at the level of the xiphoid sternum between the anterior and posterior axillary line.
The outer electrodes (blue and orange) functioned as transmitters and the inner electrodes (purple and green) were used to receive the ECG and the thoracic impedance signals. Two LEDs built into a signal box within the electrode cable indicated whether a good contact was established between patient and monitor. A further quality indicator was displayed on the Niccomo™ screen, which gave an indication of the signal quality ranging from 0 to 100%. If the quality dropped below 50% then the measurements could not be relied upon. This was usually resolved by ensuring that the sensors were firmly attached to the patient and requesting that the patient would refrain from moving if possible. The quality of signal was displayed at all times throughout the recordings.

Before the measurements were commenced, a standard blood pressure cuff, plugged into the Niccomo™ device, was placed on the patient’s arm. A blood pressure reading was taken every five minutes.
Patients enrolled in the study group were monitored continuously during their stay in the ED. For the calculation of SV, CO and CI, impedance signals of 16 heart beats were averaged (default setting of the Niccomo™ device) in order to eliminate the effect of respiration. SVR and MAP were calculated at 5-minute-intervals as they required a blood pressure measurement. All patients were followed up 24 hours later on the hospital ward where a further 10 minute recording took place.

The age and gender matched controls were recruited from the ED ‘Minor’ treatment area (as described in sections 2.2.1 and 2.3.1). Control group patients required a single 10 minute TEB measurement.
2.4.2 Transcutaneous Doppler Ultrasound

*Doppler monitor*

The USCOM (Ultrasonic Cardiac Output Monitor) was used to obtain intermittent transcutaneous Doppler Ultrasound measurement of cardiovascular parameters in patients with severe sepsis / septic shock. The USCOM is a portable unit consisting of a touch screen interface and a cleanable handheld transducer (Figure 11). The integrated software calculates cardio-haemodynamic parameters based on the measured Doppler flow profile across the aortic or pulmonary outflow tract. The obtained parameters are described in appendix 4. All recorded data was stored anonymously on the USCOM hard drive and transferred to a computer for analysis.

![USCOM interface and transducer](image-url)
**USCOM data acquisition**

To obtain the required Doppler flow profile the transducer was placed at the patient’s suprasternal notch (aortic valve) or alternatively along the left sternal edge at the level of the 3\textsuperscript{rd} intercostal space (pulmonary valve). To gain access to the suprasternal notch the patient was positioned supine (Figure 12). The pulmonary outflow tract was accessible in supine as well as sitting patients who were unable to lie flat (Figure 13).

![Figure 12. Transducer placement at the suprasternal notch (aortic window)](image12)

![Figure 13. Transducer placement left sternal edge (pulmonary window)](image13)
Prior to commencing measurements the patient’s study number, height, weight, gender and age were entered into the interface unit and gel was applied to the flat face of the transducer. The patient’s skin was inspected to ensure it was intact. The transducer was then firmly placed onto the skin and repositioned until a Doppler flow profile became visible on the screen of the interface unit. The angulation of the transducer was then carefully altered until a distinct triangular shaped flow profile was obtained. The angle was further adjusted aiming for maximum peak velocity (Figure 14).\textsuperscript{151} Once an optimal profile was obtained it was saved on the hard drive. On average three consecutive measurements were recorded of which the one with the sharpest flow profile was selected for analysis.

The measurement took no longer than two minutes. Cardio-haemodynamic data was determined from the blood flow profile across the aortic or pulmonary valve using a height/weight dependent algorithm.

\textbf{Figure 14. Example of optimal aortic valve Doppler profile.}
A distinct triangular shape with straight and continuous sides converging at a sharp peak.
2.4.3 NIRS tissue oxygen saturation (StO$_2$)

**StO$_2$ monitor**

The portable InSpectra™ StO$_2$ monitor (Hutchinson Technology$^{136}$ (Figure 15) was used to obtain continuous measurements of tissue oxygen saturation of all patients with severe sepsis / septic shock. This technology uses near-infrared (NIR) light and is based on the fundamental principle that oxygenated and deoxygenated haemoglobin have different light absorption spectra. Once the probe is positioned on the patient’s thenar eminence (Figure 16) NIR light is sent into the skeletal muscle tissue below where it is absorbed by the tissue haemoglobin. Light that has not been absorbed returns as an optical signal and is analyzed to calculate the tissue oxygen saturation (StO$_2$).

![InSpectra™ tissue oxygenation monitor](image)

Figure 15. *InSpectra™ tissue oxygenation monitor*$^{136}$
StO₂ data acquisition

The InSpectra™ StO₂ tissue oxygenation monitor required the placement of a single disposable sensor patch on the patient’s thenar eminence (Figure 16). Prior to attaching the sensor, the patient’s skin was inspected to ensure that it was intact and then gently cleaned with an alcohol wipe (Uhs Alcotip Swab) and allowed to dry. The sensor unit contained an adhesive shield to facilitate attachment to the patient’s skin and to protect measurements from ambient light interference. Once the sensor was attached to the patient it had to be connected to the optical cable before StO₂ monitoring could commence. StO₂ was monitored continuously throughout the patient’s stay in the ED whilst normal treatment continued. A 10 minute follow-up StO₂ measurement was taken 24 hours later on the hospital ward.

Figure 16. Sensor position on thenar eminence
2.5 Ethics & Consent

2.5.1 Ethical approval

Study 1 – ‘Assessment of cardio-haemodynamic parameters in adult ED patients with uncomplicated sepsis’ was approved by the Leicestershire, Northamptonshire & Rutland Research Ethics Committee 1 (REC Ref: 07/Q2501/56) on the 15th May 2007 (Appendix 5) and the University Hospitals of Leicester NHS Trust Research & Development department on the 19th June 2007 (Appendix 6).

Study 2 – ‘Assessment of cardio-haemodynamic parameters and tissue oxygen saturation in adult ED patients with severe sepsis / septic shock’ was approved by the Nottingham Research Ethics Committee 1 (REC Ref: 07/H0403/121) on the 17th December 2007 (Appendix 7) and the University Hospitals of Leicester NHS Trust Research & Development department on the 22nd February 2008 (Appendix 8).

2.5.2 Consent procedure

Suitable patients were screened for eligibility by the ‘Good Clinical Practice’ trained researcher (myself). If there were no reasons for the patient to be excluded the patient was approached and the study was explained to them using a standard set of ‘verbal prompts’ (Appendix 9). If the patient did not object to participation in this study then non-invasive haemodynamic measurements were commenced, as recommended by the Ethics Committee. The patient was given a study summary sheet (Appendix 10) and if his/her clinical condition allowed a detailed information leaflet (Appendix 11). The
patient was offered the opportunity to ask any questions. Informed consent was obtained at the earliest appropriate time as judged by the researcher (myself).

If the patient was deemed to lack capacity for consent to participate in the study his / her personal consultee was approached. A personal consultee can be any person ‘whom the person who lacks capacity would trust with important decisions about their welfare’ and who is capable and willing to act as the patient’s personal consultee for the purpose of the study.\textsuperscript{152} The study was explained to them and, if there were no objections to the patient’s participation in the study, recording of measurements commenced. The personal consultee received a detailed information leaflet (Appendix 12) and was given the opportunity to ask any question. Informed consent/assent was obtained at the earliest appropriate time.

In situations where the patient was known to lack capacity, as the result of a chronic condition, and a personal consultee could, despite efforts, not be identified a R&D approved nominated consultee was approached.

Patients who were identified as suitable controls were required to have capacity to give informed consent in order to participate in this study. Once the study was explained to them by the researcher they were given the opportunity to read the patient information leaflet (Appendix 13) and to ask any questions.

All consent forms used in these studies had been approved by the Research and Ethics Committee (an example of the used consent forms is shown in appendix 14). Only patients for whom informed consent had been obtained were included in the study, all others were excluded and their recorded measurements deleted.
**Withdrawals**

Patients were allowed to withdraw from the study at any time without providing a reason. If they withdrew, they were given the opportunity to have the data, already collected, to be excluded from the study. However, if no request was made, data collected up to the point at which the patient withdrew was to be included in the analysis.

**2.5.3 Adverse events monitoring**

All three technologies are non-invasive methods to monitor cardio-haemodynamic variables. It was not envisaged that they would cause any adverse events. No adverse effects have been reported in the literature. It was possible that the ECG electrodes could irritate the skin, though this was unlikely. If I would have become aware that a participant was potentially being harmed because of taking part in the study then the study would have been stopped and investigated accordingly. If an adverse reaction had occurred and it was believed to be related to the study intervention then this would have been logged and reported.

**2.5.4 Data protection**

All data was collated and stored in the Emergency Medicine Academic Unit, at the Leicester Royal Infirmary. Patients were allocated a unique study number and a decoding record was kept securely within the department. Patient’s confidentiality was maintained at all times.
2.6 Statistical analysis

Descriptive variables were presented as mean or median and 95% confidence interval (CI). The paired samples t-test was used to compare normally distributed continuous paired data, e.g. two sets of measurements from one cohort. To compare continuous unpaired data, such as septic with control patients, the independent samples t-test was chosen. The Kolmogorov-Smirnov-test was applied to test for normal distribution. Dichotomous variables were analysed using the Chi-square test. Two-tailed hypothesis testing was performed.

Kaplan-Meier survival analysis was used to explore probability of survival in patients with severe sepsis/septic shock.

To test for diagnostic accuracy receiver operating characteristics (ROC) curves were constructed and the area under the ROC curve (AUROC) as predictor for mortality calculated.

To assess the correlation between two continuous variables the Pearson’s coefficient was calculated. Linear regression was used to assess the direction and strength of the relationship between two continuous variables. To describe the agreement between two methods Bland-Altman plots were constructed.

All analysis was performed using Microsoft Office Excel 2007 and MedCalc®. The level of statistical significance was set at \( p < 0.01 \) (using the Bonferroni correction for multiple testing).
3 RESULTS

3.1 STUDY 1 – Assessment of cardio-haemodynamic parameters in adult Emergency Department patients with uncomplicated sepsis

3.1.1 General

Twenty nine patients who presented to the Emergency Department of the Leicester Royal Infirmary with features of sepsis during July and November 2007 were considered for inclusion. Two patients had to be excluded from enrolment in this study as one was given a working diagnosis of pulmonary embolus (PE), which was subsequently confirmed on CT pulmonary angiogram, and one patient was found to have diabetic ketoacidosis (DKA) without evidence of infection. A further two patients had to be excluded from the study, one for inability to gain informed consent and one due to a technical difficulty in recording measurements of adequate quality. Therefore 25 septic ED patients were included in the study.

The study population varied in their number of systemic inflammatory response syndrome (SIRS) criteria on arrival in the ED. There was a nearly equal distribution of patients with two (n=9), three (n=9) or four (n=7) SIRS parameters. The source of sepsis was most commonly the respiratory tract (n=10), followed by the urinary tract (n=5), skin/skeletal (n=4), abdomen (n=3), ENT/dental (n=2) and viral (n=1).
During the same study period twenty five control patients were recruited from the ED minor injury area. Figure 17 illustrates the flow of all patients through the study.

Figure 17. Flow diagram of study population
3.1.2 Study 1 – Results – Objective 1

Comparison of TEB cardio-haemodynamic parameters between septic and non-septic ED patients

Twenty five septic and twenty five non-septic control patients had TEB readings of adequate quality recorded and were included in the analysis. Both groups were well matched with regards to their demographics which are shown in Table 2.

Table 2. Characteristics of septic and control ED patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sepsis n=25</th>
<th>Control n=25</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>58 (48 – 67)</td>
<td>58 (48 – 67)</td>
<td>0.981</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (52)</td>
<td>12 (48)</td>
<td>0.999</td>
</tr>
<tr>
<td>Female</td>
<td>12 (48)</td>
<td>13 (52)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166 (161 – 172)</td>
<td>167 (162 – 172)</td>
<td>0.946</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76 (69 – 83)</td>
<td>72 (67 – 78)</td>
<td>0.380</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval) unless stated otherwise

All septic patients had their conventional physiological measurements (heart rate, respiratory rate, blood pressure, oxygen saturation and temperature) taken as part of their routine assessment on arrival in the ED. These routine parameters were also obtained from all control patients prior to their enrolment in the study. Apart from SpO2, parameters of septic patients differed significantly from those of the control cohort as depicted in Table 3.
Table 3. Routine physiological parameters on arrival in ED

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sepsis n=25</th>
<th>Control n=25</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>117 (110 – 124)</td>
<td>70 (66 – 74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temperature (⁰C)</td>
<td>38.2 (37.5 – 39.0)</td>
<td>36.5 (36.3 – 36.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory rate (min⁻¹)</td>
<td>25 (21 – 28)</td>
<td>14 (13 – 15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>97 (96 – 98)</td>
<td>98 (98 – 99)</td>
<td>0.067</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>126 (115 – 136)</td>
<td>146 (140 – 152)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)

TEB measurements of septic patients were acquired as soon as possible after the patient’s arrival in the ED. Non-septic control patients had their TEB readings taken during their stay in the ED minor injury area. On arrival in the ED septic patients had a significantly higher HR and a lower MAP than their non-septic controls. With regards to their cardio-haemodynamic measures ED patients with sepsis were found to have a significantly lower SV, SI and SVR compared to non-septic ED patients. Cardiac index was increased by 0.7 l/min/m² (95%CI 0.1 to 1.1) and cardiac output by 1.2 l/min (95%CI 0.1 to 2.4) in the septic cohort but this difference did not reach statistical significance. The TFC, a parameter primarily determined by the amount of intravascular, intra-alveolar and interstitial fluid in the thorax, was found to be similar in both cohorts. The TEB measurements of the control group were of slightly higher quality, as revealed by the quality indicator (QI). Table 4 gives a summary of the compared parameters, with those demonstrating statistical significance being shaded ‘grey’. 
Table 4. TEB parameters of septic and non-septic (control) patients on arrival in the ED

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sepsis n=25</th>
<th>Control n=25</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QI (%)</td>
<td>89 (84 – 95)</td>
<td>94 (91 – 97)</td>
<td>0.116</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>3.8 (3.3 – 4.2)</td>
<td>3.1 (2.8 – 3.4)</td>
<td>0.013</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>6.9 (6.0 – 7.8)</td>
<td>5.7 (5.0 – 6.3)</td>
<td>0.029</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>35 (31 – 39)</td>
<td>45 (41 – 49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>64 (56 – 73)</td>
<td>82 (72 – 91)</td>
<td>0.008</td>
</tr>
<tr>
<td>SVR (dynes·s·cm⁻⁵)</td>
<td>1071 (874 – 1269)</td>
<td>1435 (1263 – 1606)</td>
<td>0.006</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>89 (82 – 96)</td>
<td>100 (96 – 104)</td>
<td>0.007</td>
</tr>
<tr>
<td>TFC (1/kΩ)</td>
<td>29.0 (26.8 – 31.3)</td>
<td>27.0 (23.5 – 30.5)</td>
<td>0.319</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>110 (103 – 117)</td>
<td>70 (66 – 74)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)

The ability of each parameter to differentiate between septic and non-septic ED patients was tested using the receiver operating characteristics (ROC) analysis. The area under the ROC curve (AUROC), the ROC derived optimal cut-off and its sensitivity and specificity are presented in Table 5. The optimal cut-off was derived by giving equal value to sensitivity and specificity. The ROC curves for the three best performing parameters (AUROC >0.7), shaded in ‘grey’ in Table 5, are displayed in Figure 18.
Table 5. ROC derived values predictive of sepsis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUROC</th>
<th>Optimal cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>0.702</td>
<td>&gt; 3.0</td>
<td>80.0 (59.3-93.2)</td>
<td>52.9 (31.3-72.2)</td>
</tr>
<tr>
<td>CO</td>
<td>0.674</td>
<td>&gt; 4.8</td>
<td>84.0 (63.9-95.5)</td>
<td>48.0 (27.8-68.7)</td>
</tr>
<tr>
<td>SI</td>
<td>0.743</td>
<td>≤ 39</td>
<td>64.0 (42.5-82.0)</td>
<td>68.0 (46.5-85.1)</td>
</tr>
<tr>
<td>SV</td>
<td>0.694</td>
<td>≤ 71</td>
<td>60.0 (38.7-78.9)</td>
<td>68.0 (46.5-85.1)</td>
</tr>
<tr>
<td>SVR</td>
<td>0.760</td>
<td>≤ 1174</td>
<td>72.0 (50.6-87.9)</td>
<td>72.0 (50.6-87.9)</td>
</tr>
<tr>
<td>TFC</td>
<td>0.643</td>
<td>&gt; 26.6</td>
<td>64.0 (42.5-82.0)</td>
<td>56.0 (34.9-75.6)</td>
</tr>
</tbody>
</table>

Figure 18. ROC curves for cardiac index, stroke index and systemic vascular resistance (ED arrival)
3.1.3 Study 1 – Results – Objective 2

Change of TEB cardio-haemodynamic parameters in septic patients with normal treatment in the ED

All septic patients were continuously monitored through the TEB device in addition to their conventional physiological observations whilst receiving normal treatment for sepsis. Treatment was administered at the discretion of the responsible clinician who had no access to the recorded TEB data. All septic patients received intravenous fluids and antibiotics and if clinically indicated supplemental oxygen in the ED, though there was no standard ‘sepsis protocol’ in place at the time of the study. Patients received on average 1144 millilitre (95%CI 893 to 1397) of intravenous fluids in the ED, equating to an average of 17 millilitre/kilogram bodyweight (95% CI 12 to 21).

TEB readings of adequate quality were successfully obtained for all included septic patients on arrival and departure from the ED. The comparison of arrival and departure measurements indicated, that the treatment given in the ED had very little immediate effect on changes in cardio-haemodynamic parameters (Table 6). Having said this, there were changes seen in CO and CI that were suggestive of a trend towards ‘normal’ values. Statistically significant changes were only observed for heart rate (HR) which was reduced by 11 beats/min (95% CI -15.6 to -5.6) and thoracic fluid content (TFC), which had increased by 2.6 per kilo ohm (95%CI 1.2 to 3.9) since patients’ arrival in the ED.
Table 6. TEB measurements on arrival and departure from the ED

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ED arrival (n=25)</th>
<th>ED departure (n=25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (l/min/m²)</td>
<td>3.8 (3.3 – 4.2)</td>
<td>3.5 (3.1 – 3.9)</td>
<td>0.035</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>6.9 (6.0 – 7.8)</td>
<td>6.5 (5.6 – 7.4)</td>
<td>0.038</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>64 (56 – 73)</td>
<td>67 (57 – 76)</td>
<td>0.265</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>35 (31 – 39)</td>
<td>36 (31 – 40)</td>
<td>0.375</td>
</tr>
<tr>
<td>SVR (dynes·s·cm⁻⁵)</td>
<td>1071 (874 – 1269)</td>
<td>1112 (900 – 1325)</td>
<td>0.432</td>
</tr>
<tr>
<td>SVRI (dynes·s·cm⁻⁵/m²)</td>
<td>1957 (1577 – 2338)</td>
<td>2016 (1633 – 2398)</td>
<td>0.515</td>
</tr>
<tr>
<td>TFC (1/kΩ)</td>
<td>29.0 (26.8 – 31.3)</td>
<td>31.6 (28.8 – 34.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>110 (103 – 117)</td>
<td>99 (93 – 106)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>89 (82 – 96)</td>
<td>85 (79 – 90)</td>
<td>0.111</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>126 (115 – 136)</td>
<td>117 (108 – 125)</td>
<td>0.030</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>75 (69 – 82)</td>
<td>73 (68 – 79)</td>
<td>0.429</td>
</tr>
<tr>
<td>LCW (kg·m⁻¹)</td>
<td>7.8 (6.6 – 9.1)</td>
<td>6.9 (5.9 – 7.8)</td>
<td>0.023</td>
</tr>
<tr>
<td>LCWI (kg·m²/m²)</td>
<td>4.2 (3.6 – 4.8)</td>
<td>3.7 (3.3 – 4.1)</td>
<td>0.026</td>
</tr>
<tr>
<td>PEP (ms)</td>
<td>83 (75 – 91)</td>
<td>83 (73 – 92)</td>
<td>0.905</td>
</tr>
<tr>
<td>LVET (ms)</td>
<td>242 (228 – 256)</td>
<td>256 (234 – 277)</td>
<td>0.060</td>
</tr>
<tr>
<td>ETR (%)</td>
<td>44 (41 – 46)</td>
<td>42 (39 – 44)</td>
<td>0.090</td>
</tr>
<tr>
<td>QI (%)</td>
<td>89 (84 – 95)</td>
<td>89 (83 – 94)</td>
<td>0.837</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)
### 3.1.4 Study 1 – Results – Objective 3

#### Change of TEB cardio-haemodynamic parameters in septic ED patients after a 24-hour period of treatment

TEB measurements for 23 of the 25 septic patients were available after 24 hours of treatment. One patient had been discharged from hospital prior to the 24-hour follow-up assessment without the researcher being informed and one patient died shortly after departure from the ED. After admission to the ward patients received on average a further 1236 millilitres (95%CI 519 to 1953) of intravenous fluids over 24 hours. The paired TEB measurements obtained from the septic cohort on ED arrival and after 24 hours of treatment are presented in Table 7.

With normal treatment for sepsis the HR decreased significantly by 24 beats/min (95%CI -31 to -18) which, given the marginal changes in mean SV, resulted in a significant reduction in CI by 0.5 l/min/m$^2$ (95%CI -0.9 to -0.3). Significant changes were also seen in left ventricular ejection time (LVET), a marker of cardiac contractility, showing an increase by 40 milliseconds (95%CI 22 to 59) compared to ED arrival. There was a further increase of 3.4 per kilo ohm (95%CI 0.6 to 6.3) in the TFC by the end of 24 hours but this was not statistically significant. MAP and SVR showed no considerable changes during the first 24 hours of normal treatment.

Comparing the TEB measurements of the septic cohort obtained at 24 hours with the control data showed that nearly all parameters demonstrated a trend towards ‘normal’ values (Figure 19). This tendency was most noticeable for CI and CO where the difference between the septic cohort and controls was only 0.06 l/min/m$^2$ (95%CI -0.36 to 0.48) for cardiac index and 0.2 l/min (95%CI -0.8 to 1.2) for cardiac output.
Table 7. TEB measurements of septic patients on ED arrival and at 24 hour follow up

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ED arrival (n=23)</th>
<th>24 hour follow up (n=23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (l/min/m²)</td>
<td>3.7 (3.3 – 4.2)</td>
<td>3.2 (2.8 – 3.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>6.9 (5.9 – 7.9)</td>
<td>5.9 (5.2 – 6.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>64 (55 – 74)</td>
<td>69 (61 – 78)</td>
<td>0.102</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>35 (31 – 39)</td>
<td>38 (34 – 42)</td>
<td>0.091</td>
</tr>
<tr>
<td>SVR (dynes·s·cm⁻⁵)</td>
<td>1089 (876 – 1302)</td>
<td>1152 (1021 – 1282)</td>
<td>0.449</td>
</tr>
<tr>
<td>SVRI (dynes·s·cm⁻⁵/m²)</td>
<td>1998 (1587 – 2409)</td>
<td>2108 (1861 – 2355)</td>
<td>0.479</td>
</tr>
<tr>
<td>TFC (1/kΩ)</td>
<td>28.8 (26.4 – 31.2)</td>
<td>32.2 (28.5 – 36.0)</td>
<td>0.020</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>110 (102 – 117)</td>
<td>85 (79 – 92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>90 (81 – 97)</td>
<td>87 (80 – 93)</td>
<td>0.418</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>127 (116 – 138)</td>
<td>123 (113 – 133)</td>
<td>0.440</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>76 (69 – 83)</td>
<td>74 (68 – 79)</td>
<td>0.394</td>
</tr>
<tr>
<td>LCW (kg·m)</td>
<td>7.9 (6.5 – 9.2)</td>
<td>6.5 (5.4 – 7.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>LCWI (kg·m/m²)</td>
<td>4.2 (3.6 – 4.8)</td>
<td>3.5 (3.0 – 4.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>PEP (ms)</td>
<td>84 (75 – 93)</td>
<td>91 (82 – 100)</td>
<td>0.102</td>
</tr>
<tr>
<td>LVET (ms)</td>
<td>242 (226 – 257)</td>
<td>282 (259 – 305)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ETR (%)</td>
<td>44 (41 – 46)</td>
<td>40 (37 – 42)</td>
<td>0.001</td>
</tr>
<tr>
<td>QI (%)</td>
<td>89 (83 – 94)</td>
<td>92 (87 – 97)</td>
<td>0.208</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)
Figure 19. Comparison of cardiac output, stroke volume and systemic vascular resistance in septic patients on ED arrival, ED departure, at 24 hour with non-septic controls
3.1.5 Study 1 – Results – Objective 4

**Relationship between changes in TEB parameters and changes in MAP and HR in patients with uncomplicated sepsis**

Complete data sets were available from 23 septic patients. Comparisons were made between changes over 24 hours in measured cardio-haemodynamic and conventional circulatory parameters. CO and HR were both increased on arrival in the ED and decreased with treatment though the absolute and relative decrease in HR was more evident. The changes in SV were opposite to those of HR but less pronounced during the first 24 hours. Both, SVR and MAP were reduced in septic patients on their arrival in the ED compared to control and remained fairly static despite treatment.

Relative change over the first 24 hours whilst receiving normal treatment was calculated for each parameter and patient. The most significant changes were observed for HR -21.6% (95%CI -26.6 to -16.7) and CO -15.9% (95%CI -19.7 to -4.5). There was an increase in SV 12.7% (95%CI 1.1 to 24.4) and SVR 16.6% (95%CI -1.0 to 34.1), whilst there was no change in MAP -1.2% (95%CI -10.2 to 7.8%).

The strength of the relationship between relative changes in these parameters was assessed using Pearson’s correlation coefficient (r) (Table 8). A poor relationship between changes in CO and changes in HR and MAP over the initial 24 hour period was demonstrated. There was a strong positive association between relative changes in SVR and MAP and a weak positive relationship between SVR and HR. A moderate negative association was found between changes in SV and HR, whereas changes in
SV were weakly negative associated with MAP. The graphical illustration of these relationships is shown in Figure 20. The scatter plot shows that changes in HR or MAP were unrelated to changes in CO, as indicated by the random spread of the data points and the linear approximation of their values parallel to the abscissa. Changes in SV and HR followed the expected inverse linear pattern with bigger increases in SV being associated with a greater decrease in HR. The strongest linear relationship is shown for changes in SVR and MAP, where data points are clustered around an almost diagonal line.

Table 8. Pearson’s correlation coefficients for relative changes in TEB cardio-haemodynamic and conventional variables

<table>
<thead>
<tr>
<th></th>
<th>%ΔCO Arr/Dep</th>
<th>%ΔCO Arr/24hr</th>
<th>%ΔSVR Arr/Dep</th>
<th>%ΔSVR Arr/24hr</th>
<th>%ΔSV Arr/Dep</th>
<th>%ΔSV Arr/24hr</th>
<th>%ΔMAP Arr/Dep</th>
<th>%ΔMAP Arr/24hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>%ΔHR Arr/Dep</td>
<td>0.380</td>
<td>-0.049</td>
<td>-0.357</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.440</td>
</tr>
<tr>
<td>%ΔHR Arr/24hr</td>
<td>-0.043</td>
<td>0.410</td>
<td>-0.534</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.568</td>
</tr>
<tr>
<td>%ΔMAP Arr/Dep</td>
<td>0.310</td>
<td>0.468</td>
<td>-0.040</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%ΔMAP Arr/24hr</td>
<td>-0.157</td>
<td>0.819</td>
<td>-0.424</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%ΔSV Arr/Dep</td>
<td>0.710</td>
<td>-0.665</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%ΔSV Arr/24hr</td>
<td>0.847</td>
<td>-0.745</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%ΔSVR Arr/Dep</td>
<td>-0.681</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%ΔSVR Arr/24hr</td>
<td>-0.649</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 20.  Relationship between changes in cardio-haemodynamic and conventional parameters in septic patients with 24 hours of normal treatment
3.2 STUDY 2 – Assessment of cardio-haemodynamic parameters and tissue oxygen saturation in adult ED patients with severe sepsis or septic shock

3.2.1 General

Ninety patients who presented to the Emergency Department with features of severe sepsis / septic shock between August 2008 to October 2008 and January 2009 to March 2009 were screened for inclusion. Forty patients were excluded as per the study’s exclusion criteria. One further patient was unable to give informed consent due to lack of mental capacity and unavailability of a ‘personal consultee’. Therefore forty nine patients were included in the study. The patients’ flow through the study is illustrated in Figure 21.

Seventeen patients were classed as suffering from severe sepsis, fourteen from septic shock and eighteen from cryptic shock. The source of sepsis was most commonly the respiratory tract (n=32), followed by the urinary tract (n=9), abdomen (n=4), central nervous system (n=2), skin (n=1) and HIV related (n=1).

During the study period five more patients were recruited to the already existing control pool of non-septic ED patients. Out of this data pool twenty five patients, whose demographic data best matched those of the severe sepsis cohort, were chosen to form the control cohort for this study.
Figure 21. Flow diagram of study population
The mean age of the cohort studied was 71 years (95%CI 65 to 77) of which 35 (71%) were men. Their baseline characteristics are shown in Table 9. Nearly one quarter of patients were care home residents. Half of all patients suffered from chronic cardiovascular conditions, with hypertension being the most common.

Table 9. Characteristics of study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study participants n=49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>71 (65 – 76)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>35 (71)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (29)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170 (168 – 173)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74 (67 – 80)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>42 (86)</td>
</tr>
<tr>
<td>Care Home residency, n (%)</td>
<td>12 (24)</td>
</tr>
<tr>
<td>Past cardiovascular history, n (%)</td>
<td></td>
</tr>
<tr>
<td>Any cardiovascular morbidity</td>
<td>24 (50)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Myocardial infarct</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval) unless stated otherwise

The physiological observations taken on arrival in the ED clearly showed that the cohort was critically ill with an average early warning score (EWS) of 7, ranging from 3 to 12. More than three quarters of patients (78%) had three or more positive SIRS criteria when arriving in the ED. Nearly half of the patients (45%) were hypotensive.
and 59% had a reduced level of consciousness on arrival in the ED. The near-patient venous lactate taken on arrival measured $\geq 4$mmol in nearly two thirds (59%) of patients. Table 10 summarises the physiological parameters and blood results taken on ED arrival.

### Table 10. Physiological and biological parameter on arrival in ED

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study participants n=49</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiology on ED arrival,</strong></td>
<td></td>
</tr>
<tr>
<td>GCS score*</td>
<td>14 (14 – 15)</td>
</tr>
<tr>
<td>Temperature (°C)*</td>
<td>38 (37.3 – 38.4)</td>
</tr>
<tr>
<td>Heart rate (min$^{-1}$)</td>
<td>116 (110 – 122)</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>96 (94 – 97)</td>
</tr>
<tr>
<td>Respiratory rate (min$^{-1}$)</td>
<td>30 (28 – 34)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>101 (94 – 109)</td>
</tr>
<tr>
<td>EWS</td>
<td>7.2 (6.6 – 7.7)</td>
</tr>
<tr>
<td>MEDS score</td>
<td>9.1 (8.0 – 10.2)</td>
</tr>
<tr>
<td><strong>Need for supplemental oxygen, n (%)</strong></td>
<td>35 (71)</td>
</tr>
<tr>
<td><strong>Arrival blood results,</strong></td>
<td></td>
</tr>
<tr>
<td>White cell count (10$^9$/l)</td>
<td>16.5 (13.2 – 19.7)</td>
</tr>
<tr>
<td>Haemoglobin (g/l)</td>
<td>12.5 (12 – 13)</td>
</tr>
<tr>
<td>Platelet count (10$^9$/l)</td>
<td>273 (230 – 317)</td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
<td>5.0 (4.0 – 6.0)</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)
*Median (95% confidence interval)
MEDS Mortality in Emergency Department Sepsis score

The observed mortality in this severe sepsis /septic shock cohort was 49% (n=24). One third of all deaths occurred within 24 hours of patients’ arrival to the Emergency Department. Figure 22 illustrates the proportion of death within 24 hours, early (1 to 3 days), intermediate (4 to 13 days) and late (14 to 30 days) for this cohort. The survival
probability over time is shown in Figure 23. It illustrates that a patient’s chance of survival reduced steeply by 30% within the first 72 hours of hospital admission.

![Figure 22. Number of deaths in relation to length of survival since arrival in the ED](image)

![Figure 23. Probability of survival from sepsis with organ dysfunction over time](image)
3.2.2 Study 2 – Results – Objective 1

Comparison of cardio-haemodynamic parameters in Emergency Department patients with severe sepsis or septic shock and non-septic ED patients

Forty eight of the forty nine study group patients had TEB measurements of adequate quality obtained upon their arrival in the ED. The control cohort consisted of twenty five patients. All of the seventy three patients were included in the analysis. Both groups were well matched in view of their demographics. There were proportionally more men in the study group but this was not statistically significant. Table 11 summarises their characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Severe sepsis /shock n= 48</th>
<th>Control n=25</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>71 (65 – 77)</td>
<td>69 (61 – 76)</td>
<td>0.603</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>Male 35 (73)</td>
<td>15 (60)</td>
<td>0.385</td>
</tr>
<tr>
<td></td>
<td>Female 13 (27)</td>
<td>10 (40)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171 (168 – 174)</td>
<td>169 (164 – 174)</td>
<td>0.445</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74 (68 – 80)</td>
<td>74 (69 – 79)</td>
<td>0.994</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval) unless stated otherwise

The TEB measurements obtained in the control group were of higher quality than the study group measurements, as indicated by the quality index (QI). The difference however was not statistically significant and the quality index of all obtained TEB readings was well above the 50 % mark which is the manufacturer’s recommended cut
off point for reliable data. The difference in CI between study group and control was 0.3 l/min/m$^2$. Though this was in keeping with the pre-defined minimum clinical significant difference it did not reach statistical significance, as the standard deviation was larger than anticipated. Patients with severe sepsis / shock were found to have a significantly lower SV and stroke index SI than their controls. Systemic vascular resistance was significantly lower in the study cohort as was the MAP. Severely septic patients had a significantly higher TFC, a parameter primarily determined by the amount of intravascular, intra-alveolar and interstitial fluids in the thorax. Table 12 gives an overview of all compared parameters.

### Table 12. TEB parameters in severe sepsis/ septic shock on ED arrival compared to control

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Severe sepsis n= 48</th>
<th>Control n=25</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QI (%)</td>
<td>84 (78 – 89)</td>
<td>93 (89 – 96)</td>
<td>0.015</td>
</tr>
<tr>
<td>CI (l/min/m$^2$)</td>
<td>3.4 (3.1 – 3.7)</td>
<td>3.1 (2.8 – 3.4)</td>
<td>0.135</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>6.4 (5.6 – 7.1)</td>
<td>5.7 (5.0 – 6.4)</td>
<td>0.215</td>
</tr>
<tr>
<td>SI (ml/m$^2$)</td>
<td>32 (29 – 35)</td>
<td>44 (40 – 49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>59 (53 – 64)</td>
<td>82 (72 – 91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SVR (dynes·s·cm$^{-5}$)</td>
<td>984 (844 – 1123)</td>
<td>1466 (1279 – 1653)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>75 (70 – 81)</td>
<td>102 (97 – 108)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TFC (1/kΩ)</td>
<td>31.5 (29.8 – 33.2)</td>
<td>26.4 (24.5 – 28.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>111 (104 – 118)</td>
<td>71 (66 – 76)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)
Comparison was also made between measurements available from the severe sepsis cohort at the 24 hour follow up (n=37) and the control group (Table 13). The lower number of severe septic patients at 24 hours was due to death (n=8), refusal to follow up (n=2) and equipment failure (n=1), section 3.2.3 contains a more detailed explanation. Despite these drop-outs both groups remained well matched in view of age (p=0.71), gender (p=0.21), height (p=0.23) and weight (p=0.58).

Table 13. TEB parameters in severe sepsis/shock at 24 follow up compared to controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Severe sepsis n=37</th>
<th>Control n=25</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QI (%)</td>
<td>84 (78-90)</td>
<td>93 (89 – 96)</td>
<td>0.019</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>3.0 (2.7-3.2)</td>
<td>3.1 (2.8-3.4)</td>
<td>0.538</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>5.7 (5.0-6.4)</td>
<td>5.7 (5.0-6.4)</td>
<td>0.974</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>35 (31-38)</td>
<td>44 (40-49)</td>
<td>0.001</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>66 (58-75)</td>
<td>82 (72-91)</td>
<td>0.015</td>
</tr>
<tr>
<td>SVR (dynes·s·cm⁻⁵)</td>
<td>1075 (929-1221)</td>
<td>1466 (1279-1653)</td>
<td>0.003</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>76 (70-81)</td>
<td>102 (97-108)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TFC (1/ķΩ)</td>
<td>38.6 (34.5-42.6)</td>
<td>26.4 (24.5-28.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>87 (81-94)</td>
<td>71 (66-76)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)
There was no statistical or clinical significant difference in CI or CO between the two
groups. At 24 hours the severe sepsis cohort still had a significantly lower SVR and
MAP as well as a higher HR compared to the control group. There was no statistical
significant difference in SV but there was in SI. The severe sepsis group had at 24
hours a significantly higher TFC than the control cohort.

Receiver operating characteristics (ROC) analysis was used to assess the ability of
each cardio-haemodynamic parameter to discriminate between severely septic and
non-septic ED patients on arrival. The area under the ROC curve (AUROC), the ROC
derived optimal cut-off and its sensitivity and specificity are presented in Table 14. The
ROC curves for the four bests performing parameters with an AUROC greater than 0.7
(shaded in grey) are displayed in Figure 24.

Table 14. ROC derived values predictive of severe sepsis on ED arrival

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUROC</th>
<th>Optimal cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>0.588</td>
<td>&gt; 3.1</td>
<td>54.8 (38.7-70.2)</td>
<td>60.0 (38.7-78.9)</td>
</tr>
<tr>
<td>CO</td>
<td>0.576</td>
<td>&gt; 4.8</td>
<td>76.2 (60.5-87.9)</td>
<td>44.0 (24.4-65.1)</td>
</tr>
<tr>
<td>SI</td>
<td>0.810</td>
<td>≤ 37</td>
<td>76.2 (60.5-87.9)</td>
<td>76.0 (54.9-90.6)</td>
</tr>
<tr>
<td>SV</td>
<td>0.770</td>
<td>≤ 69</td>
<td>78.6 (63.2-89.7)</td>
<td>72.0 (50.6-87.9)</td>
</tr>
<tr>
<td>SVR</td>
<td>0.822</td>
<td>≤ 1094</td>
<td>79.0 (62.7-90.4)</td>
<td>80.0 (59.3-93.2)</td>
</tr>
<tr>
<td>TFC</td>
<td>0.740</td>
<td>&gt; 27</td>
<td>76.2 (60.5-87.9)</td>
<td>64.0 (42.5-82.0)</td>
</tr>
</tbody>
</table>
Figure 24. ROC curves for stroke index, stroke volume, systemic vascular resistance and thoracic fluid content (ED arrival)
3.2.3 Study 2 – Results – Objective 2

Change of cardio-haemodynamic parameters in severe sepsis / septic shock patients with normal treatment in the ED and after 24 hours

All patients were continuously monitored in the Emergency Department using the equipment as described under section 2.4, whilst receiving normal treatment for severe sepsis / septic shock. At the time of the study there was no standard sepsis protocol in place, hence treatment was given at the discretion of the clinician responsible. Clinicians had access to conventional monitoring equipment but not to the cardio-haemodynamic readings. All patients received intravenous fluids and antibiotics and, if clinically indicated, supplemental oxygen as part of their ED treatment. Patients received on average 1327 millilitres (95%CI 1051 to 1604) of intravenous fluid whilst in the ED equating to an average of 20 mls/kg bodyweight (95% CI 15 to 24). After admission to a hospital ward patients received on average a further 2234 millilitre (95%CI 1559 to 2910) of fluids within the first 24 hours. None of the patients received inotropic therapy, vasopressors or blood products whilst in the ED. Only one patient was temporarily commenced on Noradrenaline whilst on the intensive care unit but this had been discontinued well before the 24 hour follow up.

**TEB measurements**

TEB readings on arrival in the Emergency Department were successfully obtained for all but one patient who suffered from severe cervical spondylosis making the placement of the dual sensor patches impossible. Equipment failure prevented the
recording of TEB ED departure data for one patient. Therefore paired TEB data on
arrival and departure from the ED was available for 47 patients. The obtained TEB
recordings were all of acceptable quality remaining well above the 50% reliability
mark throughout. Table 15 gives a summary of the recorded TEB parameters on arrival
and departure from the ED.

Neither CI, CO, SV nor SVR were found to have changed significantly with normal
treatment received in the ED. There was however, a significant increase in TFC and a
significant decrease in left cardiac work (LCW), HR and blood pressure by the time
the patient left the ED.
Table 15.  TEB measurements of severely septic patients on ED arrival and departure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ED arrival (n=47)</th>
<th>ED departure (n=47)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CI (l/min/m²)</strong></td>
<td>3.4 (3.1-3.7)</td>
<td>3.2 (2.9-3.5)</td>
<td>0.038</td>
</tr>
<tr>
<td><strong>CO (l/min)</strong></td>
<td>6.4 (5.6-7.1)</td>
<td>5.9 (5.3-6.5)</td>
<td>0.028</td>
</tr>
<tr>
<td><strong>SV (ml)</strong></td>
<td>60 (54-67)</td>
<td>60 (54-65)</td>
<td>0.789</td>
</tr>
<tr>
<td><strong>SI (ml/m²)</strong></td>
<td>32 (29-35)</td>
<td>32 (30-35)</td>
<td>0.930</td>
</tr>
<tr>
<td><strong>SVR (dynes·s·cm⁻⁵)</strong></td>
<td>978 (833-1124)</td>
<td>872 (782-961)</td>
<td>0.121</td>
</tr>
<tr>
<td><strong>SVRI (dynes·s·cm⁻⁵/m²)</strong></td>
<td>1774 (1547-2001)</td>
<td>1614 (1460-1768)</td>
<td>0.126</td>
</tr>
<tr>
<td><strong>TFC (1/kΩ)</strong></td>
<td>31.7 (29.9-33.5)</td>
<td>34.2 (31.9-36.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>HR (beats/min)</strong></td>
<td>110 (102-117)</td>
<td>102 (94-109)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>MAP (mmHg)</strong></td>
<td>76 (70-82)</td>
<td>67 (61-73)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td>113 (104-122)</td>
<td>101 (93-109)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>DBP (mmHg)</strong></td>
<td>62 (57-67)</td>
<td>54 (49-60)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>LCW (kg·m)</strong></td>
<td>6.3 (5.0-7.5)</td>
<td>5.2 (4.2-6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>LCWI (kg·m/m²)</strong></td>
<td>3.3 (2.7-3.9)</td>
<td>2.7 (2.2-3.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PEP (ms)</strong></td>
<td>84 (72-97)</td>
<td>85 (73-96)</td>
<td>0.978</td>
</tr>
<tr>
<td><strong>LVET (ms)</strong></td>
<td>237 (225-249)</td>
<td>250 (236-265)</td>
<td>0.060</td>
</tr>
<tr>
<td><strong>ETR (%)</strong></td>
<td>42 (40-44)</td>
<td>41 (39-43)</td>
<td>0.251</td>
</tr>
<tr>
<td><strong>QI (%)</strong></td>
<td>84 (79-90)</td>
<td>81 (74-88)</td>
<td>0.227</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)
Areas shaded grey highlight statistically significant differences
At the 24 hour assessment point only 41 patients were still alive, two of which had already been excluded from analysis. A further two patients refused follow up measurements, making 37 paired data available for comparing change over 24 hours. Table 16 gives a summary of measured TEB parameters on arrival in the ED and at the 24 hour follow up. Figure 25 depicts the changes during the first 24 hours using box and whisker plots for selected parameters.

The data shows that 24 hours of normal treatment resulted in a significant reduction in CI and CO which was mainly attributable to the significant decrease in HR as the SV remained essentially unchanged. There was a further significant increase in TFC reflecting the ongoing administration of intravenous fluids within the first 24 hours of hospital admission. Compared to ED arrival there was also a significant increase in the left ventricular ejection time (LVET), a marker of contractility. Though there was an increase in SV and SVR at 24 hours compared to arrival in the ED these changes were not significant.

The significant reduction in blood pressure (MAP, SBP or DBP) and in LCW found on departure from the ED had disappeared after 24 hours of normal treatment. This raises the question whether the decline seen on departure from ED was simply the effect of cardiovascular deterioration in those who died within 24 hours. However, when excluding these eight patient from the analysis altogether the significant difference in MAP (78 mmHg vs. 70 mmHg; p=0.008) and LCW (6.7kg m vs. 5.6kg m, p=0.003) between arrival and departure from the ED remained.
Table 16. TEB measurements in severely septic patients on ED arrival and at 24 hour follow up

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ED arrival (n=37)</th>
<th>24 hour follow up (n=37)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (l/min/m²)</td>
<td>3.5 (3.1-3.9)</td>
<td>3.0 (2.7-3.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>6.7 (5.8-7.6)</td>
<td>5.7 (5.0-6.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>64 (56-72)</td>
<td>66 (58-75)</td>
<td>0.502</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>34 (30-39)</td>
<td>35 (31-38)</td>
<td>0.477</td>
</tr>
<tr>
<td>SVR (dynes·s·cm⁻⁵)</td>
<td>961 (775-1148)</td>
<td>1075 (929-1221)</td>
<td>0.223</td>
</tr>
<tr>
<td>SVRI (dynes·s·cm⁻⁵/m²)</td>
<td>1764 (1489-2038)</td>
<td>2006 (1792-2220)</td>
<td>0.147</td>
</tr>
<tr>
<td>TFC (1/kΩ)</td>
<td>31.4 (29.2-33.5)</td>
<td>38.6 (34.5-42.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>107 (99-115)</td>
<td>87 (81-94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>78 (70-85)</td>
<td>76 (70-81)</td>
<td>0.635</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>115 (103-127)</td>
<td>114 (104-124)</td>
<td>0.856</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>63 (57-70)</td>
<td>62 (57-66)</td>
<td>0.543</td>
</tr>
<tr>
<td>LCW (kg·m)</td>
<td>6.7 (5.1-8.3)</td>
<td>5.6 (4.5-6.6)</td>
<td>0.057</td>
</tr>
<tr>
<td>LCWI (kg·m/m²)</td>
<td>3.5 (2.7-4.2)</td>
<td>2.9 (2.4-3.3)</td>
<td>0.056</td>
</tr>
<tr>
<td>PEP (ms)</td>
<td>81 (66-96)</td>
<td>83 (74-92)</td>
<td>0.808</td>
</tr>
<tr>
<td>LVET (ms)</td>
<td>243 (229-257)</td>
<td>277 (262-292)</td>
<td>0.002</td>
</tr>
<tr>
<td>ETR (%)</td>
<td>42 (40-45)</td>
<td>40 (37-41)</td>
<td>0.025</td>
</tr>
<tr>
<td>QI (%)</td>
<td>86 (81-91)</td>
<td>84 (78-90)</td>
<td>0.578</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)

Areas shaded grey highlight statistically significant differences
Figure 25. Differences in cardiac output, stroke volume and thoracic fluid content in severely septic patients between measurement taken on ED arrival, ED departure and at 24 hour follow up; compared with control
**Transcutaneous Doppler measurements**

Transcutaneous Doppler measurements were successfully obtained for 46 patients on arrival in the ED. Two sets of measurements were lost due to hardware system error and in one patient it was not possible to acquire a reading of acceptable quality. Paired measurements of the 46 patients taken on arrival and departure from the ED were compared and are presented in Table 17.

As with the TEB measurements there were no significant changes in Doppler cardiac output, cardiac index, stroke volume or stroke index during the patients’ stay in the ED. Heart rate was the only parameter found to be significantly reduced on ED departure though the difference was not clinically meaningful.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ED arrival (n=46)</th>
<th>ED departure (n=46)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (l/min/m²)</td>
<td>3.8 (3.4-4.1)</td>
<td>3.6 (3.2-4.0)</td>
<td>0.027</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>7.1 (6.4-7.8)</td>
<td>6.8 (6.1-7.5)</td>
<td>0.034</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>67 (60-73)</td>
<td>67 (61-74)</td>
<td>0.605</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>35 (32-38)</td>
<td>36 (32-39)</td>
<td>0.628</td>
</tr>
<tr>
<td>VP (m/s)</td>
<td>1.05 (0.97-1.13)</td>
<td>1.01 (0.92-1.09)</td>
<td>0.064</td>
</tr>
<tr>
<td>MPG (mmHg)</td>
<td>2.1 (1.8-2.4)</td>
<td>2.0 (1.7-2.4)</td>
<td>0.355</td>
</tr>
<tr>
<td>VTI (cm)</td>
<td>18.2 (16.5-19.9)</td>
<td>18.6 (16.7-20.4)</td>
<td>0.370</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>109 (103-116)</td>
<td>103 (96-109)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MD (m/min)</td>
<td>19.6 (17.7-21.5)</td>
<td>18.7 (16.8-20.7)</td>
<td>0.038</td>
</tr>
<tr>
<td>ET% (%)</td>
<td>49 (46-52)</td>
<td>48 (45-50)</td>
<td>0.217</td>
</tr>
<tr>
<td>FT (ms)</td>
<td>273 (261-284)</td>
<td>284 (270-298)</td>
<td>0.041</td>
</tr>
<tr>
<td>SVV (%)</td>
<td>38 (30-46)</td>
<td>34 (26-41)</td>
<td>0.264</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)

Areas shaded grey highlight statistically significant differences
Comparison was also made between Doppler measurements obtained on ED arrival and at 24 hour follow-up. From the 46 patients seven patients had died within the 24 hours and two patients refused further measurements. Therefore 37 paired readings were available for comparison. Table 18 summarises the data.

The data shows a significant reduction in Doppler CI and CO after a 24 hour period of normal treatment. Since SV remained essentially unchanged this reduction is a result of the decrease in HR which was statistically and clinically significant. There was also a significant increase in flow time (FT), also known as systolic ejection time, at 24 hours compared to arrival in the ED.

### Table 18. Doppler measurements on ED arrival and at 24 hour follow up

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ED arrival (n=37)</th>
<th>24 hour follow up (n=37)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (l/min/m²)</td>
<td>3.8 (3.4-4.3)</td>
<td>3.4 (3.0-3.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>7.3 (6.5-8.1)</td>
<td>6.4 (5.7-7.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>69 (62-76)</td>
<td>71 (64-78)</td>
<td>0.392</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>36 (32-40)</td>
<td>37 (34-40)</td>
<td>0.423</td>
</tr>
<tr>
<td>VP (m/s)</td>
<td>1.07 (0.97-1.17)</td>
<td>0.98 (0.89-1.07)</td>
<td>0.009</td>
</tr>
<tr>
<td>MPG (mmHg)</td>
<td>2.1 (1.8-2.4)</td>
<td>2.0 (1.7-2.4)</td>
<td>0.355</td>
</tr>
<tr>
<td>VTI (cm)</td>
<td>18.6 (16.7-20.5)</td>
<td>19.6 (17.8-21.5)</td>
<td>0.114</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>108 (101-115)</td>
<td>92 (85-98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MD (m/min)</td>
<td>20.0 (17.7-22.2)</td>
<td>17.8 (15.8-19.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>ET% (%)</td>
<td>49 (46-52)</td>
<td>47 (44-49)</td>
<td>0.123</td>
</tr>
<tr>
<td>FT (ms)</td>
<td>274 (262-287)</td>
<td>310 (295-325)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SVV (%)</td>
<td>36 (29-44)</td>
<td>23 (16-30)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)
Areas shaded grey highlight statistically significant differences
3.2.4 Study 2 – Results – Objective 3

Comparison of cardio-haemodynamic parameters in survivors and non-survivors from severe sepsis or septic shock

Twenty four out of the 49 patients died within 30 days of presenting to the ED with severe sepsis / septic shock (49% mortality). The majority of deaths (63%) occurred within 72 hours. Non-survivors were significantly older than survivors. They were more likely to be care home residents and to suffer from chronic cardiovascular illness than survivors though this was not found to be statistically significant. Table 19 shows the baseline characteristics of survivors and non-survivors from severe sepsis / septic shock.

Table 19. Baseline characteristics of survivors and non-survivors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survivors n= 25</th>
<th>Non-survivors n=24</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>64 (54-74)</td>
<td>79 (74-85)</td>
<td>0.008</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>Male 20 (80)</td>
<td>15 (62)</td>
<td>0.282</td>
</tr>
<tr>
<td></td>
<td>Female 5 (20)</td>
<td>9 (38)</td>
<td>0.282</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174 (170-178)</td>
<td>166 (162-171)</td>
<td>0.006</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77 (69-85)</td>
<td>70 (60-79)</td>
<td>0.238</td>
</tr>
<tr>
<td>Care home residency, n (%)</td>
<td>4 (16)</td>
<td>8 (33)</td>
<td>0.292</td>
</tr>
<tr>
<td>Past cardiovascular history, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cardiovascular morbidity</td>
<td>9 (36)</td>
<td>15 (63)</td>
<td>0.109</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1(4)</td>
<td>4 (17)</td>
<td>0.306</td>
</tr>
<tr>
<td>Myocardial infarct</td>
<td>4 (16)</td>
<td>4 (17)</td>
<td>0.771</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>2 (8)</td>
<td>4 (17)</td>
<td>0.602</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (16)</td>
<td>7 (29)</td>
<td>0.454</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>0.466</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval) unless stated otherwise
Physiological parameters taken on the arrival in the ED did not differ significantly between the two groups of patients. Non-survivors scored significantly higher on the ‘Mortality in Emergency Department Sepsis’ (MEDS) score and had a significantly higher venous lactate (Table 20).

Table 20. Conventional parameters on arrival in the Emergency Department

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Survivors n= 25</th>
<th>Non-survivors n=24</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiological signs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>38.1 (37.7-38.6)</td>
<td>37.4 (36.7-38.1)</td>
<td>0.062</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>117 (109-124)</td>
<td>115 (106-125)</td>
<td>0.825</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>97 (95-98)</td>
<td>94 (92-97)</td>
<td>0.101</td>
</tr>
<tr>
<td>Respiratory rate (min⁻¹)</td>
<td>28 (26-31)</td>
<td>33 (29-36)</td>
<td>0.064</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>106 (94-117)</td>
<td>97 (88-107)</td>
<td>0.262</td>
</tr>
<tr>
<td><strong>Scoring systems</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EWS</td>
<td>6.7 (6.0-7.5)</td>
<td>7.7 (6.9-8.4)</td>
<td>0.072</td>
</tr>
<tr>
<td>MEDS score</td>
<td>7.5 (6.1-8.9)</td>
<td>10.8 (9.3-12.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
<td>3.7 (2.8-4.5)</td>
<td>6.3 (4.5-8.1)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)

When classifying the participants on their arrival in the Emergency Department in accordance to their degree of sepsis the severity of illness was greater amongst non-survivors (p=0.023). Sepsis related shock was seen in 83% of non-survivors (n=20) with cryptic shock being the most prevalent (n=11). Whereas, only half of the survivors (n=12) suffered from sepsis related shock of which seven cases were cryptic shock. The respiratory tract was the most common source of sepsis in both survivors (60%) and non-survivor (71%). There was a similar prevalence of uro-sepsis in both groups (survivors 20% and non-survivors 17%).
Non-survivors received on average more intravenous fluid in the Emergency Department than survivors ((1956mls (95%CI 1469 to 2444) vs. 1576mls (95%CI 1160 to 1993), p=0.226)). After leaving the ED non-survivors continued to receive more intravenous fluid compared to survivors within the first 24 hours ((2906mls (95%CI 2054 to 3759) vs. 1787mls (95%CI 808 to 2765), p=0.101)).

**TEB measurements**

TEB cardio-haemodynamic measurements on arrival in the ED were available for 48 patients of whom there were 23 non-survivors and 25 survivors. Table 21 compares TEB parameters of both cohorts taken on arrival in the ED. Survivors had an increased cardiac index (ΔCI=0.3; 95%CI -0.3 to 1.0) and cardiac output (ΔCO=1.3; 95%CI -0.1 to 2.7) compared to non-survivors. Though the difference in CI was clinically significant it did not reach statistical significance. There were no statistically significant differences in any of the other TEB parameters between the two groups on arrival in the ED.

ED departure measurements were available for 47 patients (23 non-survivors and 24 survivors). The comparisons of both cohorts are presented in Table 22. Following normal treatment for sepsis in the ED the differences in cardiac index and output as seen on arrival had diminished. Apart from the left ventricular filling time (LVET) and the ejection time ratio (ETR) there were no statistically significant differences between survivors and non-survivors on departure from the ED.

Within 24 hours of presenting to the ED with severe sepsis / septic shock eight patients had died and two of the survivors refused to participate in the follow-up
measurements. Thus data from 37 patients (15 non-survivors and 22 survivors) were available for comparison at 24 hours (Table 23). There was a noticeable difference in the SV, which in survivors had started to normalise and was thus significantly greater than in non-survivors ($\Delta SV=21; 95\% CI 5$ to $36$). No other significant differences were found between the two cohorts.

Table 21. TEB measurements of survivors and non-survivors on ED arrival

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Survivors (n=25)</th>
<th>Non-survivors (n=23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (l/min/m²)</td>
<td>3.6 (3.1-4.0)</td>
<td>3.3 (2.8-3.7)</td>
<td>0.291</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>7.0 (5.9-8.1)</td>
<td>5.7 (4.7-6.6)</td>
<td>0.061</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>65 (55-75)</td>
<td>53 (46-61)</td>
<td>0.063</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>33 (29-37)</td>
<td>31 (27-34)</td>
<td>0.377</td>
</tr>
<tr>
<td>SVR (dynes·s·cm⁻⁵)</td>
<td>906 (699-1112)</td>
<td>1075 (878-1273)</td>
<td>0.224</td>
</tr>
<tr>
<td>SVRI (dynes·s·cm⁻⁵/m²)</td>
<td>1712 (1392-2032)</td>
<td>1817 (1496-2137)</td>
<td>0.632</td>
</tr>
<tr>
<td>TFC (l/kΩ)</td>
<td>31.2 (28.5-33.9)</td>
<td>31.8 (29.4-34.2)</td>
<td>0.736</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>111 (102-120)</td>
<td>111 (99-123)</td>
<td>0.988</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>76 (68-83)</td>
<td>75 (66-84)</td>
<td>0.859</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>115 (102-129)</td>
<td>105 (93-116)</td>
<td>0.219</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>61 (55-67)</td>
<td>62 (54-70)</td>
<td>0.783</td>
</tr>
<tr>
<td>LCW (kg·m)</td>
<td>6.5 (5.2-7.9)</td>
<td>5.5 (3.4-7.5)</td>
<td>0.339</td>
</tr>
<tr>
<td>LCWI (kg·m/m²)</td>
<td>3.3 (2.7-3.9)</td>
<td>3.1 (2.0-4.2)</td>
<td>0.664</td>
</tr>
<tr>
<td>PEP (ms)</td>
<td>76 (69-83)</td>
<td>92 (68-116)</td>
<td>0.191</td>
</tr>
<tr>
<td>LVET (ms)</td>
<td>231 (214-247)</td>
<td>240 (221-259)</td>
<td>0.448</td>
</tr>
<tr>
<td>ETR (%)</td>
<td>42 (39-45)</td>
<td>43 (40-46)</td>
<td>0.689</td>
</tr>
<tr>
<td>QI (%)</td>
<td>89 (85-93)</td>
<td>77 (67-88)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)
Table 22.  TEB measurements of survivors and non-survivors on ED departure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Survivors (n=24)</th>
<th>Non-survivors (n=23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (l/min/m²)</td>
<td>3.2 (2.8-3.5)</td>
<td>3.2 (2.7-3.7)</td>
<td>0.841</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>6.2 (5.4-6.9)</td>
<td>5.6 (4.6-6.7)</td>
<td>0.388</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>62 (54-71)</td>
<td>57 (49-65)</td>
<td>0.364</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>32 (28-35)</td>
<td>33 (29-36)</td>
<td>0.728</td>
</tr>
<tr>
<td>SVR (dynes·s·cm⁻⁵)</td>
<td>851 (732-971)</td>
<td>922 (780-1065)</td>
<td>0.422</td>
</tr>
<tr>
<td>SVRI (dynes·s·cm⁻⁵/m²)</td>
<td>1635 (1429-1840)</td>
<td>1609 (1357-1860)</td>
<td>0.866</td>
</tr>
<tr>
<td>TFC (1/kΩ)</td>
<td>33.2 (29.9-36.5)</td>
<td>35.2 (32.0-38.5)</td>
<td>0.352</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>101 (92-110)</td>
<td>102 (90-115)</td>
<td>0.889</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>68 (60-75)</td>
<td>67 (58-76)</td>
<td>0.960</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>104 (93-115)</td>
<td>98 (88-108)</td>
<td>0.434</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>54 (47-61)</td>
<td>55 (46-64)</td>
<td>0.798</td>
</tr>
<tr>
<td>LCW (kg·m )</td>
<td>5.3 (4.2-6.4)</td>
<td>5.1 (3.3-6.9)</td>
<td>0.828</td>
</tr>
<tr>
<td>LCWI (kg·m/m²)</td>
<td>2.7 (2.2-3.2)</td>
<td>2.8 (1.9-3.6)</td>
<td>0.834</td>
</tr>
<tr>
<td>PEP (ms)</td>
<td>89 (68-109)</td>
<td>83 (71-94)</td>
<td>0.605</td>
</tr>
<tr>
<td>LVET (ms)</td>
<td>230 (217-244)</td>
<td>273 (248-297)</td>
<td>0.003</td>
</tr>
<tr>
<td>ETR (%)</td>
<td>38 (35-41)</td>
<td>44 (40-48)</td>
<td>0.009</td>
</tr>
<tr>
<td>QI (%)</td>
<td>89 (83-94)</td>
<td>72 (59-85)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)

Areas shaded grey highlight statistically significant differences
Table 23. TEB measurements of survivors and non-survivors at 24 hour follow-up

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Survivors (n=22)</th>
<th>Non-survivors (n=15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (l/min/m²)</td>
<td>3.0 (2.7-3.4)</td>
<td>2.8 (2.2-3.4)</td>
<td>0.393</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>6.1 (5.2-7.0)</td>
<td>5.0 (3.8-6.2)</td>
<td>0.099</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>74 (63-85)</td>
<td>53 (44-63)</td>
<td>0.004</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>37 (33-42)</td>
<td>30 (25-36)</td>
<td>0.023</td>
</tr>
<tr>
<td>SVR (dynes·s·cm⁻⁵)</td>
<td>989 (853-1123)</td>
<td>1263 (883-1642)</td>
<td>0.055</td>
</tr>
<tr>
<td>SVRI (dynes·s·cm⁻⁵/m²)</td>
<td>1893 (1688-2098)</td>
<td>2224 (1559-2889)</td>
<td>0.169</td>
</tr>
<tr>
<td>TFC (1/kΩ)</td>
<td>37.1 (31.2-43.0)</td>
<td>41.1 (35.9-46.2)</td>
<td>0.274</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>84 (76-92)</td>
<td>94 (83-104)</td>
<td>0.136</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>76 (68-83)</td>
<td>75 (66-84)</td>
<td>0.914</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>115 (104-127)</td>
<td>108 (93-124)</td>
<td>0.433</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>61 (55-67)</td>
<td>61 (53-69)</td>
<td>0.906</td>
</tr>
<tr>
<td>LCW (kg·m)</td>
<td>5.9 (4.5-7.3)</td>
<td>4.7 (3.4-5.9)</td>
<td>0.135</td>
</tr>
<tr>
<td>LCWI (kg·m²)</td>
<td>2.9 (2.4-3.5)</td>
<td>2.6 (2.0-3.2)</td>
<td>0.411</td>
</tr>
<tr>
<td>PEP (ms)</td>
<td>79 (71-87)</td>
<td>89 (67-111)</td>
<td>0.268</td>
</tr>
<tr>
<td>LVET (ms)</td>
<td>289 (271-306)</td>
<td>257 (231-282)</td>
<td>0.033</td>
</tr>
<tr>
<td>ETR (%)</td>
<td>39 (37-42)</td>
<td>40 (35-44)</td>
<td>0.924</td>
</tr>
<tr>
<td>QI (%)</td>
<td>88 (80-97)</td>
<td>77 (67-88)</td>
<td>0.108</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)
Areas shaded grey highlight statistically significant differences
Figure 26 illustrates the chronological patterns of selected cardio-haemodynamic parameters of survivors and non-survivors during the first 24 hours since arrival in the ED. Survivors had a persistently higher CO and SV whereas SVR and TFC were higher in non-survivors.

CO measured on arrival in the ED was higher in survivors than in non-survivors or non-septic controls (red dotted line). Within 24 hours of treatment the CO of survivors had decreased reaching a similar value as seen in controls whilst CO of non-survivors had further declined.

SV was reduced in survivors and more so in non-survivors compared with non-septic controls. Whilst there was a marked improvement in SV in survivors after 24 hours SV remained seriously reduced in non-survivors. When comparing the change in SV over time between survivors and non-survivors there was no significant difference in $\Delta SV$ on ED departure ($\Delta SV = -1.9; 95\% CI -11.1 to 7.4, p=0.688$). However, after 24 hours of initial sepsis management, there was a statistically significant difference in $\Delta SV$ between survivors and non-survivors ($\Delta SV = 17.0; 95\% CI 8.5 to 25.5, p<0.001$).

SVR was lower in survivors on arrival in the ED and increased only marginally during the first 24 hours. In contrast, SVR of non-survivors increased to nearly the control value after 24 hours of treatment.

TFC on arrival in the ED was increased in both cohorts compared to the mean value of the control group. During the first 24 hours there was a steady rise in TFC in survivors and non-survivors which, considering the amount of intravenous fluids administered to both groups of septic patients, was to be expected.
LCW, an indicator of the amount of work performed by the left ventricle each minute, was markedly lower in non-survivors, declining steadily during the first 24 hours. Survivors exhibited a higher LCW on ED arrival, this reached a similar value to non-survivors on ED departure but rose again within 24 hours of treatment.
Figure 26. Patterns of cardio-haemodynamic parameters of survivors (grey solid line) and non-survivors (black scattered line).
Grey squares (■) represent mean values in survivors; black triangles (▲) mean values in non-survivors; red dashed lines represent the mean value of the non-septic control; green dashed line represents smallest value of the ‘Normal range’\textsuperscript{153}.
The ability of each TEB parameter to discriminate survivors from non-survivors was tested using the receiver operating characteristics (ROC) analysis. The area under the ROC curve (AUROC) for each parameter is shown in Table 24. Parameters with an AUROC greater than 0.7 are highlighted in grey colour.

Table 24. Area under the ROC curve for TEB parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ED arrival</th>
<th>ED departure</th>
<th>24 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (l/min/m²)</td>
<td>0.603</td>
<td>0.491</td>
<td>0.577</td>
</tr>
<tr>
<td></td>
<td>(0.441-0.751)</td>
<td>(0.330-0.654)</td>
<td>(0.384-0.754)</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td><strong>0.702</strong></td>
<td>0.594</td>
<td>0.646</td>
</tr>
<tr>
<td></td>
<td>(0.541-0.833)</td>
<td>(0.427-0.746)</td>
<td>(0.451-0.811)</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>0.647</td>
<td>0.588</td>
<td><strong>0.754</strong></td>
</tr>
<tr>
<td></td>
<td>(0.484-0.788)</td>
<td>(0.421-0.741)</td>
<td>(0.563-0.892)</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>0.566</td>
<td>0.531</td>
<td><strong>0.706</strong></td>
</tr>
<tr>
<td></td>
<td>(0.404-0.718)</td>
<td>(0.367-0.691)</td>
<td>(0.512-0.857)</td>
</tr>
<tr>
<td>SVR (dynes·s·cm⁻⁵)</td>
<td>0.656</td>
<td>0.588</td>
<td>0.641</td>
</tr>
<tr>
<td></td>
<td>(0.482-0.804)</td>
<td>(0.417-0.745)</td>
<td>(0.443-0.810)</td>
</tr>
<tr>
<td>SVRI (dynes·s·cm⁻⁵/m²)</td>
<td>0.565</td>
<td>0.515</td>
<td>0.576</td>
</tr>
<tr>
<td></td>
<td>(0.392-0.727)</td>
<td>(0.348-0.680)</td>
<td>(0.379-0.756)</td>
</tr>
<tr>
<td>TFC (1/kΩ)</td>
<td>0.527</td>
<td>0.585</td>
<td>0.620</td>
</tr>
<tr>
<td></td>
<td>(0.367-0.683)</td>
<td>(0.419-0.739)</td>
<td>(0.425-0.790)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>0.480</td>
<td>0.510</td>
<td><strong>0.701</strong></td>
</tr>
<tr>
<td></td>
<td>(0.323-0.639)</td>
<td>(0.347-0.671)</td>
<td>(0.507-0.853)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>0.534</td>
<td>0.518</td>
<td>0.492</td>
</tr>
<tr>
<td></td>
<td>(0.361-0.702)</td>
<td>(0.348-0.685)</td>
<td>(0.303-0.683)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.605</td>
<td>0.545</td>
<td>0.593</td>
</tr>
<tr>
<td></td>
<td>(0.428-0.763)</td>
<td>(0.373-0.709)</td>
<td>(0.396-0.771)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>0.514</td>
<td>0.494</td>
<td>0.538</td>
</tr>
<tr>
<td></td>
<td>(0.342-0.684)</td>
<td>(0.326-0.663)</td>
<td>(0.344-0.724)</td>
</tr>
<tr>
<td>LCW (kg·m⁻¹)</td>
<td>0.669</td>
<td>0.565</td>
<td><strong>0.636</strong></td>
</tr>
<tr>
<td></td>
<td>(0.492-0.816)</td>
<td>(0.393-0.727)</td>
<td>(0.438-0.806)</td>
</tr>
<tr>
<td>LCWI (kg·m²/m²)</td>
<td>0.625</td>
<td>0.519</td>
<td>0.581</td>
</tr>
<tr>
<td></td>
<td>(0.448-0.780)</td>
<td>(0.349-0.686)</td>
<td>(0.384-0.760)</td>
</tr>
<tr>
<td>PEP (ms)</td>
<td>0.546</td>
<td>0.474</td>
<td>0.557</td>
</tr>
<tr>
<td></td>
<td>(0.384-0.702)</td>
<td>(0.314-0.637)</td>
<td>(0.366-0.737)</td>
</tr>
<tr>
<td>LVET (ms)</td>
<td>0.582</td>
<td><strong>0.721</strong></td>
<td><strong>0.734</strong></td>
</tr>
<tr>
<td></td>
<td>(0.418-0.734)</td>
<td>(0.556-0.851)</td>
<td>(0.542-0.878)</td>
</tr>
<tr>
<td>ETR (%)</td>
<td>0.564</td>
<td><strong>0.721</strong></td>
<td>0.457</td>
</tr>
<tr>
<td></td>
<td>(0.401-0.718)</td>
<td>(0.556-0.851)</td>
<td>(0.275-0.648)</td>
</tr>
</tbody>
</table>
ROC curves were constructed for the best performing parameters. On arrival in the ED only cardiac output was found to have a good discriminatory power (Figure 27). Giving equal value to sensitivity and specificity, a CO of greater than 5.1 l/min was found to be the optimal derived cut-off to discriminate between survival and death. This was found to be 81.8% sensitive (95%CI 59.7 to 94.8) and 55.0% specific (95%CI 31.5 to 76.9) for survival. It had a positive likelihood ratio (LR+) of 1.82, negative likelihood ratio (LR-) of 0.33, a positive predictive value (PPV) of 66.7 and a negative predictive value (NPV) of 73.3.

Figure 27.   Receiver operating characteristics curve for cardiac output (ED arrival)
On departure from the ED there were two parameters with a good discriminatory power for survival, left ventricular ejection time (LVET) and ejection time ratio (ETR). Figure 28 presents the ROC curves for both parameters. The optimal cuff-off derived from the ROC for LVET to discriminate between survival and death was 260 or less and for ETR 41 or less. A LVET of \( \leq 260 \) was 95.2% sensitive (95%CI 76.2 to 99.9) and 42.1% specific (95%CI 20.3 to 66.5) for survival. It had a LR+ of 1.65, a LR- of 0.11, a PPV of 64.5 and a NPV of 88.9. An ETR of \( \leq 41 \) had a sensitivity of 76.2% (95%CI 52.8 to 91.8), a specificity of 68.4% (95%CI 43.4 to 87.4), a LR+ of 2.41, a LR- of 0.35, a PPV of 72.7 and a NPV of 72.2.

Figure 28. Receiver operating characteristics curves for LVET and ETR (ED departure)
At the 24 hour follow-up assessment there were four parameters with good discriminating qualities, the best of which was the SV followed by LVET, SI and HR. The ROC curves of all four parameters are presented in Figure 29. The ROC derived optimal cut-off for each parameter and its sensitivity, specificity, LR+, LR-, PPV and NPV are shown in Table 25. None of the identified cut-offs had a high sensitivity. HR was found to have the highest specificity (100%) and highest PPV (100%) for survival followed by the SV (91% and 91% respectively). Interestingly, whilst a low LVET on ED departure was found to be predictive of survival from severe sepsis the opposite applied after 24 hours of treatment.

Figure 29. ROC curves for stroke volume, stroke index, heart rate and left ventricular ejection time (at 24 hours)
Table 25. ROC derived values predictive of survival at 24 hours

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Optimal cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR+</th>
<th>LR-</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV</td>
<td>&gt;67</td>
<td>52.6 (28.9-75.6)</td>
<td>90.9 (58.7-99.8)</td>
<td>5.79</td>
<td>0.52</td>
<td>90.9</td>
<td>52.6</td>
</tr>
<tr>
<td>LVET</td>
<td>&gt;265</td>
<td>73.7 (48.8-90.9)</td>
<td>72.7 (39.0-94.0)</td>
<td>2.7</td>
<td>0.36</td>
<td>82.4</td>
<td>61.5</td>
</tr>
<tr>
<td>SI</td>
<td>&gt;37</td>
<td>52.6 (28.9-75.6)</td>
<td>81.8 (48.2-97.7)</td>
<td>2.89</td>
<td>0.58</td>
<td>83.3</td>
<td>50.0</td>
</tr>
<tr>
<td>HR</td>
<td>≤76</td>
<td>42.1 (20.3-66.5)</td>
<td>100 (71.5-100)</td>
<td>Infinite</td>
<td>0.58</td>
<td>100</td>
<td>50.0</td>
</tr>
</tbody>
</table>

**Transcutaneous Doppler measurements**

Transcutaneous Doppler readings on arrival in the ED were available for 46 patients of whom 23 survived. Table 26 depicts Doppler parameter of survivors and non-survivors taken on their arrival in the ED. Similar to TEB measurements survivors were found to have a markedly higher CO and SV than non-survivors. There was also a noticeable difference in mean pressure gradient (MPG) which was distinctively higher in survivors.

ED departure measurements were available for 43 patients (22 survivors and 21 non-survivors). Table 27 compares the measured parameters of both cohorts. Following the initial resuscitative treatment in the ED there was now a statistical significant difference in SV between survivors and non-survivors. Cardiac output remained markedly higher in survivors, as did MPG. Survivors had a higher velocity time integral (VTI) and peak velocity (VP), a marker of contractility.
Table 26. Doppler measurements of survivors and non-survivors on ED arrival

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Survivors (n=23)</th>
<th>Non-survivors (n=23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (l/min/m²)</td>
<td>4.0 (3.4 – 4.6)</td>
<td>3.4 (3.0 – 3.8)</td>
<td>0.085</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>7.7 (6.6 – 8.7)</td>
<td>6.2 (5.3 – 7.0)</td>
<td>0.028</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>72 (62 – 82)</td>
<td>58 (50 – 65)</td>
<td>0.022</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>38 (33 – 43)</td>
<td>32 (28 – 36)</td>
<td>0.057</td>
</tr>
<tr>
<td>VP (m/s)</td>
<td>1.12 (0.97 – 1.27)</td>
<td>0.96 (0.89 – 1.04)</td>
<td>0.051</td>
</tr>
<tr>
<td>MPG (mmHg)</td>
<td>2.4 (1.8 – 2.9)</td>
<td>1.7 (1.5 – 2.0)</td>
<td>0.033</td>
</tr>
<tr>
<td>VTI (cm)</td>
<td>19.5 (16.8 – 22.2)</td>
<td>16.5 (14.5 – 18.4)</td>
<td>0.063</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>108 (100 – 117)</td>
<td>110 (100 – 121)</td>
<td>0.779</td>
</tr>
<tr>
<td>MD (m/min)</td>
<td>21.1 (17.9 – 24.3)</td>
<td>17.7 (15.7 – 19.7)</td>
<td>0.065</td>
</tr>
<tr>
<td>ET% (%)</td>
<td>50 (46 – 54)</td>
<td>48 (44 – 51)</td>
<td>0.436</td>
</tr>
<tr>
<td>FT (ms)</td>
<td>278 (264 – 291)</td>
<td>266 (247 – 285)</td>
<td>0.312</td>
</tr>
<tr>
<td>SVV (%)</td>
<td>36 (23 – 50)</td>
<td>40 (31 – 49)</td>
<td>0.658</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)
Table 27. Doppler measurements of survivors and non-survivors on ED departure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Survivors (n=22)</th>
<th>Non-survivors (n=21)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (l/min/m²)</td>
<td>3.8 (3.3 – 4.4)</td>
<td>3.4 (2.9 – 3.8)</td>
<td>0.174</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>7.4 (6.4 – 8.5)</td>
<td>6.2 (5.3 – 7.1)</td>
<td>0.070</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>76 (65 – 86)</td>
<td>59 (52 – 65)</td>
<td>0.006</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>39 (33 – 45)</td>
<td>32 (29 – 35)</td>
<td>0.037</td>
</tr>
<tr>
<td>VP (m/s)</td>
<td>1.09 (0.94 – 1.23)</td>
<td>0.93 (0.87 – 0.99)</td>
<td>0.048</td>
</tr>
<tr>
<td>MPG (mmHg)</td>
<td>2.4 (1.7 – 3.0)</td>
<td>1.6 (1.4 – 1.8)</td>
<td>0.029</td>
</tr>
<tr>
<td>VTI (cm)</td>
<td>20.5 (17.3 – 23.7)</td>
<td>16.5 (14.9 – 18.1)</td>
<td>0.030</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>100 (91 – 109)</td>
<td>106 (96 – 116)</td>
<td>0.371</td>
</tr>
<tr>
<td>MD (m/min)</td>
<td>20.2 (16.9 – 23.4)</td>
<td>17.2 (15.2 – 19.3)</td>
<td>0.122</td>
</tr>
<tr>
<td>ET% (%)</td>
<td>47 (43 – 50)</td>
<td>49 (45 – 53)</td>
<td>0.462</td>
</tr>
<tr>
<td>FT (ms)</td>
<td>287 (265 – 309)</td>
<td>281 (261 – 301)</td>
<td>0.669</td>
</tr>
<tr>
<td>SVV (%)</td>
<td>32 (24 – 40)</td>
<td>35 (23 – 48)</td>
<td>0.592</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)

Following 24 hours of treatment eight patients had died and two survivors refused further measurements leaving a total of 36 assessments available for comparison (Table 28). At this stage there was very little difference in CO between survivors and non-survivors. Though there was a subtle increase in SV in both cohorts, but this did not affect the distinct difference between survivors and non-survivors. The heart rate was more reduced in survivors, which would have contributed to the decreased difference in CO between the two cohorts.
Table 28. Doppler measurements of survivors and non-survivors at 24 hours

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Survivors (n=20)</th>
<th>Non-survivors (n=16)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (l/min/m²)</td>
<td>3.4 (2.8 – 3.9)</td>
<td>3.3 (2.8 – 3.9)</td>
<td>0.909</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>6.6 (5.6 – 7.6)</td>
<td>6.2 (5.0 – 7.4)</td>
<td>0.612</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>78 (68 – 88)</td>
<td>62 (54 – 70)</td>
<td>0.017</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>40 (35 – 45)</td>
<td>33 (29 – 37)</td>
<td>0.058</td>
</tr>
<tr>
<td>VP (m/s)</td>
<td>1.00 (0.86 – 1.14)</td>
<td>0.96 (0.84 – 1.07)</td>
<td>0.596</td>
</tr>
<tr>
<td>MPG (mmHg)</td>
<td>2.0 (1.5 – 2.6)</td>
<td>1.7 (1.3 – 2.1)</td>
<td>0.302</td>
</tr>
<tr>
<td>VTI (cm)</td>
<td>21.3 (18.3 – 24.2)</td>
<td>17.6 (15.7 – 19.4)</td>
<td>0.042</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>86 (77 – 94)</td>
<td>100 (90 – 110)</td>
<td>0.027</td>
</tr>
<tr>
<td>MD (m/min)</td>
<td>18.0 (14.9 – 21.0)</td>
<td>17.6 (14.8 – 20.4)</td>
<td>0.872</td>
</tr>
<tr>
<td>ET% (%)</td>
<td>45 (42 – 48)</td>
<td>49 (44 – 54)</td>
<td>0.132</td>
</tr>
<tr>
<td>FT (ms)</td>
<td>320 (299 – 341)</td>
<td>297 (277 – 318)</td>
<td>0.124</td>
</tr>
<tr>
<td>SVV (%)</td>
<td>18 (13 – 23)</td>
<td>28 (15 – 41)</td>
<td>0.133</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)

The receiver operating characteristics (ROC) analysis was used to test the ability of each Doppler derived parameter to predict outcome from sepsis. The area under the ROC curve (AUROC) for each parameter is shown in Table 29. Parameters with a good predictability, as indicated by an AUROC greater than 0.7, are highlighted in ‘grey’.
Table 29. AUROC values for transcutaneous Doppler parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ED arrival</th>
<th>ED departure</th>
<th>24 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (l/min/m²)</td>
<td>0.651 (0.497 – 0.786)</td>
<td>0.605 (0.444 – 0.751)</td>
<td>0.491 (0.321 – 0.662)</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>0.698 (0.545 – 0.825)</td>
<td>0.698 (0.539 – 0.828)</td>
<td>0.606 (0.430 – 0.764)</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>0.685 (0.532 – 0.814)</td>
<td>0.737 (0.581 – 0.859)</td>
<td>0.767 (0.591 – 0.894)</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>0.651 (0.489 – 0.791)</td>
<td>0.717 (0.557 – 0.845)</td>
<td>0.696 (0.515 – 0.842)</td>
</tr>
<tr>
<td>VP (m/s)</td>
<td>0.637 (0.475 – 0.780)</td>
<td>0.666 (0.504 – 0.804)</td>
<td>0.530 (0.351 – 0.702)</td>
</tr>
<tr>
<td>MPG (mmHg)</td>
<td>0.653 (0.491 – 0.793)</td>
<td>0.677 (0.515 – 0.813)</td>
<td>0.602 (0.421 – 0.766)</td>
</tr>
<tr>
<td>VTI (cm)</td>
<td>0.682 (0.520 – 0.817)</td>
<td>0.702 (0.541 – 0.833)</td>
<td>0.708 (0.528 – 0.851)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>0.542 (0.387 – 0.692)</td>
<td>0.576 (0.416 – 0.725)</td>
<td>0.731 (0.558 – 0.865)</td>
</tr>
<tr>
<td>MD (m/min)</td>
<td>0.653 (0.497 – 0.789)</td>
<td>0.626 (0.465 – 0.768)</td>
<td>0.495 (0.325 – 0.666)</td>
</tr>
<tr>
<td>ET% (%)</td>
<td>0.542 (0.387 – 0.691)</td>
<td>0.515 (0.358 – 0.670)</td>
<td>0.612 (0.436 – 0.770)</td>
</tr>
<tr>
<td>FT (ms)</td>
<td>0.622 (0.465 – 0.762)</td>
<td>0.529 (0.371 – 0.683)</td>
<td>0.650 (0.473 – 0.801)</td>
</tr>
<tr>
<td>SVV (%)</td>
<td>0.575 (0.413 – 0.726)</td>
<td>0.503 (0.345 – 0.661)</td>
<td>0.585 (0.404 – 0.751)</td>
</tr>
</tbody>
</table>

Values expressed as mean (95% confidence interval)
3.2.5 Study 2 – Results – Objective 4

Relationship between TEB cardio-haemodynamic and conventional parameters

The chronological patterns of cardiac output, stroke volumes, systemic vascular resistance, heart rate and mean arterial pressure during the first 24 hours after arrival in the ED were compared and are illustrated in Figure 30. HR and CO were both elevated on ED arrival and decreased nearly parallel over the first 24 hour period reaching, by then, near normal values. The SV, which was very low on ED arrival, gradually increased over time following an opposite pattern to HR and CO. Changes in SVR and MAP followed a similar pattern. Both were reduced on arrival in the ED, reached their lowest point on ED departure and increased again by the end of the first 24 hours.

Pearson’s correlation coefficient was used to assess the relationship between the cardio-haemodynamic and the conventional parameters at the three assessment points. Table 30 contains the correlation coefficients (r) for all pairs of variables. There was no strong correlation between any of the parameters. HR was found to have a weak positive association with CO and a negligible negative association with SV and SVR. MAP was weakly correlated with CO and SV on departure from the ED and at 24 hours whilst the correlation was negligible on ED arrival. Systemic vascular resistance and mean arterial pressure were found to have a weak positive association on arrival and departure from the ED and virtually no correlation at 24 hours.
Figure 30. Patterns of cardio-haemodynamic and conventional parameters in patients with severe sepsis or septic shock
Table 30. Pearson’s correlation coefficients for cardio-haemodynamic and conventional variables

<table>
<thead>
<tr>
<th></th>
<th>CO ED arr</th>
<th>CO ED dep</th>
<th>CO 24 hrs</th>
<th>SV ED arr</th>
<th>SV ED dep</th>
<th>SV 24 hrs</th>
<th>SVR ED arr</th>
<th>SVR ED dep</th>
<th>SVR 24 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR ED arr</td>
<td>0.286</td>
<td>-0.269</td>
<td>-0.130</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR ED dep</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.510</td>
<td>-0.264</td>
<td>-0.329</td>
</tr>
<tr>
<td>HR 24 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.306</td>
<td>-0.239</td>
<td>-0.189</td>
</tr>
<tr>
<td>MAP ED arr</td>
<td>0.259</td>
<td>0.210</td>
<td></td>
<td>0.407</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP ED dep</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.358</td>
<td>0.342</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP 24 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.418</td>
<td>0.395</td>
<td>0.134</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Ability of parameters to discriminate between good and poor outcome**

Area under the ROC curve values (section 3.2.4 Table 24) were used to compare the ability of cardio-haemodynamic parameters, conventional HR and BP to discriminate between good and poor outcome from severe sepsis or septic shock. Conventional HR and MAP taken on arrival and departure from the ED were not able to differentiate survivors from non-survivors. CO however, was found to be a good discriminator for outcome in severely septic patients on arrival in the ED but not so for subsequent assessments. Both SV and HR were found to be helpful in distinguishing between survivors and non-survivors after 24 hours of treatment whereas SVR and MAP were found to be of no help.
3.2.6 Study 2 – Results – Objective 5

Comparison of simultaneous TEB and transcutaneous Doppler ultrasound cardio-haemodynamic measurements

Cardio-haemodynamic measurements using TEB and transcutaneous Doppler ultrasound (USCOM) were obtained simultaneously on patients’ arrival and departure from the ED and after 24 hours. TEB readings on ED arrival and departure were available for forty seven patients compared to forty six transcutaneous Doppler assessments. At the 24 hour follow up a total of thirty seven TEB and USCOM measurements were successfully obtained. Both devices measured an array of parameters and five of these were identical. These were CO, CI, SV, SI and HR, and a comparison was made of all five variables.

Measurements obtained using TEB were generally lower than their simultaneous acquired USCOM values. This trend remained unchanged throughout the 24 hour assessment period and is illustrated in Figure 31. USCOM measurements are shown as black squares (■) and TEB values as grey diamonds (◆). The graphs illustrate that when comparing the TEB and USCOM measurements for the entire cohort the patterns of change were very similar.
To assess the strength of the association between each of the matched TEB and USCOM variables the Pearson’s correlation coefficient was used, assuming a linear relationship. The strongest association was found for HR followed by CO, whereas TEB and USCOM stroke index measurements were only weakly correlated. Table 31 contains the Pearson’s correlation coefficient (r) for each matched variable.
Graphical illustrations of the strength of the relation and the agreement between paired TEB and USCOM measurement of CO, SV and HR obtained during the three assessment points are shown in Figure 32. Though there appears to be an acceptable to good correlation for the three measured variables the agreement between measurements was less than perfect as indicated by the wide limits of agreements (mean ± 2SD) of the Bland-Altman plots with several measurements outside this range. The mean difference between TEB and USCOM measurements was always less than ‘zero’ which points to the fact that TEB tends to give lower readings than USCOM.
Figure 32. Relationship between paired TEB and USCOM cardiac output (CO), stroke volume (SV) and heart rate (HR) measurements presented as Scatter and Bland-Altman plots.
3.2.7 Study 2 – Results – Objective 6

Assessment of tissue oxygen saturation in severely septic ED patients; its change with normal treatment and relationship to outcome

3.2.7.1 Tissue oxygen saturation in severely septic ED patients

Tissue oxygen saturation (StO₂) measurements were obtained for all forty nine patients during their stay in the Emergency Department. The mean StO₂ for the entire cohort on arrival in the ED was 72% (95%CI 69 to 75) which on departure from the ED had increased to 75% (95%CI 72 to 78; p=0.061).

At the 24 hour follow up StO₂ data for thirty nine patients was available as eight patients had died and two had refused to participate in the final assessment. The StO₂ for the remaining cohort after 24 hour of normal treatment increased to 77% (95%CI 73 to 80).

The StO₂ in patients (n=18) with cryptic shock, a condition characterised by global ischaemia, a raised lactate and a deceptively normal blood pressure, was 72% (95%CI 68 to 76) for arrival in the ED and 74% (95%CI 67 to 80) for departure from the ED. Neither of these was significantly different from severely septic ‘non-cryptic shock’ patients (p=0.916, p=0.570 respectively).
3.2.7.2  **Comparison of tissue oxygen saturation in survivors and non-survivors from severe sepsis**

Survivors and non-survivors from severe sepsis / septic shock were identical in their StO$_2$ measurements (72%) on arrival in the ED. Whilst in survivors StO$_2$ (78%) improved with normal treatment for sepsis in the ED, it remained unchanged in non-survivors (72%). This difference was still present after 24 hours of normal treatment on the hospital wards. Table 32 summarises the StO$_2$ values recorded in both cohorts.

**Table 32. Tissue oxygen saturation in survivors and non-survivors from severe sepsis / septic shock**

<table>
<thead>
<tr>
<th></th>
<th>Survivors (n=25)*</th>
<th>Non-survivors (n=24)*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ED arrival</strong></td>
<td>72 (68-76)</td>
<td>72 (68-76)</td>
<td>0.974</td>
</tr>
<tr>
<td><strong>ED departure</strong></td>
<td>78 (74-81)</td>
<td>72 (66-78)</td>
<td>0.079</td>
</tr>
<tr>
<td><strong>24 hour follow up</strong></td>
<td>81 (77-84)</td>
<td>73 (68-78)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

*reduced number of participants at 24 hour follow up resulting in n=23 survivors and n=16 non-survivors

Whereas StO$_2$ in survivors (p=0.006) changed significantly with treatment administered in the ED, the change in non-survivors was insignificant (p=0.936).

After leaving the ED StO$_2$ in survivors continued to improve, reaching normal values, whilst there was very little change in non-survivors (p=0.164).

Patients who survived for less than 24 hours had a markedly reduced StO$_2$ (65%) on arrival and departure from the ED (64%) compared to patients who died at a later stage (75% and 76% respectively). In survivors, those who required a hospital stay of seven
days or less had a higher StO\textsubscript{2} on arrival in the ED and a greater improvement within
the first 24 hours compared to those who spent more than seven days in hospital.
Figure 33 illustrates the various patterns of tissue oxygen saturation measurements in
short and long stay survivors (scattered and solid red lines) and early and late non-
survivors (solid and scattered black lines).

![Figure 33](image_url)

**Figure 33.** Changes in StO\textsubscript{2} in early and late non-survivors and
survivors with short and long hospital stay

StO\textsubscript{2} on arrival in the ED was found to be a poor discriminator between death and
survival in patients presenting with severe sepsis / septic shock (AUROC=0.512). Its
differentiating power was slightly better on departure from the ED (AUROC=0.634).
However, when used to predict early death (<24 hours) StO\textsubscript{2} on arrival and departure
from the ED was found to perform well (AUROC\textsubscript{EDarr}=0.735, 95%CI 0.589 to 0.851;
AUROC\textsubscript{EDdep}=0.768, 95%CI 0.626 to 0.877).
3.2.7.3 **Relationship between StO\textsubscript{2} and pulse oximetry oxygen saturation (SpO\textsubscript{2})**

StO\textsubscript{2} and SpO\textsubscript{2} readings were available at all three assessment points. Changes in StO\textsubscript{2} and SpO\textsubscript{2} over time followed a different pattern as illustrated in Figure 34. On arrival in the ED SpO\textsubscript{2} was found to be within the normal range in survivors ((97\% (95\%CI 95 to 98)) and non-survivors ((95\% (95\%CI 92 to 97)) whereas StO\textsubscript{2} was markedly reduced in all patients. With normal treatment administered in the ED there was a marked improvement in StO\textsubscript{2} in survivors (p=0.006) whilst SpO\textsubscript{2} ((97\% (95\%CI 95 to 99), p=0.564)) did not change. Contrary to this, in non-survivors, StO\textsubscript{2} remained unchanged on departure from the ED (p=0.936) whilst SpO\textsubscript{2} had slightly increased ((97\% (95\%CI 94 to 99), p=0.276)). At the 24-hour follow-up survivors had normal StO\textsubscript{2} and SpO\textsubscript{2} measurements compared to readings below the normal range seen in non-survivors.
Figure 34. Changes in StO\textsubscript{2} and SpO\textsubscript{2} in survivors and non-survivors during the first 24 hours

When plotting the StO\textsubscript{2} and SpO\textsubscript{2} measurements taken on arrival and departure from the ED into a scatter diagram (Figure 35) there was no association between the two parameters. This was confirmed by the Pearson’s correlation coefficient which was $r=0.111$ for ED arrival and $r=0.020$ for ED departure.

StO\textsubscript{2} on arrival and departure from the ED was found to be only marginally better than SpO\textsubscript{2} in discriminating between survivors and non-survivors as demonstrated by the areas under the ROC curve (Table 33).
Table 33. Area under the ROC curve values for tissue oxygen saturation and pulse oximetry oxygen saturation on arrival and departure from the ED

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>StO₂ ED&lt;sub&gt;arrival&lt;/sub&gt;</td>
<td>0.571</td>
<td>0.407 – 0.724</td>
</tr>
<tr>
<td>StO₂ ED&lt;sub&gt;departure&lt;/sub&gt;</td>
<td>0.634</td>
<td>0.484 – 0.767</td>
</tr>
<tr>
<td>SpO₂ ED&lt;sub&gt;arrival&lt;/sub&gt;</td>
<td>0.534</td>
<td>0.372 – 0.691</td>
</tr>
<tr>
<td>SpO₂ ED&lt;sub&gt;departure&lt;/sub&gt;</td>
<td>0.489</td>
<td>0.330 – 0.650</td>
</tr>
</tbody>
</table>

Figure 35. Relationship between tissue oxygen saturation (StO₂) and pulse oximetry oxygen saturation (SpO₂) on arrival and departure from the ED
3.2.7.4 **Relationship between StO$_2$ and cardio-haemodynamic parameters**

TEB and Doppler data obtained on patient’s arrival was used to assess the relationship between StO$_2$ and haemodynamic parameters. As illustrated by the Pearson’s correlation coefficient (Table 34) there was no strong association between StO$_2$, reflecting local oxygenation, and any of the global haemodynamic parameters. There was however, a weak positive relationship between StO$_2$ and SV and a weak negative between StO$_2$ and SVR.

<table>
<thead>
<tr>
<th></th>
<th>CO</th>
<th>CI</th>
<th>SV</th>
<th>SI</th>
<th>SVR</th>
<th>SVRI</th>
<th>HR</th>
<th>MAP</th>
<th>TFC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEB</strong></td>
<td>0.147</td>
<td>0.116</td>
<td>0.211</td>
<td>0.189</td>
<td>-0.352</td>
<td>-0.315</td>
<td>-0.175</td>
<td>-0.200</td>
<td>-0.030</td>
</tr>
<tr>
<td><strong>Doppler</strong></td>
<td>0.322</td>
<td>0.182</td>
<td>0.315</td>
<td>0.005</td>
<td>--</td>
<td>--</td>
<td>-0.001</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
4 DISCUSSION

These two studies were undertaken to explore the benefit of non-invasive monitoring in the management of sepsis and septic shock in the Emergency Department, a phase in which previous data is very sparse. The general aims of this thesis, as stated on page 44, will be considered.

4.1 To determine whether patients with sepsis have abnormal cardio-haemodynamic parameters on arrival in the ED compared with normal controls

The results of both studies have shown that patients presenting to the ED with uncomplicated (study 1) or severe sepsis (study 2) have a measurable difference in their TEB cardio-haemodynamic indices compared to non-septic ED patients.

Septic patients in both studies were found to have an increased CI and CO whereas SV and SVR were significantly reduced in comparison to controls. In addition, severely septic patients had a markedly reduced StO₂. HR was significantly increased to the same level in both septic cohorts. Mean arterial pressure was significantly reduced in both septic cohorts with a more pronounced reduction in the severely septic cohort. These findings are in keeping with the well described haemodynamic state of sepsis characterized by increased cardiac output and low SVR, but have not been previously well documented in the early stages of sepsis management. Figure 36 depicts the overall physiological derangements seen in severely septic patients on arrival to the Emergency Department.
**Cardiac output.** CO, a determinant of oxygen delivery to the tissues, increases in clinical conditions where there is a greater oxygen demand by the tissues, such as sepsis. Although the tissue’s oxygen requirement increases with more severe disease, severely septic patients in my study demonstrated a smaller increase in CO and CI compared to patients with uncomplicated sepsis. It could be argued that with disease progression the ability to augment CO is impaired thus a smaller increase in CO was observed in severely septic patients. Another contributing factor could be due to age related changes of cardiac function. It has been shown that cardiac function and therefore cardiac output decreases with age.\textsuperscript{154, 155} Since severely septic patients were on average ten years older than the uncomplicated sepsis cohort, their baseline CO would have likely been lower. Such age related cardiac impairment may have contributed to the smaller increase in CO in the severe sepsis cohort.

**Heart rate.** Tachycardia, a recognised feature of sepsis, is believed to be a response to cardiac underfilling, fever and adrenergic stimulation. Whilst an increase in heart
rate has the potential to increase cardiac output it also causes restriction of diastolic filling and subsequently a reduction in stroke volume. Interestingly, both septic cohorts mounted a nearly identical tachycardic response but a greater reduction in SV was seen in the severely septic group. This implies that the observed difference in cardiac output must be mainly attributable to SV changes.

*Stroke volume.* Currently there is conflicting evidence as to whether SV diminishes with age. Earlier studies suggested a decline in SV with age but this was not confirmed in a more recent publication.\textsuperscript{156-158} Since the severely septic cohort was older their SV at baseline may have been lower than that of the uncomplicated sepsis cohort. However, increasing age has been shown to affect the ability of the heart to respond to stress. Considering the increased prevalence of cardiovascular disease in the elderly, the haemodynamic changes seen with ageing are likely to be a combination of physiological ageing and chronic cardiovascular disease. Two recent studies of SV in exercise have shown that the ability to augment and maintain SV at increased exercise intensity was found to be impaired in older men and women.\textsuperscript{159, 160}

Although it has been demonstrated that SV increases as a result of physical stress this is not the case in sepsis. Contrary to earlier belief that SV is maintained in sepsis, recent ICU studies reported a reduction in left ventricular SV.\textsuperscript{53, 161, 162} Stroke volume, a main component of CO, is regulated by the difference in end diastolic volume (EDV) and the end-systolic volume (ESV). When exposed to physical stress younger people increase their SV predominantly through a decrease in ESV, whereas in the elderly the increase in SV occurs through an increase in EDV with ESV remaining fairly static.\textsuperscript{163}
How might this explain the changes seen in my patients? In sepsis, as a result of intravascular fluid depletion, venous return is commonly reduced. With venous return being a major determining factor of preload, a fall in venous return will reduce the preload and therefore the EDV. A reduction in EDV will subsequently lower the SV, as observed in both of my studies. A reduction in SV may also be attributable to an increase in the ESV which is regulated by cardiac contractility and afterload. Myocardial contractility is difficult to measure in real life but a number of studies using an experimental sepsis model have demonstrated depressed myocardial contractility. In the light of these findings it would seem likely that the combination of impaired cardiac contractility and reduced preload results in a decreased SV in septic patients regardless of age.

*Systemic vascular resistance.* Reflecting primarily peripheral arteriolar tone, SVR is a commonly used estimate of afterload. I found a reduced SVR in sepsis with a greater decline in those with severe sepsis / septic shock, thus septic patients are likely to have had a reduced afterload. As previously mentioned, afterload is the second key determinant of ESV. Under normal physiological conditions a reduction in afterload would lead to a decrease in ESV and therefore to an increase in SV. This however, appears not to apply to sepsis where changes in SVR were not found to have an effect on SV.

Though cardiovascular dysfunction is a recognised manifestation of sepsis, clinical data on cardiac physiology in sepsis, particularly during the pre-intensive care unit stage, is sparse. Current understanding of the cardiovascular changes in sepsis and septic shock rely upon studies undertaken in ICU settings and animal studies. Not only were their findings of limited applicability to septic ED patients
they also convey conflicting results. Whilst earlier studies\textsuperscript{166, 167} found a normal left ventricular ejection fraction and a normal SV in septic patients, a more recent study\textsuperscript{162} described the exact opposite.

There may be a number of reasons for these inconsistent findings. Firstly, the studied populations were very heterogeneous, most likely due to lack of defined criteria for sepsis and septic shock. Control groups were either poorly defined or historical data was used instead. The timing of the haemodynamic evaluations varied and in some cases measurements were obtained after patients had been stabilised and received adequate fluid resuscitation. Finally, studies used different methods to assess cardiovascular function. Despite their differences the general consensus is that in sepsis myocardial function is impaired. Furthermore, it is thought that the degree of myocardial functional impairment is related to sepsis severity.\textsuperscript{168}

Despite the evidence of altered cardio-haemodynamics in sepsis the underlying pathophysiological mechanisms are not yet clearly understood. Several factors and mechanism are thought to be responsible, of which circulating mediators, such as cytokines and nitrous oxide, are believed to play a key part.\textsuperscript{168} Mitochondrial dysfunction has also been described in sepsis and was found to be related to illness severity and outcome. Other mechanisms considered are microcirculatory and metabolic changes as well as contractile and autonomic dysfunction which are likely to be mediated by circulating inflammatory compounds.\textsuperscript{168} Until there is better understanding of the pathophysiological causes for sepsis induced myocardial depression, clinical management needs to focus on patient identification and initiation of directed and supportive therapy at the earliest stage.
Thoracic Fluid Content. Microvascular hyperpermeability is considered to be a feature of sepsis. Though this phenomenon has been confirmed by experimental studies the clinical diagnosis of capillary leakage at the patients’ bedside remains challenging.\textsuperscript{169} To date there is no published data on the use of TFC to evaluate fluid distribution in sepsis. TFC is determined by intra- and extravascular fluid within the chest. Under normal physiological conditions fluid will be predominantly located intravascularly. In sepsis however, the extent of extravascular fluid increases as a result of mediator induced progressive capillary hyperpermeability. In my study the TFC of patients with uncomplicated sepsis did not differ significantly from controls, which is likely to indicate the absence of any major fluid shift. Severely septic patients however, had a significantly higher TFC value on arrival in the ED than non-septic controls. Since sepsis is characterised by relative and absolute hypovolaemia the measured elevated TFC is highly indicative of pulmonary capillary leakage. My data suggests that TFC measurements may serve as a bedside method to diagnose capillary leak syndrome in patients with sepsis.

Tissue oxygen saturation. Study data on StO$_2$ was only available for the severely septic cohort. However, when compared with published ‘normal’ StO$_2$ values (healthy volunteers) severely septic patients had markedly reduced StO$_2$ measurements on arrival in the ED. This implies that patients with severe sepsis or septic shock have a measurable microcirculatory dysfunction and inadequate tissue oxygenation prior to the initiation of any treatment. This important secondary outcome finding is further discussed in sections 4.3.2 and 4.4.2.
[4.1] SUMMARY – To determine whether patients with sepsis have abnormal cardio-haemodynamic parameters on arrival in the ED compared with normal controls

Prior to this thesis there was no published data on early cardio-haemodynamic changes in septic patients before administration of any treatment. When comparing septic patients to normal controls my work shows that they have clearly abnormal haemodynamic parameters. This thesis provides the first evidence that even patients with uncomplicated sepsis, who are not haemodynamically compromised by conventional measurements, have significantly altered SV and SVR compared to non-septic ED patients. The data also shows that severely septic ED patients have a measurable microcirculatory dysfunction as indicated by the abnormal StO₂ values on arrival in the ED.
4.2 To determine whether abnormal cardio-haemodynamic parameters normalise with treatment

4.2.1 Change of cardio-haemodynamic parameters in septic ED patients with normal treatment in the ED

In uncomplicated sepsis, resuscitation in the ED did not result in important differences between most of the TEB cardio-haemodynamic variables obtained on arrival and departure from the ED. There were, however, two exceptions TFC and HR which showed a statistically significant increase and decrease respectively.

Severely septic patients exhibited a similar degree of change in their cardio-haemodynamics following the resuscitative management in ED. In addition, the severely septic cohort demonstrated a significant fall in MAP and left cardiac work (LCW). Interestingly, in spite of a decrease in heart rate and an anticipated increase in venous blood volume owing to the administration of intravenous fluids to all septic patients in the ED, an important change in SV was not observed. This was surprising as I had expected SV to increase with treatment.

Under normal conditions an increase in venous blood volume will result in an increase in central venous pressure (CVP), a parameter commonly used as a surrogate marker for cardiac preload. CVP reflects the right ventricular end-diastolic pressure (RVEDP) which, in the absence of left ventricular impairment (ejection fraction >50%), mirrors changes in the left ventricular end diastolic pressure (LVEDP). Thus it would be expected that an increase in central venous blood volume would result, to some extent, in an increase in left ventricular end diastolic volume (LVEDV) and therefore SV, if
the left ventricular end systolic volume (LVESV) was kept constant. An increase in SV was not observed in either of the septic cohorts and there are a number of possible explanations for this.

Firstly the amount of fluid given in the ED was likely to have been too small to sufficiently augment the CVP and thus the preload. Severely septic patients received on average 1.3 litre of crystalloid fluid whilst in the ED, which is less than half of the amount that was given to the control arm in the ‘Early goal directed therapy’ (EGDT) study\(^3\) and about one third of that given to the EGDT intervention group\(^3, 24\).

Secondly, even if the administration of intravenous fluids resulted in an increase in CVP this may not have had the effect on preload that would have been expected under normal conditions. A recent paper had shown that patients with septic shock failed to augment their LVEDV, as measured by transthoracic echocardiography, despite venous volume expansion to a CVP of greater than 12mmHg.\(^{162}\) This is contrary to earlier studies using a combination of thermodilution and radionuclide angiography, which described an increase in LVEDV owing to volume loading.\(^{53, 171}\) Though all three studies included patients with septic shock, their diagnostic criteria varied, as did the timing of the measurements and the treatment given to the patients. Parker et al.\(^{53}\) studied a very young cohort with an average age of 43.6 years. With advancing age the ventricles become stiffer, ventricular compliance declines and myocardial relaxation time increases, resulting in impaired filling.\(^{155}\) This may explain why Parker et al.\(^{53}\) observed an 100% increase in LVEDV in their relatively young septic shock patients whereas others\(^{162, 171}\) studying older septic shock patients found only a minimal or no increase in LVEDV.
A third reason for the lack of increase in SV amongst septic patients in my research study could be impaired cardiac contractility. This theory is supported by a previously published study looking at quantifying ventricular contractility amongst septic patients. The authors assessed the response to an intravenous fluid load in patients with uncomplicated sepsis, septic shock and non-septic critical illness by measuring changes in left ventricular stroke work index (LVSWI), which is a marker of contractility. They found that septic patients had a much smaller increase in LVSWI than controls following the fluid load and that patients with septic shock were barely able to augment their LVSWI which was significantly lower compared to controls. This would suggest that patients with severe sepsis have an abnormal cardiac response to fluid resuscitation due to a markedly reduced ventricular contractility.

There are some parallels between these findings and the changes seen in the patient data presented in this thesis. Since LVSWI is a function of stroke index (SI), measured changes in SI will be reflected in LVSWI. Similar to Ognibene et al. I found that patients with uncomplicated sepsis demonstrated a minor increase in stroke volume whilst severely septic patients were unable to show any SV augmentation despite administration of intravenous fluids. This would suggest that from the early stage of sepsis ventricular contractility is impaired and that cardiac performance is not noticeably improved by increasing CVP through venous volume load. This may also explain, why in severe sepsis, fluid resuscitation targeted to a fixed CVP endpoint had no significant impact on hospital mortality.

In my study severely septic patients became more hypotensive despite initial fluid resuscitation in the ED. Given the fact that severe sepsis is a state of profound
intravascular deficit the worsening hypotension is likely to be a combination of inadequate fluid therapy, increasing vasodilatation and microvascular leakage.

Though fluid resuscitation received in the ED may have not been adequate to augment the systemic blood pressure of severely septic patients there was a measurable increase in their fluid status as indicated by the rise in TFC. Thoracic fluid content is primarily determined by the amount of intravascular, intra-alveolar and interstitial fluids in the thorax. It is not commonly used to evaluate a patient’s fluid status. The current understanding about the association between TEB derived TFC and thermodilution parameters is limited to the findings of a few studies with very small sample sizes. Whilst one study in chronic heart failure patients found a moderate positive correlation between TFC and left ventricular diastolic pressures two other studies found that TFC did not correlate with pulmonary capillary wedge and right atrial pressures. Though there is lack of correlating TFC with established invasive modalities TEB TFC measurements were found to be of value in the assessment of the fluid status in critically ill ED patients. This has been confirmed by a more recent study demonstrating that TFC is a reliable measurement of thoracic fluid status and tracks fluid changes well.

Although this research project was not designed to assess the effect of intravenous fluid administration, the data from both septic cohorts imply that there is a weak positive correlation between the amount of fluids given per kg/bodyweight and absolute changes in TFC whilst in the ED. This association was more pronounced in the uncomplicated sepsis group ($r^2=0.48$ vs. $r^2=0.32$) which may be explained by the persistent peripheral vasodilatation and global microvascular leakage in severe sepsis or septic shock. Considering the existing challenge to assess fluid therapy of septic
patients in routine clinical practice the potential of TFC to monitor fluid resuscitation warrants further exploration.

Another parameter believed to be indicative of fluid responsiveness in critically ill patients is stroke volume variation (SVV). SVV, a naturally occurring phenomenon due to respiration, is thought to decrease in response to an increase in preload. Current evidence, which is based on mechanically ventilated surgical patients using semi-invasive techniques, is inconsistent though there is a trend in favour of the usefulness of SVV in this selective group of patients. The results from my research project do not support the use of transcutaneous Doppler ultrasound derived SVV to predict fluid responsiveness given the lack of association between SVV and changes in SV ($r^2<0.01$). Possible explanations for this are the variability in respiratory pattern of spontaneously breathing critically ill patients and the earlier described sepsis induced myocardial dysfunction.

The resuscitative management in the ED resulted in an overall improved StO$_2$ amongst severely septic patients, just reaching the lower limit of the ‘normal’ range for StO$_2$. This finding concurs with the concept of improved tissue oxygenation by restoring tissue perfusion through fluid resuscitation. Interestingly, though initial fluid resuscitation resulted in a noticeable improvement in microcirculatory function this was not observed for macrocirculatory perfusion markers, such as SVR or MAP.
4.2.2 Change of cardio-haemodynamic parameters in septic ED patients after 24 hours of normal treatment

Whilst there were negligible changes in haemodynamic parameters following the treatment period in the ED in both septic cohorts subsequent sepsis management over 24 hours resulted in a significant reduction in CO, CI and HR and an increase in left ventricular ejection time (LVET). StO$_2$ measurements of severely septic patients were within the normal range, an important though not statistical significant change from the initial assessment. Figure 37 illustrates the physiological status of severely septic patients compared to normal, after the initial 24 hour sepsis management. Whereby the width of the arrow signifies the extent of abnormality and the direction of the arrow indicates the directional change from normal.

Figure 37. Physiological parameters after 24 hours of treatment compared to controls
The reduction in CO and CI was mainly attributable to the decline in HR as SV remained low. LVET, a function of ventricular contractility, represents the isotonic phase of the ventricular systole.\textsuperscript{180} It is generally accepted that LVET is inversely proportional to HR.\textsuperscript{181} For this reason the increase in LVET observed in both studies was most likely the result of HR reduction rather than a result of improved contractility. This assumption is supported by the fact that SV and SI remained essentially unchanged despite 24 hours of treatment, thus endorsing the concept of prolonged myocardial depression in sepsis.

After 24 hours of sepsis management there was a significant increase in TFC amongst severely septic patients but virtually no change in patients with uncomplicated sepsis. Despite patients with severe sepsis / septic shock receiving, on average, one third more intravenous fluids than those with uncomplicated sepsis the proportional increase in TFC was far greater than would have been expected based upon the absolute fluid administration. A likely explanation for this observation would be ongoing or even worsening pulmonary capillary hyperpermeability over 24 hours leading to an increase in extravascular fluid.

\textbf{[4.2] SUMMARY – To determine whether abnormal cardio-haemodynamic parameters normalise with treatment}

My data shows that initial resuscitative treatment in uncomplicated or severe sepsis does not result in pronounced immediate changes in patients’ haemodynamics. However, when assessed after the initial 24 hour treatment period cardio-
haemodynamic parameters of patients with uncomplicated or severe sepsis began to normalise. This trend towards ‘normality’ was more pronounced in patients with uncomplicated sepsis, a finding which was not unexpected. Though, after 24 hours of treatment, septic patients were found to have near normal HR and CO their cardiac function had not returned to normal, as indicated by the persistently low SV.

TFC continued to rise during the 24 hours treatment period, which was most evident in severely septic patients, indicative of increased capillary hyperpermeability.

Contrary to the pattern of change seen in haemodynamic parameters, StO$_2$, a marker of microcirculatory function, was found to reach near normal values with initial fluid resuscitation. These patterns, observed and presented in this thesis for the first time, substantiate the concept that restoration of the microcirculatory function precedes that of the macrocirculation.
4.3 To determine whether the degree of initial abnormality is related to outcome

4.3.1 Comparison of initial cardio-haemodynamic parameters in survivors and non-survivors from severe sepsis / septic shock

Survivors and non-survivors were very similar in their baseline characteristics with the exception for age. Non-survivors were found to be significantly older than those surviving septic illness. No significant differences were seen in their initial conventional physiological parameters or ‘Early Warning Score’ (EWS) results. There were however, differences in their mean ‘Mortality in Emergency Department Sepsis’ (MEDS) score and venous lactate measurement, with values being significantly higher in non-survivors.

No statistically significant differences in initial cardio-haemodynamic parameters were found between survivors and non-survivors. Though not significant, there was a noticeable difference in CO and SV (Figure 38).
Whilst survivors demonstrated the ability to augment their CO in response to sepsis, this ability was lacking in non-survivors, who were merely able to maintain a CO similar to the control group. This concurs with the findings of a recently published study reporting a significantly lower cardiac index in non-survivors from severe sepsis.\textsuperscript{182} Napoli et al.\textsuperscript{182} hypothesised that the difference in CI may be the result of inadequate fluid resuscitation since non-survivors received on average 530mls less.
Though this is plausible it was unlikely to be the cause in the Napoli et al.\textsuperscript{182} study given the very similar CVP measurements (10.3 versus 10.0) in both cohorts. A more likely explanation for the observed greater CO in patients with a favourable outcome from severe sepsis / septic shock is a lesser degree of myocardial depression and thus a smaller decrease in SV.

The data from my study has shown that SV was reduced in all severely septic patients and though the reduction was far greater in non-survivors, it did not reach statistical significance. This said, the lack of statistical power may have caused a type II error given the wide 95\% confidence intervals. In view of this and the fact that a difference in SV of 18\% would be deemed clinically meaningful further exploration in a future trial is needed.

Since all initial measurements were taken prior to fluid administration, fluid under-resuscitation does not appear to play a pivotal role. Other factors that affect stroke volume are contractility, compliance and afterload. Interestingly, left ventricular ejection time (LVET) a marker of contractility was found to be no different in relation to outcome. Systemic vascular resistance, an estimate of afterload, was insignificantly lower in survivors and may have contributed to some extent to the larger SV seen in survivors. Though ventricular compliance was not measured in this research study it is conceivable that impaired compliance had an effect on SV differences seen in this research study. This concept is supported by a number of previous studies indicating an impaired ventricular compliance in septic patients as a result of abnormal ventricular filling and relaxation.\textsuperscript{183-185}
Contrary to previous beliefs\textsuperscript{43} initial heart rate was not found to be related to outcome. In fact, HR was identical in both groups. The view that initial HR predicts outcome from severe sepsis and septic shock is based on two studies from the 1980s\textsuperscript{186, 187}. Since both studies had been conducted in intensive care units and initial measurements were commenced once circulatory shock was present, describing their finding as ‘initial’ is misleading and not reflective of changes seen in the very early phase of sepsis.

Of all measured haemodynamic parameters, TEB cardiac output demonstrated the best discriminatory power for survival on ED arrival, as indicated by the AUROC (0.702). Though CO may be an useful early predictor of outcome from severe sepsis, the identified optimal cut off for cardiac output greater than 5.1 l/min in favour of survival, lacks sufficient sensitivity (82\%) and specificity (55\%) to be used as a ‘rule out’ or ‘rule in’ tool.

4.3.2 Comparison of initial tissue oxygen saturation (StO\textsubscript{2}) in survivors and non-survivors

Tissue oxygen saturation (StO\textsubscript{2}) was seriously impaired in all severely septic patients on their arrival in the ED prior to the initiation of treatment, hence initial StO\textsubscript{2} measurements were not found to be predictive of outcome.

Tissue oxygen saturation provides information about oxygenation within the microcirculation. It has become evident that microcirculatory dysfunction plays a key role in the pathogenesis of sepsis and that the derangement is more severe in patients with the worst outcome\textsuperscript{188-190}. These findings are based on ICU patients with severe
sepsis or septic shock who were already receiving treatment. As such they do not provide information on early microcirculatory changes in severe sepsis.

In contrast to the findings of my research, a recent prospective study of high-risk trauma patients showed that tissue oxygen saturation measured upon their arrival in the Emergency Room predicts development of multiple organ failure and death.\textsuperscript{191} This concept of early determination of poor outcome had been initially confirmed in a porcine haemorrhagic shock model.\textsuperscript{192}

In neither sepsis nor trauma is the complex pathogenesis responsible for microcirculatory disturbance clearly understood. The complex interactions of different biological structures and processes within the body are thought to be responsible for the microvascular dysfunction in sepsis. Circulating inflammatory mediators, such as cytokines, are believed to play a pivotal role, alongside activated dysfunctional complement and coagulation cascades and leucocytes.\textsuperscript{193, 194} As a knock-on effect endothelial permeability increases, thrombosis and sludging of red blood cells in the microvasculature develops. This leads to an impaired microvascular blood flow and oxygen delivery, a fact that has been confirmed by the StO\textsubscript{2} measurements of my study. Observed changes in StO\textsubscript{2} in the severely septic cohort are further discussed in \textit{section 4.4.2}.
[4.3] **SUMMARY – To determine whether the degree of initial abnormality is related to outcome**

The results of my thesis demonstrate that survivors from severe sepsis / septic shock do not differ significantly in their degree of initial abnormality in haemodynamics and StO$_2$ compared to non-survivors. However, patients with a favourable outcome had a higher CO and a lesser reduction in SV on arrival in the ED. Given the wide confidence intervals, these findings warrant further exploration as they may identify a group of patients who may benefit from a different sepsis management. A future trial should not only focus on initial CO and SV measurements but also on the dynamic changes in response to initial resuscitative treatment to determine their potential to guide early sepsis management.
4.4 To determine whether normalisation of cardio-haemodynamic parameters with treatment is related to outcome

4.4.1 Comparison of cardio-haemodynamic parameters following normal treatment in survivors and non-survivors from severe sepsis / septic shock

As depicted in section 4.1 septic patients had deranged cardio-haemodynamic values compared to non-septic controls. It was further shown in section 4.2 that administration of normal treatment resulted in measurable though not significant changes. Previous studies amongst critically ill ED patients have demonstrated that normalisation of cardiovascular and tissue perfusion markers was associated with a good outcome.\textsuperscript{82, 91} It was therefore anticipated that patients with a good outcome would display a normalisation of their cardio-haemodynamic parameters.

Of those patients presenting with uncomplicated sepsis to the ED all but one survived (4\% mortality). With initial treatment this cohort showed a clear trend towards normalisation of cardio-haemodynamic parameters with the exception of TFC.

In contrast, the chronological patterns of cardio-haemodynamic parameters of severely septic patients differed depending on the patient’s outcome. The pattern in survivors of severe sepsis / septic shock was similar to that seen in uncomplicated sepsis, with a trend to normality in cardiovascular parameters over 24 hours. In contrast, non-survivors did not show this normalisation with continuing abnormality of CO, SV and StO\textsubscript{2}. Figure 39 illustrates the observed physiological state seen in survivors and non-
survivors after 24 hours of treatment. The overall lack of improvement in myocardial function as seen in non-survivors is likely to be a reflection of irreversible cardiac dysfunction due to sepsis. These observations, the first in the emergency care phase, are consistent with previous ICU studies describing irreversible depression of cardiac function in patients succumbing to septic shock.\textsuperscript{53, 161, 195}

![Figure 39. Physiological state of survivors and non-survivors after 24 hours of treatment compared to controls](image-url)
Since survival appears to be associated with the ability to improve cardiac performance would a more aggressive treatment approach alter the prognosis of those with a potentially poor outcome? According to a study in septic ICU patients non-survivors failed to augment their cardiac function despite the administration of inotropic agents, suggesting serious and potentially irreversible myocardial depression.\(^\text{196}\) Even if prevention of disease progression may not be possible, early identification of septic patients with a poor prognosis will aid clinical decision making, even if this is simply to decide on the ceiling of treatment.

As for TFC, this parameter continued to increase with treatment in survivors and non-survivors. Non-survivors had a higher TFC and had received more intravenous fluids, although neither finding was statistically significant. Though early aggressive fluid resuscitation within the first hours of sepsis presentation was found to be associated with a good outcome, subsequent aggressive fluid administration may actually be harmful.\(^\text{3, 197}\) Most of the infused fluid will eventually disperse into the extravascular space, a process which is expedited in sepsis due to increased vascular permeability, hence exacerbating tissue oedema and worsening organ perfusion. Whilst these are valid points they are unlikely to be applicable to the patients of my research study, since none of the patients received excessive amounts of intravenous fluids compared to other studies\(^\text{3, 197}\).

Contrary to what would have been expected, after 24 hours of treatment, non-survivors had a markedly higher SVR, approaching the value found in normal controls. The impact of sepsis on SVR and its association with outcome from sepsis has not been studied in depth in clinical settings. There is evidence to suggest that poor outcome from septic shock is linked with a low SVR.\(^\text{198, 199}\) Systemic vascular resistance,
defined as resistance to the blood flow offered by the systemic circulation, is predominantly determined by the calibre of the arterioles. A number of sepsis models have demonstrated that endothelial-derived nitric oxide plays an important role in the flow regulation of arterioles.\textsuperscript{200, 201} There is also evidence that altered synthesis and release of nitric oxide and disruption of endothelial signalling affecting the dilator control mechanisms for arterioles, contributes to a decreased SVR in sepsis.\textsuperscript{202} A possible explanation for the higher than expected SVR in severely septic patients in my research study may be the fact that TEB SVR was calculated using MAP and CO rather than being measured. Since SVR is inversely proportional to CO and non-surviving septic patients had a markedly lower CO their calculated SVR would have been higher since the MAP was nearly identical in both cohorts.

\textbf{4.4.2 Comparison of change in tissue oxygen saturation (StO\textsubscript{2}) following normal treatment in survivors and non-survivors}

A key finding of this research project is the measurable normalisation of StO\textsubscript{2}, a marker of microcirculatory function, in survivors following the initial treatment, whilst macrocirculatory parameters were only starting to demonstrate a trend towards ‘normal’ after 24 hours of sepsis management.

Until recently the assessment of microcirculatory changes in critically ill patients was limited due to the need for cumbersome measuring equipment. The use of StO\textsubscript{2} monitoring has been described in different cohorts of critically ill patients such as trauma and septic ICU patients.\textsuperscript{128-131, 203-205} Nearly all studies concluded that StO\textsubscript{2} values were lower in critically ill patients compared to healthy controls and some suggested that low StO\textsubscript{2} values were predictive of poor outcome. Two recently
published studies assessing StO$_2$ in severely septic ICU patients found no difference in baseline StO$_2$ measurements in survivors and non-survivors from severe sepsis/septic shock but a significantly lower StO$_2$ reperfusion slope in non-survivors after three minutes of induced arterial ischemia.$^{130,205}$

Two other ICU studies looked at StO$_2$ values without induced ischemia in severely septic patients after completion of the EGDT resuscitation treatment.$^{203,204}$ They found that low StO$_2$ values were associated with poor outcome despite early optimisation of haemodynamic parameters.

Data on the microcirculatory assessment of septic patients in the ED is sparse. A recent study utilising orthogonal polarisation spectral imaging to visualise sublingual microcirculation in ED patients with severe sepsis reported greater microcirculatory derangement in non-survivors from an early stage, defined as ‘within 6 hours of commencing early goal directed therapy’. $^{206}$ Those findings are in keeping with the results from my research study of persistently low StO$_2$ readings in non-survivors despite normal resuscitative treatment.

The fact that StO$_2$ in survivors began to normalise with initial resuscitative treatment in the ED, as demonstrated in my study, indicates that patients with a good prognosis have the ability to rapidly improve their microcirculatory derangement, whilst those with a poor outcome lack this type of response. This raises the question as to whether septic patients, who fail to respond to normal ED treatment, as measured by lack of improvement in StO$_2$, would have their prognosis improved by a therapeutic strategy that targets early optimisation of StO$_2$. 
SUMMARY – To determine whether normalisation of cardio-haemodynamic parameters with treatment is related to outcome

The ability to normalise cardio-haemodynamic parameters and StO$_2$ with treatment is associated with a good outcome. Whilst StO$_2$ of survivors reached a near normal value with the initial resuscitation such immediate effect was not observed for macrocirculatory parameters. Within 24 hours of treatment survivors from severe sepsis demonstrated a trend towards normal for nearly all haemodynamic parameters, a pattern similar to that seen in patients with uncomplicated sepsis. Non-survivors however, lacked this ability, which is likely to be a reflection of ongoing serious cardiac dysfunction.
4.5 To determine which non-invasive monitoring modality is most strongly related to outcome

Early risk stratification in sepsis is crucial to improve outcome given the high morbidity and mortality associated with severe sepsis / septic shock. Owing to the heterogeneity of the clinical manifestation of sepsis, early risk stratification remains challenging and conventional physiological and laboratory parameters were not found to be helpful. There is a clear need for clinically useful biomarkers to aid identification of high risk septic patients.

My research is the first study to assess the cardio-haemodynamic response to severe sepsis / septic shock in its early phase, by using a range of non-invasive technologies, and how this response is related to outcome. Two of the modalities, TEB and transcutaneous Doppler, provided a wide range of cardio-haemodynamic parameters. The third device measured tissue oxygen saturation, a marker of microcirculatory function.

My work shows that, as expected, the cardio-haemodynamic responses to sepsis are complex and not homogenous. There was evidence of cardiovascular and microcirculatory dysfunction amongst all patients with severe sepsis / septic shock, with a distinct pattern for survival. Early measurements in the ED showed that survivors predominantly exhibited a high CO with a lesser reduction in SV and low SVR whereas non-survivors primarily demonstrated a ‘normal’ CO with a low or normal SVR. There was no difference in StO₂ on ED arrival.
In response to the initial ED sepsis management a distinct pattern emerged for SV and StO$_2$. Following the initial and the subsequent 24 hour treatment, survivors demonstrated the ability to augment their stroke volume and to normalise their tissue oxygenation whereas both parameters remained unchanged in non-survivors.

There is no previous published data comparing StO$_2$ and SpO$_2$. Though both are measures of oxygenation, StO$_2$ reflects oxygenation within the microcirculation whereas SpO$_2$ is a surrogate marker of global oxygenation. The distinct chronological pattern of StO$_2$ from the early phase of sepsis heralds the fact of ongoing impaired microcirculatory oxygenation in patients with poor outcome, despite having normal SpO$_2$ values. This concurs with the concept of sepsis induced tissue hypoxia preceding global hypoxia. It further suggests that StO$_2$ can provide early prognostic information about outcome from severe sepsis / septic shock and has the potential to aid identification of patients who would benefit from more intensive therapy.

Contrary to previous beliefs my data has shown that severely septic patients have a reduced SV, with the greatest reduction in non-survivors. This concurs with a recent study by Napoli et al.$^{182}$ The changes in SV over time exhibited a distinct pattern for survival whereby survivors had the ability to augment their SV in response to treatment but non-survivors did not; an observation which supports the concept of reversible myocardial dysfunction in survivors from sepsis originally described by Parker et al.$^{53}$.

Both TEB and USCOM measured SV. Overall both technologies measured higher values in the surviving cohort though TEB measurements were persistently lower. The cause of this discrepancy is not clear. Given the fact that signal acquisition using the
USCOM was not always perfect due to the patients’ habitus or inability to remain still during the measurement, underestimation of haemodynamic values would have been expected. Underestimation of haemodynamic parameters by the TEB method due to motion artefacts is a possibility, although measurements obtained in this research project had higher values than those of a comparable cohort in the Napoli et al.\textsuperscript{182} study.

The study was powered to detect a difference in cardiac index for survival. Though the predetermined minimal clinical significant difference for CI of $\geq 0.3 \text{ l/min/m}^2$ was observed on ED arrival, this lacked statistical significance due to higher than expected variation. In subsequent measurements this difference was even smaller. This is contrary to a very recent study using TEB in a cohort of ED patients (n=55) eligible for EGDT, where survivors had a significantly higher CI (3.2 vs. 2.3, $p=0.02$) following ED resuscitation.\textsuperscript{182} Noticeably, non-survivors in the Napoli et al.\textsuperscript{182} study had a surprisingly low mean heart rate (67 bpm) which was very different to the HR of 102 bpm found in non-survivors after ED sepsis management in my study. This in itself may explain the disparate findings. (Personal communication with Dr Napoli did not offer any further explanation.)

As expected conventional parameters such as HR, BP and SpO\textsubscript{2} did not show a distinct pattern for survival on arrival or departure from the ED. At the 24 hour follow up HR and SpO\textsubscript{2} differed for survival, but interestingly there was no distinct difference for BP. Since hypotension is believed to be associated with worse outcome from sepsis, non-survivors were expected to have a lower BP than survivors. Even sepsis related non-sustained hypotension (systolic BP <100mmHg) was reported to be associated with a threefold higher risk of mortality.\textsuperscript{208} This is much higher than in my severe
sepsis study, where the association between hypotension and mortality was weak (relative risk of death of 1.2).

[4.5] SUMMARY – To determine which non-invasive monitoring modality is most strongly related to outcome

Predicting patient outcome based on parameters taken on arrival in the ED is difficult. Of all measured haemodynamic parameters CO and its determinant SV were found to be the best discriminatory variables for survival on ED arrival, an observation that concurs with the concept of worse myocardial dysfunction in patients with poor outcome. With the instigation of initial sepsis treatment macrocirculatory parameters (CO and SV) lost their discriminating ability, whilst another variable, StO\textsubscript{2}, showed a distinct pattern for survival. This pattern continued throughout the initial 24 hour treatment period and is indicative of early normalisation of the sepsis induced microcirculatory derangement. At the end of the 24 hour treatment period of all the cardiovascular parameters, only SV demonstrated a distinct pattern for survival.

My work demonstrates that these parameters, in particular StO\textsubscript{2} and SV, have the potential to act as biomarkers of poor outcome and thus enable the identification of high risk patients who may have their prognosis improved by a more intensive treatment strategy.
5 CONCLUSIONS

5.1 Research findings

This thesis examined cardio-haemodynamic parameters in septic ED patients and explored their potential value in the early management of sepsis and septic shock. Five general aims were addressed in this thesis, the finding for each of these objectives were:

[1] To determine whether patients with sepsis have abnormal cardio-haemodynamic parameters on arrival in the ED compared with normal controls

a) This research project has shown that ED patients with sepsis / septic shock have measurable abnormal cardio-haemodynamic indices on arrival in the ED. The direction of physiological derangement was the same for patients with uncomplicated or severe sepsis.

b) Septic patients were found to have a higher cardiac output and cardiac index than the age and gender matched control group patients, but these differences were not statistically significant.

c) Stroke volume and stroke index in both septic cohorts was significantly lower than in the age and gender matched control group. This is likely to be a reflection of impaired myocardial contractility, a feature of sepsis induced myocardial depression.
d) Systemic vascular resistance was found to be significantly lower in both septic cohorts. This reduction was most pronounced for patients with severe sepsis / septic shock.

e) Septic patients of both groups were found to be tachycardic, exhibiting a heart rate which was significantly higher than that of control group patients. Mean arterial pressure remained within the accepted normal range for patients with uncomplicated sepsis but was significantly reduced in patients with severe sepsis / septic shock.

f) Severely septic ED patients had a measureable microcirculatory dysfunction on arrival in the Emergency Department, as indicated by the markedly reduced tissue oxygen saturation (StO$_2$) measurements. It is not known whether patients with uncomplicated sepsis have a similar abnormality.

In light of these findings I hypothesise that early identification of septic patients may be improved by including haemodynamic parameters and StO$_2$ measurement as part of the initial assessment in the ED.

[2] To determine whether abnormal cardio-haemodynamic parameters normalise with treatment

g) Initial resuscitative management in the ED did not result in important immediate changes in cardio-haemodynamic parameter of patients with uncomplicated or severe sepsis. However, this lack of change might have been masked by the relatively small amount of fluid resuscitation that was given.
h) After 24 hours of sepsis management a trend towards ‘normal’ haemodynamics emerged in both septic cohorts. This trend was more pronounced in patients with uncomplicated sepsis.

i) Following the initial ED management tissue oxygen saturation of severely septic patients demonstrated a trend towards ‘normal’ values, which is likely to be a reflection of the beginning of microcirculatory improvement following treatment.

[3] To determine whether the degree of initial abnormality is related to outcome

j) No statistically significant differences in initial cardio-haemodynamic or StO₂ measurements taken on arrival in the ED were found between survivors and non-survivors. However, survivors had a greater cardiac output owing to a lesser reduction in stroke volume, suggestive of a lesser degree of myocardial dysfunction in patients with a favourable prognosis. These findings warrant further exploration using cardiac output and stroke volume as biomarkers to define a high risk group.

[4] To determine whether normalisation of cardio-haemodynamic parameters with treatment is related to outcome

k) Following early resuscitative sepsis management StO₂ measurements improved in survivors, reaching the lower end of the normal range, but remained abnormal in non-survivors. Thus in patients with a good prognosis the microcirculatory
derangement responded well to initial sepsis management raising the question whether non-responders may have their prognosis improved by a more intensive approach to early sepsis resuscitation.

1) Patients with uncomplicated sepsis (4% mortality), demonstrated a clear trend towards normalisation of cardio-haemodynamic indices with 24 hours of treatment. A similar pattern was seen in survivors from severe sepsis / septic shock (49% mortality). Patients who did not show a tendency to normalise within 24 hours had a poor outcome. The overall lack of improvement in cardiovascular function, as seen in non-survivors, is likely to be indicative of ongoing myocardial dysfunction.

[5] To determine which non-invasive monitoring modality is most strongly related to outcome

m) Of all studied parameters StO₂ and SV were most strongly related with outcome from severe sepsis / septic shock. SV was found to have good discriminatory power for survival throughout the initial 24 hours. This ability to discriminate was strongest at the end of the initial 24 hour sepsis management period. Though StO₂ on arrival in the ED lacked discriminating power for survival, a distinct outcome related pattern for StO₂ emerged following the initial resuscitative treatment with early normalisation in survivors.
**SUMMARY OF CONCLUSION**

This thesis is the first description of cardio-haemodynamic parameters in septic patients at their entry to hospital (ED). The data shows that septic patients have initially abnormal haemodynamics and abnormal tissue oxygen saturation which is indicative of macro and microcirculatory derangements. The study also demonstrates that the microcirculatory function starts to normalise in survivors after the initial resuscitative treatment in the ED whilst haemodynamic parameters, reflecting the macrocirculation, remained abnormal. Another key finding is, that the initially abnormal cardio-haemodynamic parameters began to normalise after 24 hours of treatment and that the failure to show signs of normalisation was associated with poor outcome.

Of all the parameters studied the two variables most strongly related to outcome were StO\textsubscript{2} and SV. Both parameters warrant further exploration to define their role as biomarkers for early disease progression and poor outcome. This might identify a group of high risk patients, who may have their outcome improved by a more intensive treatment strategy.

Any future trial will need also to focus on dynamic changes of haemodynamic parameters, in particular SV and StO\textsubscript{2} in response to initial resuscitative treatment to determine their potential to guide early sepsis management.
### What is already known on this topic

- Septic shock is characterised by increased cardiac output and low systemic vascular resistance (ICU phase)
- Early instigation of appropriate sepsis management improves outcome from sepsis
- Sepsis management directed at CVP and SvO\(_2\) does not improve outcome from sepsis
- One quarter of septic patients progress to severe sepsis / septic shock

### What this thesis adds

- Septic shock is characterised by increased cardiac output and low systemic vascular resistance (ED phase)
- Septic patients, who are not haemodynamically compromised by conventional measurements, have abnormal cardio-haemodynamic parameters prior to instigation of treatment
- Ability to normalise cardio-haemodynamic parameters with initial treatment is related to good outcome
- Normalisation of microcirculatory function precedes that of the macrocirculation
- StO\(_2\) and stroke volume are strongly related to outcome from sepsis and have the potential to act as biomarkers to indentify high risk patients
5.2 Limitations

There are a number of limitations to this research project. A potential weakness of both studies was the use of a convenience sample. Convenience sampling is known for its potential to create bias and may account for the higher proportion of male patients recruited to the severely septic cohort. However, a consecutive sample would have not been feasible owing to the fact that the entire recruitment and data acquisition was carried out by a single researcher (myself).

Despite every effort, follow up was incomplete. Whilst only two patients from the uncomplicated sepsis group were lost to follow up (n=1 death; n=1 drop out), there were 10 attritions in the severe sepsis group (n=8 deaths; n=2 drop outs). This could have resulted in an under or overestimation of the observed difference in haemodynamics between cohorts.

Lack of standard sepsis management could have caused confounding, resulting in an erroneous interpretation of the studies’ findings. Whilst this is a potential risk for any observational study it is less likely to have had an important effect, since early resuscitative treatment was very similar regardless of outcome.

Though the researcher was not involved in the direct clinical care of the patients enrolled in either study, given their observational nature, there is the potential that the researcher’s presence may have influenced the care the patients received (Hawthorne effect). This may have had an impact on patient's mortality and as such the results may have underestimated the true difference in cardio-haemodynamic parameters between survivors and non-survivors.
Although both studies were based on sample size calculations there was greater variance within the groups than expected causing overall lack of power. This may have caused a type II error as indicated by the relatively wide confidence intervals, which encompass clinically significant differences.

30-day in-hospital mortality was used as the primary endpoint for assessing the relationship and predictability of cardio-haemodynamic parameters on mortality from severe sepsis or septic shock. However, there may have been multiple other factors that contributed to the death of a patient.

There may be limitations to the generalisability of the findings. Firstly, all enrolled patients received clinical care in keeping with normal local practice but this may differ considerably from sepsis management in other departments. Secondly, strict exclusion criteria were used in order to explore the value of non-invasive cardio-haemodynamic parameters and tissue oxygen saturation in the early management of sepsis. Therefore the results of this thesis may not be generalisable to other groups of patients.
5.2 The next stage

This thesis has identified a number of areas that warrant further exploration in future trials:

Co-diagnostic / therapeutic intervention

1) This thesis has identified a number of parameters, StO\textsubscript{2} and SV being the most promising, which have the potential to act as biomarkers for disease progression and poor outcome. To validate the link between these potential biomarkers and clinical outcome a multi-centre prospective study of broadly defined septic ED patients receiving standard sepsis management is needed.

2) The data of this thesis also shows that normalisation of haemodynamics with treatment is associated with good outcome. This generates the question as to whether high risk patients may have their prognosis improved by using a treatment strategy targeted at normalisation of specific haemodynamic biomarkers, such as StO\textsubscript{2} or SV. To explore this hypothesis a study would be required to determine the relationship between specific biomarkers as therapeutic endpoints and clinical outcome.

3) Once biomarker based resuscitation / therapeutic endpoints have been identified a therapeutic trial comparing early sepsis management directed by non-invasive haemodynamic (biomarker) endpoints versus conventional management is warranted.

4) Since sepsis is a complex clinical condition using a single biomarker may not yield optimal discriminatory power. However, combining haemodynamic and biochemical biomarkers, such as lactate clearance or brain natriuretic peptide, in a
predictive model may significantly enhance disease progression and outcome predictability. Once a predictive model has been derived from a prospective data set, internal and external validation of this model, ideally, as part of a multi-centre study will be required.

**Diagnostics**

4) Since septic patients were found to have clearly abnormal haemodynamics, as demonstrated in this thesis, a diagnostic study is needed to determine the role of clinically useful haemodynamic biomarkers to aid early diagnosis of sepsis at the point of entering the Emergency Department.
6 REFERENCES


42. Waisbren BA. Bacteremia due to gram-negative bacilli other than the salmonella: A clinical and therapeutic study. *Arch Intern Med.* 1951;88:467-488.


108. USCOM -The Basics. USCOM Ltd. Published April 2008.


151. USCOM - Quick guide.: USCOM Ltd. Published April 2008.

152. Guidance on nominating a consultee for research involving adults who lack capacity to consent. Department of Health; 2008.


APPENDICES

Appendix 1. Applying research methodology in the acute setting

Conducting research in critically ill Emergency Department patients presents a number of challenges. There are issues with ethical approval, identification/recruitment, obtaining consent, meeting clinical and research needs and patient follow up, to name just a few. After securing funding, the biggest hurdle to overcome is getting a favourable decision from the Research and Ethics committees, which is not uncommonly hinged upon the informed consent procedure. Informed consent is a process that should allow patients adequate time to make an informed decision. Whilst this is feasible in an out-patient setting it is impossible to apply to research in critical illness, where most patients are physically and mentally unable to follow such a lengthy process. There are probably several ways to overcome this problem, the approach that I have used in this research project is described as follows.

After convincing the Research and Ethics committee of the importance of my proposed research I had to attain their approval of the proposed informed consent process. The approach that I found successful was by attending the Ethics Committee meeting and describing a patient’s journey through the research, with emphasis upon the conflict between meeting their clinical needs and obtaining informed consent in the Emergency Department, since most patients would have been too unwell to give informed consent. It was the lay person who felt that approaching such ill patients, even for limited (provisional) consent, would be inappropriate and that, considering the non-invasive nature of the research, measurements should be commenced at the earliest suitable time after having explained the study in very brief and simple terms using ‘Verbal
prompts’ (Appendix 9) to the patients. Informed consent was then to be sought once the patient’s condition had improved. This approach allowed me to enrol patients who at the time of recruitment would have not been able to provide informed consent.

Since sepsis would also affect patients who permanently lack capacity or may result in lack of capacity in cases with poor outcome, ethical approval was obtained for a ‘Personal Consultee’ (formerly personal representative) who was to be approached for their assent to the patient’s participation in the study. During the study it became apparent that despite a reasonable effort it was not always possible to identify a ‘Personal Consultee’ and approval for a ‘Nominated Consultee’ (formerly legal representative) was sought.

Identifying suitable patients as soon as they arrived in the ED was another challenge. Though the ED had an electronic patient’s data base displaying the patient’s presenting complaint this information, in terms of identifying patients with sepsis, was not particularly helpful. Furthermore, suitable patients arrived at unpredictable times thus it would not have been feasible for a single researcher to be present at all times in the ED. To address this shortfall awareness amongst ED staff needed to be raised. This was done by spending most of my time in ED at the beginning of the project to personally explain the research project to members of staff and encouraging them to participate in the identification process. Other methods used were the display of the research’s inclusion criteria in the department, handing out pocket cards to staff and regular email up-dates about the project’s progress.
It was anticipated that connecting a patient to two additional monitors plus performing transcutaneous Doppler measurement may be problematic and might potentially interfere with clinical care, fortunately this was not the case.

The experience I have gained from carrying out clinical research in a busy Emergency Department is very valuable. Being aware of potential difficulties and having developed strategies to overcome these obstacles will assist me in both the delivery and supervision of Emergency Care research in the future.
Appendix 2. Patient Entry Form

University Hospitals of Leicester NHS

Emergency Department
Laeicester Royal Infirmary
Lembor
LE5 2PW
Tel: 0116 255 5000
Fax: 0116 255 7365

STUDY:
Assessment of cardio-haemodynamics in adult ED patients with severe sepsis or septic shock.

Principal Investigator: Prof TJ Coats, Professor of Emergency Medicine
Principal Researcher: Dr C Vow noct, Specialist Registrar Emergency Medicine

PATIENT ENTRY FORM

INFORMATION ABOUT TRIAL ENTRY
Date: / / 2009 Arrival Time: ___ : ___ hrs Recruitment Time: ___ : ___ hrs

Study explained to
Patient: Y / N Representative: Y / N

Consent obtained from
• Patient
Date: / / 2009 Time: ___ : ___ hrs By: .............................................
• Representative

IF consent not obtained in ED explain why:

INFORMATION ABOUT THE PATIENT
ED identification number: ___ ___ ___ ___ Trial number: ___ ___ ___ ___

Date of birth: ___ / ___ / ___ Age: ___ years

Weight: ___ Kg Height: ___ cm

Gender: Female Male

* S for study group, C for control group

INFORMATION ABOUT PATIENT’S PAST MEDICAL HISTORY

<table>
<thead>
<tr>
<th>IHD / CAD</th>
<th>MI</th>
<th>Arrhythmia</th>
<th>Hypertension</th>
<th>Heart failure</th>
<th>Terminal illness (what type?)</th>
</tr>
</thead>
</table>

INFORMATION ABOUT PATIENT’S CURRENT DRUG HISTORY

<table>
<thead>
<tr>
<th>B-blocker</th>
<th>ACE inhibitor</th>
<th>Ca-channel blocker</th>
<th>Nitrates</th>
<th>Diuretics</th>
</tr>
</thead>
</table>

INFORMATION ABOUT PATIENT’S SOCIAL HISTORY

<table>
<thead>
<tr>
<th>Lives at Home</th>
<th>Warden controlled</th>
<th>Nursing Home</th>
</tr>
</thead>
</table>

TEBASE study Patient Entry Form

Version 01 09/07/2008
Appendix 3. **TEB parameters measured in this thesis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>Cardiac index l/min/m²</td>
</tr>
<tr>
<td>CO</td>
<td>Cardiac output l/min</td>
</tr>
<tr>
<td>SV</td>
<td>Stroke volume ml</td>
</tr>
<tr>
<td>SI</td>
<td>Stroke volume index ml/m²</td>
</tr>
<tr>
<td>SVR</td>
<td>Systemic vascular resistance (dynes·s·cm⁻⁵)</td>
</tr>
<tr>
<td>SVRI</td>
<td>Systemic vascular resistance index (dynes·s·cm⁻⁵/m²)</td>
</tr>
<tr>
<td>TFC</td>
<td>Thoracic fluid content 1/kΩ</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate beats/min</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean arterial pressure mmHg</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure mmHg</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure mmHg</td>
</tr>
<tr>
<td>LCW</td>
<td>Left cardiac work load kg·m</td>
</tr>
<tr>
<td>LCWI</td>
<td>Left cardiac work load index kg·m/m²</td>
</tr>
<tr>
<td>PEP</td>
<td>Pre-ejection period ms</td>
</tr>
<tr>
<td>LVET</td>
<td>Left ventricular ejection time ms</td>
</tr>
<tr>
<td>ETR</td>
<td>Ejection time ratio %</td>
</tr>
<tr>
<td>QI</td>
<td>Quality indicator %</td>
</tr>
</tbody>
</table>
### Appendix 4. Doppler parameters measured in this thesis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>Cardiac index</td>
<td>l/min/m²</td>
</tr>
<tr>
<td>CO</td>
<td>Cardiac output</td>
<td>l/min</td>
</tr>
<tr>
<td>SV</td>
<td>Stroke volume</td>
<td>ml</td>
</tr>
<tr>
<td>SI</td>
<td>Stroke volume index</td>
<td>ml/m²</td>
</tr>
<tr>
<td>VP</td>
<td>Peak Velocity</td>
<td>m/s</td>
</tr>
<tr>
<td>MPG</td>
<td>Mean pressure gradient</td>
<td>mmHg</td>
</tr>
<tr>
<td>VTI</td>
<td>Velocity time integral</td>
<td>cm</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
<td>beats/min</td>
</tr>
<tr>
<td>MD</td>
<td>Minute distance</td>
<td>m/min</td>
</tr>
<tr>
<td>ET%</td>
<td>Ejection time percentage</td>
<td>%</td>
</tr>
<tr>
<td>FT</td>
<td>Flow time</td>
<td>ms</td>
</tr>
<tr>
<td>SVV</td>
<td>Stroke volume variation</td>
<td>%</td>
</tr>
</tbody>
</table>
Appendix 5. Ethics approval – Study 1

National Research Ethics Service
Leicestershire, Northamptonshire & Rutland Research Ethics Committee 1
1 Standard Court
Park Row
Nottingham
NG1 6GN
Telephone: 0115912344 Ext: 68575
Facsimile: 01159123500

15 May 2007

Professor Timothy Coats
Professor of Emergency Medicine
Leicester University
Emergency Department, Leicester Royal Infirmary
Infirmary Square
Leicester, LE1 5WW

Dear Professor Coats,

Full title of study: Assessment of cardiac output in septic adult patients using non-invasive Thoracic Electrical Bioimpedance
REC reference number: 07/Q2501/58

Thank you for your letter of 23 April 2007, responding to the Committee’s request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application</td>
<td></td>
<td>15 February 2007</td>
</tr>
<tr>
<td>Investigator CV</td>
<td></td>
<td>12 February 2007</td>
</tr>
<tr>
<td>Protocol</td>
<td>1.0</td>
<td>31 January 2007</td>
</tr>
<tr>
<td>Peer Review</td>
<td></td>
<td>01 February 2007</td>
</tr>
<tr>
<td>Participant Information Sheet: Patient Information Leaflet (control group)</td>
<td>2.0</td>
<td>16 April 2007</td>
</tr>
<tr>
<td>Participant Information Sheet: Patient Information Leaflet</td>
<td>2.0</td>
<td>16 April 2007</td>
</tr>
<tr>
<td>Participant Information Sheet: Summary Information Leaflet (patient)</td>
<td>1.0</td>
<td>16 April 2007</td>
</tr>
</tbody>
</table>

This Research Ethics Committee is an advisory committee to East Midlands Strategic Health Authority.
R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.


Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

Feedback on the application process

Now that you have completed the application process you are invited to give your view of the service you received from the National Research Ethics Service. If you wish to make your views known please use the feedback form available on the NRES website at:

https://www.nresform.org.uk/AppForm/Modules/Feedback/EthicalReview.aspx

We value your views and comments and will use them to inform the operational process and further improve our service.

With the Committee's best wishes for the success of this project

Yours sincerely

Dr C Edwards/Ms L Ellis
Chair/Co-ordinator

Email: Linda.ellis@nottinghamshirecounty-tptc.nhs.uk

Enclosures: Standard approval conditions
Site approval form

Copy to: R&D office for NHS care organisation at lead site - University Hospitals Leicester NHS Trust
Appendix 6. R&D approval – Study 1

University Hospitals of Leicester

DIRECTORATE OF RESEARCH AND DEVELOPMENT
Director: Professor D Rowbotham
Assistant Director: John Hampton
Co-ordinator: C Cannaby
Direct Dial: 0116 258 4614
Fax No: 0116 258 4226
EMail: chris.cannaby@uhl-tr.nhs.uk

19 June 2007
Professor Timothy Coats
A&E Dept
LR1
Infirmary Square
LE1 5WW

Dear Professor Coats

ID: 10294
Assessment of cardiac output in septic adult patients using non-invasive Thoracic Electrical Bioimpedance

LREC Ref: 07/Q2501/56

MREC Ref:

Sponsor
UHL NHS Trust

Funder
Departmental funds

Please note that Trust Indemnity ceases on: 19/08/2008

As you are aware all research undertaken within the NHS requires both a favourable ethical opinion from an independent ethics committee, and R&D Approval from each NHS Trust it is taking place within. We have received confirmation that your study has gained a favourable opinion from the local Ethics Committee. All papers submitted have also been reviewed by University Hospitals of Leicester NHS Trust R&D Office and I am pleased to confirm NHS R&D Approval from the Trust, on the following conditions:

- All papers submitted to this office are followed to the letter; should any amendments or changes be required these must be submitted to this office.
- Only researchers detailed on the second page of this letter are to be involved in the study. If this changes, the changes must be submitted to this office as a non-substantial amendment.
- Your study is now covered by NHS Indemnity, as required, and excluding aspects covered by external indemnity, e.g. ABI, University. This indemnity is in place to the above date – the end date you supplied. Should you wish your study to extend past this date you must notify the R&D Office, as not doing so would mean you are no longer covered to conduct your research. One method for this is through Annual Reports, see over page.
- Ongoing Pharmacovigilance and safety reporting is essential in all research studies. Serious Adverse Events (SAE), Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Events (SUSAR) must be reported appropriately and timely. Please ensure you are aware of our SOP on Safety Reporting which is available on the UHL R&D web pages: http://www.uhl-tr.nhs.uk/our-services/research-development
- Your application detailed resources to be used in this study, you must ensure the budget detailed is followed as the Trust will not cover any additional costs associated to this research.
- If honorary research contracts have been issued it is your responsibility to ensure this/these are kept up to date.

Trust Headquarters, Gwendolen House, Gwendolen Road, Leicester, LE5 4QF

220
Reporting Requirements
Within University Hospitals of Leicester we are keen to encourage well structured, good quality
research, to ensure this high standard is achieved and maintained we are keen to make you aware of
national and local reporting requirements:

- Annual & Final Reports on the progress are required each year, or final on completion. These reports
  are needed by both the R&D Office and local Ethics Committee. Templates for these reports are
  available on the R&D & NRES website, and we look forward to the receipt of these on the anniversary
  of your ethics approval, and on the completion of your study.
- Additionally Annual Safety Reports are required for CT-Imp (Clinical Trials of Investigational
  Medicinal Products) studies and should be submitted to the MHRA annually 80 days prior to the
  anniversary of MHRA Approval.

We are aware that undertaking research in the NHS comes with a range of regulatory responsibilities
and have attached to this letter, forming part of your R&D approval, an information sheet to ensure you
are aware of these responsibilities.

The R&D Office is keen to support research, researchers and facilitate approval. If you have any
questions regarding this or other research you wish to undertake in the Trust please feel welcome to
contact this office again. The Trust wishes you success with your research.

Below is a list of the Researchers Approved to work on this Application within UHL

Professor Timothy Coats
Dr Christiane Voelkerk

Yours sincerely

John Hampton
Assistant Director for Research and Development
Appendix 7.  Ethics approval – Study 2

National Research Ethics Service
Nottingham Research Ethics Committee 1
1 Standard Court
Park Row
Nottingham
NG1 5GN

Telephone: 01159123344 Ext: 36368
Facsimile: 01159123300

17 December 2007
Professor Timothy J Coats
Professor of Emergency Medicine
Leicester University
Emergency Department Academic Unit,
Leicester Royal Infirmary
Leicester, LE1 5WW

Dear Professor Coats,

Full title of study:  Assessment of cardio-haemodynamics in adult Emergency Department patients with severe sepsis or septic shock.

REC reference number: 07/H0403/121

Thank you for your letter of 05 December 2007, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application</td>
<td></td>
<td>31 July 2007</td>
</tr>
<tr>
<td>Investigator CV</td>
<td></td>
<td>14 November 2007</td>
</tr>
<tr>
<td>Investigator CV - Chief Investigator</td>
<td></td>
<td>26 June 2007</td>
</tr>
<tr>
<td>Protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary/Synopsis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This Research Ethics Committee is an advisory committee to East Midlands Strategic Health Authority.
R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.


Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

Here you will find links to the following

a) Providing feedback. You are invited to give your view of the service that you have received from the National Research Ethics Service on the application procedure. If you wish to make your views known please use the feedback form available on the website.
b) Progress Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
c) Safety Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
d) Amendments. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
e) End of Study/Project. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nationalres.org.uk.

07/H0403/121 Please quote this number on all correspondence

With the Committee’s best wishes for the success of this project

Yours sincerely

[Signature]

Dr K Pointon / Ms T Wheat
Chair / Coordinator

Email: trish.wheat@nottspcl.nhs.uk

Enclosures: Standard approval conditions
Site approval form

Copy to: R&D office for NHS care organisation at lead site - UHL
Appendix 8. R&D approval – Study 2

University Hospitals of Leicester NHS Trust

DIRECTORATE OF RESEARCH AND DEVELOPMENT
Director: Professor D Rowbotham
Assistant Director: John Hampton
Co-ordinator: C Cannaby
Direct Dial: 0116 258 4614
Fax No: 0116 258 4226
EMail: chris.cannaby@uhl-tr.nhs.uk

22 February 2008
Professor Timothy Coats
A&E Dept
LRI
Infirmary Square
LE1 5WW

Dear Professor Coats

ID: 10407 Assessment of cardio-haemodynamics in adult Emergency Department patients with severe sepsis or septic shock.

Sponsor UHL NHS Trust
Funder Departmental funding

Please note that Trust Indemnity ceases on: 22/11/08

As you are aware all research undertaken within the NHS requires both a favourable ethical opinion from an independent ethics committee, and R&D Approval from each NHS Trust it is taking place within. We have received confirmation that your study has gained a favourable opinion from the local Ethics Committee. All papers submitted have also been reviewed by University Hospitals of Leicester NHS Trust R&D Office and I am pleased to confirm NHS R&D Approval from the Trust, on the following conditions:

- All papers submitted to this office are followed to the letter; should any amendments or changes be required these must be submitted to this office.
- Only researchers detailed on the second page of this letter are to be involved in the study. If this changes, the changes must be submitted to this office as a non-substantial amendment.
- Your study is now covered by NHS Indemnity, as required, and excluding aspects covered by external indemnity, e.g. ABPI, University. This indemnity is in place to the above date – the end date you supplied. Should you wish your study to extend past this date you must notify the R&D Office, as not doing so would mean you are no longer covered to conduct your research. One method for this is through Annual Reports, see over page.
- Ongoing Pharmacovigilance and safety reporting is essential in all research studies. Serious Adverse Events (SAE), Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Events (SUSAR) must be reported appropriately and timely. Please ensure you are aware of our SOP on Safety Reporting which is available on the UHL R&D web pages: http://www.uhl-tr.nhs.uk/our-services/research-development
- Your application detailed resources to be used in this study, you must ensure the budget detailed is followed as the Trust will not cover any additional costs associated to this research.
- If honorary research contracts have been issued it is your responsibility to ensure this/these are kept up to date.

Trust Headquarters, Gwendolen House, Gwendolen Road, Leicester, LE5 4QF

225
Reporting Requirements
Within University Hospitals of Leicester we are keen to encourage well structured, good quality research; to ensure this high standard is achieved and maintained we are keen to make you aware of national and local reporting requirements:

- Annual & Final Reports on the progress are required each year, or final on completion. These reports are needed by both the R&D Office and local Ethics Committee. Templates for these reports are available on the R&D & NRES website, and we look forward to the receipt of these on the anniversary of your ethics approval, and on the completion of your study.
- Additionally Annual Safety Reports are required for CT-IMP (Clinical Trials of Investigational Medicinal Products) studies and should be submitted to the MHRA annually 60 days prior to the anniversary of MHRA Approval.

We are aware that undertaking research in the NHS comes with a range of regulatory responsibilities and have attached to this letter, forming part of your R&D approval, an information sheet to ensure you are aware of these responsibilities.

The R&D Office is keen to support research, researchers and facilitate approval. If you have any questions regarding this or other research you wish to undertake in the Trust please feel welcome to contact this office again. The Trust wishes you success with your research.

Below is a list of the Researchers Approved to work on this Application within UHL
Professor Timothy Coats
Dr Christiane Vonwerk

Yours sincerely

John Hampton
Assistant Director for Research and Development
Appendix 9. Verbal Prompts

Study Title: Assessment of cardio-haemodynamics in adult ED patients with severe sepsis or septic shock.

Name of Researchers: Professor Tim Coats
Dr Chris Vorwerk
Emergency Department, Leicester Royal Infirmary

VERBAL PROMPTS

Septic patients presenting to the Emergency department at the Leicester Royal Infirmary, who meet the inclusion criteria of this research study, but who are too unwell to give informed consent, will have the study explained to them by a member of the research team. If verbal consent is given the monitoring will be commenced and formal consent will be obtained at a later stage. The explanation will be tailored to the individual patient using the following template.

‘Dear [name of patient] we are currently doing a research study in our emergency department looking at how the heart is working in patients who have an infection. This involves the use of a special heart and oxygen monitor and needs me to put on an entire 5 sticky patches (like the ECG test that you have had done). Two patches will be placed on the neck, two on the chest and one on the thumb. This special machine will then measure how the normal treatment which you will receive in the Emergency Department is reducing the extra work your heart is doing. Taking part in this study will not affect your treatment. I will explain things in more detail when you are feeling better, but is okay if I go ahead and record this special type of ECG? ’

The patient will be connected to the special monitor and the measurement will start. However, if it is felt that the additional monitoring may cause any distress to the patient, then the measurement will be stopped. (Previous experience with this technique has reassured us that this has not yet happened.)
Appendix 10. Summary Information Leaflet

SUMMARY INFORMATION LEAFLET (patient)

Study Title:
Assessment of cardio-haemodynamics in adult patients with severe sepsis or septic shock.

Principal Investigator: Prof TJ Coats, Professor of Emergency Medicine

You are invited to take part in a research study, carried out at the Leicester Royal Infirmary to find better ways of treating patients with sepsis, which is a severe illness caused by an infection. Despite advances in Medicine it can be difficult to properly diagnose and treat patients with sepsis. We hope that the use of a special monitoring machine, similar to an ECG machine, will improve the care of patients with sepsis in the future.

You have been chosen to participate in this study, because you are suffering from sepsis. Participation is entirely voluntary and you are free to withdraw from the research at any time. This will have no effect on the standard of care you receive. If you decide to take part in this research study, you will be connected to an additional monitor which will measure what your heart is doing whilst your body is fighting off an infection and whilst you are receiving treatment for it. In order to obtain these measurements we will have to place ECG electrode patches (sticky patches) onto your neck and chest and one onto your thumb. Your normal treatment will continue throughout. In order to assess how the normal treatment, which you receive, is reducing the extra work your heart is doing, we would need monitor you for 24 hours.

There are no known risks using this type of monitoring machine. There are no advantages or disadvantages for you in taking part in this study. However we hope that the information obtained from this study will improve the care and clinical management of patient, suffering from a similar condition to yours, in the future.

Your participation in this study and any data obtained about you will be kept strictly confidential.

Should you decide to participate in this study you will be given a detailed information sheet about this research study. You will also have the opportunity to ask any questions and to discuss any concerns with a member of the research team.

We would like to take this opportunity to thank you for reading this.

Prof Tim Coats  
Professor of Emergency Medicine  
Division of Cardiovascular Science  
Leicester University

Dr Chris Vorwerk  
Research Registrar  
Emergency Department  
Leicester Royal Infirmary

TEBAS 2 Study  Summary Information Leaflet  Version 1.0  dated 22/06/2007
Appendix 11. Patient Information Leaflet (study group)

University Hospitals of Leicester NHS Trust
Emergency Department
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0116 254 6646
Fax: 0116 254 7555

PATIENT INFORMATION LEAFLET

Study Title:
Assessment of cardio-haemodynamics in adult patients with severe sepsis or septic shock.

Principal Investigators: Prof TJ Coats, Professor of Emergency Medicine

You are invited to take part in a research study, carried out at the Leicester Royal Infirmary to find ways to improve the management of septic patients. Before you decide whether to take part, it is important that you understand why the research is being done and what it will involve.

Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you would wish to take part.

What is the purpose of this study?
Each year more than a million people suffer from sepsis, which is a severe illness caused by an infection. Despite advances in medicine it can be difficult to diagnose and to properly treat sepsis. It is important to find better ways of managing patients with sepsis. We hope, that the use of a special monitoring machine, which will give us more information than the routine observation (such as blood pressure, heart rate), will help to improve the care of septic patients in the future.

Why have I been chosen?
You have been chosen, because you are suffering from an infection which caused sepsis.

Do I have to take part?
It is up to you to decide whether or not to take part. If you decide to take part you will be asked to sign a consent form. Participation is entirely voluntary and you are free to withdraw from the research at any time without giving a reason. A decision to withdraw or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?
The study will not affect the normal treatment which you will receive. None of your treatment will be delayed or changed. You will be connected to an additional monitor that will allow us to measure how your heart is working whilst your body is fighting an infection. In order to obtain such measurement we will have to place sensor patches (sticky patches) onto your chest and neck and one onto your thumb. To assess how the normal treatment, which you receive, is reducing the extra work your heart is doing, we would need to monitor you continuously for 24 hours. We will also carry out three 2-minute recordings of your heart using an ultrasound machine, with the ultrasound probe being placed onto your neck.

What do I have to do?
You do not have to do anything different whilst the measurements are conducted.

What are the possible disadvantages and risks of taking part?
There are no known risks using this type of monitoring device. It is possible that the sticky patches may irritate the skin, however this is unlikely. If we become aware that a participant might potentially be harmed because of taking part in this study then the study will be stopped and investigated accordingly.
What are the possible benefits of being in this study?
There are no direct advantages for you in taking part in this study. However, we hope that the information obtained from this study will improve the care and clinical management of patients suffering from a similar condition to yours, in the future.

What if new information becomes available?
The short duration of this research study makes such an event less likely; however, should new information become available, your research doctor will discuss it with you. If you decide to withdraw from the study your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

What if there is a problem?
If you are concerned about any aspect of the study you should ask to speak to the researcher, who will do their best to answer your questions. Please see contact details provided at the end of the information leaflet. If you are harmed as a direct consequence of taking part in this study, you will be covered by Leicester University Hospitals NHS Trust’s indemnity. Compensation arrangements apply to negligent harm only. If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms would be available to you.

What information will you collect about me?
We will need your weight, height, date of birth and blood pressure. We will also need to know whether you suffer from any heart problems and whether you take any medication for your heart.

Will my taking part in the research study be kept confidential?
Yes, all information about you and your participation in this study will be kept strictly confidential. The only people allowed to look at the information are the members of the research team. Data for the research study will be stored securely and will be anonymised.

What will happen to the results of the research study?
We will publish the results of the study in a medical journal, so that other doctors can benefit from the knowledge, but personal information about you will not be included and there will be no way that you could be identified. We will send you a copy if you wish.

Who is organising and funding the research?
The Academic Department of Emergency Medicine, which is part of the Division of Cardiovascular Science, Leicester University.

Who has reviewed this study?
All research that involves NHS patients must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the committee is satisfied that your rights will be respected, that risks have been reduced to an minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

If I have any questions regarding this study or wish to express any concerns, who can I contact?
Dr Chris Vorwerk, Research Registrar, Emergency Department, Leicester Royal Infirmary
Tel: 0116 258 5168  email: chris.vorwerk@uhl-tr.nhs.uk

Prof Tim Coats, Professor of Emergency Medicine, Division of Cardiovascular Science, Leicester University
Tel: 0116 2585168  email: Tim.Coats@uhl-tr.nhs.uk

We would like to take this opportunity to thank you for reading this.

If you decide to participate in this research project you will be given a copy of this information sheet and a signed consent form to keep.
Appendix 12. Consultee Information leaflet

RELATIVE / LEGAL REPRESENTATIVE INFORMATION LEAFLET

Study Title:
Assessment of cardio-haemodynamics in adult patients with severe sepsis or septic shock.

Principal Investigator: Prof TJ Coats, Professor of Emergency Medicine

Your relative is invited to take part in a research study, carried out at the Leicester Royal Infirmary to find ways to improve the management of patients with sepsis. Before you decide for your relative to take part, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you would wish for your relative to take part.

What is the purpose of this study?
Each year more than a million people suffer from Sepsis, which is a severe illness caused by an infection. Sepsis can be difficult to diagnose and to properly treat sepsis. It is important to find better ways of managing patients with sepsis. We hope, that the use of a special monitoring machine, which will give us more information than the routine observation (such as blood pressure, heart rate), will help to improve the care of septic patients in the future.

Why has my relative been chosen?
Your relative has been chosen, because he/she is suffering from sepsis.

Does my relative have to take part?
It is up to you to decide whether or not your relative should take part in the research study. If you decide for your relative to take part you will be asked to sign an ‘assent’ form. Participation is entirely voluntary and your relative is free to withdraw from the research at any time without giving a reason. A decision to withdraw or a decision not to take part, will not affect the care your relative receives.

What will happen to my relative if he/she takes part?
Your relative will be connected to an additional monitor that will allow us to measure how the heart is working whilst the body is fighting off an infection. In order to obtain such measurement we will have to place 4 sensor patches (sticky patches) onto chest and neck and one onto the thumb. To assess how the normal treatment, which your relative receive, is reducing the extra work your heart is doing, we would need to leave the monitor connected for 24 hours. We will also carry out three 2-minute recordings of the heart using an ultrasound machine, with the ultrasound probe being placed onto the neck. The study will not affect in any way the normal treatment which your relative will receive.

What does my relative have to do?
Your relative will not have to do anything different whilst the measurements are conducted.

What are the possible disadvantages and risks of taking part?
There are no known risks using this type of monitoring device. It is possible that the sticky patches may irritate the skin, however this is unlikely. If we become aware that a participant might potentially being harmed because of taking part in this study then the study will be stopped and investigated accordingly.
What are the possible benefits of being in this study?
The there are no direct advantages in taking part in this study. However we hope that the information obtained from this study will improve the care of septic patient in the future.

What if new information becomes available?
The short duration of this research study makes such an event very unlikely, however should new information become available, the research doctor will discuss it with you.

What if there is a problem?
If you are concerned about any aspect of the study you should ask to speak to the researcher, who will do their best to answer your questions. Please see contact details provided at the end of the information leaflet. If your relative is harmed as a direct consequence of taking part in this study, he/she will be covered by Leicester University Hospitals NHS Trust’s indemnity. Compensation arrangements apply to negligent harm only. If you wish to complain, or have any concerns about any aspect of the way you have been approached or the way your relative has been treated during the course of this study, the normal NHS complaints mechanism would be available to you.

What information will you collect about my relative?
We will need his/her weight, height and date of birth. We will also need to know whether your relative suffers from any heart problems and whether he/she takes any medication for heart problems.

Will my relative’s taking part in the research study be kept confidential?
Yes, all information about your relative and his/her participation in this study will be kept strictly confidential. The only people allowed to look at the information are the members of the research team. Data for the research study will be stored securely and will be anonymised.

What will happen when the research is finished?
We will publish the results of the study in a medical journal, so that other doctors can benefit from the knowledge, but personal information about your relative will not be included and there will be no way that your relative could be identified. We will send you a copy if you wish.

Who is organising and funding the research?
The Academic Department of Emergency Medicine, which is part of the Division of Cardiovascular Science, Leicester University.

Who has reviewed this study?
All research that involves NHS patients must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that your relative will not come to any harm if he/she takes part. However approval means that the committee is satisfied that your relative’s rights will be respected, that risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

If I have any questions regarding this study or wish to express any concerns, who can I contact?
Dr Chris Vorwerk, Research Registrar, Emergency Department, Leicester Royal Infirmary
Tel: 0116 258 8168 email: chris.vorwerk@uhl-tr.nhs.uk

Prof Tim Coats, Professor of Emergency Medicine, Division of Cardiovascular Science, Leicester University
Tel: 0116 2585168 email: Tim.coats@uhl-tr.nhs.uk

We would like to take this opportunity to thank you for considering your relative’s participation in this study.

If you decide to participate in this research project you will be given a copy of this information sheet and a signed consent form to keep.
Appendix 13. Patient Information Leaflet (control group)

University Hospitals of Leicester

NHS Trust

Emergency Department
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0116 258 5844
Fax: 0116 204 7935

PATIENT INFORMATION LEAFLET
(CONTROL GROUP)

Study Title:
Assessment of cardio-haemodynamics in adult patients with severe sepsis or septic shock.

Principal Investigator: Professor TJ Coats, Professor of Emergency Medicine

You are invited to take part in a research study, carried out at the Leicester Royal Infirmary to find ways to improve the management of septic patients. Before you decide whether to take part, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you would wish to take part.

What is the purpose of this study?
Each year more than a million people suffer from sepsis, which is a severe illness caused by an infection. Despite advances in medicine it can be difficult to diagnose and to properly treat sepsis. It is important to find better ways of managing patients with sepsis. We hope, that the use of a special monitoring machine, which will give us more information than the routine observation (such as blood pressure, heart rate), will help to improve the care of septic patients in the future.

Why have I been chosen?
In order to assess what the heart is doing during sepsis, we will need to obtain measurements about the heart from patients who are not seriously ill. You have been chosen, because you do not suffer from an infection/sepsis and your age and gender matches one of the septic patients in the research study.

Do I have to take part?
It is up to you to decide whether or not to take part. If you decide to take part you will be asked to sign a consent form. Participation is entirely voluntary and you are free to withdraw from the research at any time without giving a reason.

What will happen to me if I take part?
Taking part in the study will have no impact on the treatment you receive in the Emergency Department. You will be connected to a special monitor that will allow us to measure how your heart is working. In order to obtain such measurement we will have to place ECG electrodes (sticky patches) onto your chest and neck. After the 10 minutes recording your participation in this study will end.

What do I have to do?
During the measurement, which will take about 10 minutes, we would like you to sit still and talk as little as possible.

What are the possible disadvantages and risks of taking part?
There are no known risks using this type of monitoring device. It is possible that the ECG electrodes may irritate the skin, however this is unlikely. If we become aware that a participant might potentially be harmed because of taking part in this study then the study will be stopped and investigated accordingly.

TEBAS 2 Study Patient Information Leaflet (CG) Version 1.0 dated 22/06/2007
What are the possible benefits of being in this study?
There are no benefits for you in taking part in this study. However we hope that the information obtained from this study will improve the care and clinical management of patient suffering from sepsis in the future.

What if there is a problem?
If you are concerned about any aspect of the study you should ask to speak to the researcher, who will do their best to answer your questions. Please see contact details provided at the end of the information leaflet. If you are harmed as a direct consequence of taking part in this study, you will be covered by Leicester University Hospitals NHS Trust's indemnity. Compensation arrangements apply to negligent harm only. If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms would be available to you.

What information will you collect about me?
We will need your weight, height, date of birth and blood pressure. We will also need to know whether you suffer from any heart problems and whether you take any medication for your heart. Measured data on how your heart is working will be kept and used to form a reference database for future projects.

Will my taking part in the research study be kept confidential?
Yes, all information about you and your participation in this study will be kept strictly confidential. The only people allowed to look at the information are the members of the research team. Data for the research study will be stored securely and will be anonymised.

What will happen to the results of the research study?
We will publish the results of the study in a medical journal, so that other doctors can benefit from the knowledge, but personal information about you will not be included and there will be no way that you could be identified. We will send you a copy if you wish.

Who is organising and funding the research?
The Academic Department of Emergency Medicine, which is part of the Division of Cardiovascular Science, Leicester University.

Who has reviewed this study?
All research that involves NHS patients must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However approval means that the committee is satisfied that your rights will be respected, that risks have been reduced to an minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

If I have any questions regarding this study or wish to express any concerns, who can I contact?
Dr Chris Vorwerk, Research Registrar, Emergency Department, Leicester Royal Infirmary
Tel: 0116 256 5108 email: chris.vorwerk@uhl-tr.nhs.uk

Prof Tim Coats, Professor of Emergency Medicine, Division of Cardiovascular Science, Leicester University
Tel: 0116 2585168 email: Tim.Coats@uhl-tr.nhs.uk

We would like to take this opportunity to thank you for reading this.

If you decide to participate in this research project you will be given a copy of this information sheet and a signed consent form to keep.
Appendix 14. Consent Form – Study 2

University Hospitals of Leicester NHS Trust

Emergency Department
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0116 255 5168
Fax: 0116 204 7335

Centre number:
Patient Identification Number for this trial:
Study Number:

CONSENT FORM
(Study Group)

Study Title: Assessment of cardio-haemodynamics in adult ED patients with severe sepsis or septic shock.

Name of Researchers: Professor Tim Coats
Dr Chris vonwerk
Emergency Department, Leicester Royal Infirmary

Please Initial box

1. I confirm that I have read and understand the information sheet dated 22nd June 2007, (Version 1.0) for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the research team or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

4. I agree to take part in the above study.

Name of Patient ___________________________ Date ____________ Signature ___________________________

Name of Person taking consent (if different from researcher) ___________________________ Date ____________ Signature ___________________________

Researcher ___________________________ Date ____________ Signature ___________________________

3 copies required: one copy for patient; one for researcher; one to be kept with hospital notes

TEBAS 2 Study Patient Consent Form (SG) Version 1.0 dated 22/06/2007
Appendix15. MD related / derived publications /presentations

Publications


Abstracts

Vorwerk C, Coats T. Predictive value of tissue oxygen saturation upon mortality in Emergency Department patients with sepsis. Crit Care Med 2011; (accepted for publication)


Oral presentations

Vorwerk C. Normalisation of tissue oxygen saturation in ED patients with severe sepsis or septic shock is related to mortality. CEM conference, Roderick Little Prize Session, London Sept 2009.

Due to third party copyright restrictions the published articles have been removed from the appendix of the electronic version of this thesis. The unabridged version can be consulted, on request, at the University of Leicester’s David Wilson Library.