THE HAEMODYNAMICS OF RATE
ADAPTIVE PACING: USE OF AN
AMBULATORY NUCLEAR MONITOR

A DISSERTATION FOR THE DEGREE OF DOCTOR OF MEDICINE,
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ABSTRACT

This thesis evaluates the optimal pacing haemodynamics during rate adaptive pacing using an ambulatory nuclear monitor (Capintec VEST). Comparisons of different pacing modes were performed:

i) VVI with DDD.

ii) DDD with optimal AV delay at rest with VVIR.

iii) DDD with optimal AV delay with DDD with a short AV delay in patients with normal and impaired left ventricles.

iv) DDD with DDDR in chronotropically incompetent and competent patients.

Relative cardiac output was measured and significant variation was assessed by statistical methods. The optimal pacing rate for constant exercise was studied for VVIR pacing and an algorithm to produce optimal haemodynamics was investigated.

DDD pacing was found to be superior to VVI during activities of daily living. However, no advantage was detected between DDD over VVIR pacing during exercise, except in patients with impaired left ventricles.

An optimal rate band was defined and shown to increase non-linearly with increasing workload. No correlation was found between the mean of this band and predicted peak heart rate. It was therefore not possible to predict this mean rate by straightforward means.

A new parameter 'Total Active Time' (TAT) was defined, as the time from the beginning of cardiac contraction to the end of the filling phase. TAT was calculated from the optimal rate data. This was transformed into a heart rate and plotted against the paced rate. The intersection was defined as the Haemodynamic Maximum Sensor Rate (HMSR) and this rate was shown to lie within the optimal rate band.

In conclusion, the optimal pacing rate is an individual parameter and not age related. It is proposed that the HMSR can be used to dynamically limit the upper rate in order to automatically optimise pacing haemodynamics. This method is considered superior to the development of dual sensor devices.
ACKNOWLEDGEMENTS

The original work described in this thesis was performed during my appointment as Research Fellow at Groby Road Hospital (March 1992 - January 1994) and Glenfield Hospital (February 1994 - December 1994). I was the primary investigator in all parts of the study, although it could not have been performed without assistance. I am grateful to Hazel Williams, Medical Physics Technician, who operated the Gamma Camera and Staff Nurse Anne Shepherd who supervised the injections of technetium. In addition, I am grateful for the help of the Physiological Measurement Technicians particularly Karen Tindall who supervised the blind pacemaker programming. Dr Clifford J Garratt (Senior Lecturer, Glenfield Hospital) who has provided invaluable help with the writing of this thesis. Professor David de Bono who provided the finishing touches. Dr Douglas Skehan (Consultant Cardiologist, Glenfield Hospital, supervisor) who had the foresight to realise the potential of the Vest for studying pacemaker haemodynamics and who provided the most valuable help with study design and data interpretation. In addition, I am grateful to Cardiac Pacemakers Incorporated who provided the financial support for much of the study. Particularly Julio Spinelli who first stimulated my interest in the "optimal rate" and whose theory of "Total Active Time" has come to life within this thesis.

Last but by no means least I have to thank Dr Richard Edwards who spent many hours over a pint or two of lager, reading this thesis and checking its grammatical and scientific content. Without whose continual prompting and support this thesis probably would not exist.
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LIST OF ABBREVIATIONS

AAI  Fixed rate atrial pacing.
ATHR Active Time Heart Rate.
AV  Atrio-Ventricular
bpm Beats per minute
CO  Cardiac Output.
DDD Dual chamber sensing and pacing.
DDDR Dual chamber rate responsive pacing.
EDV/M End Diastolic Volume per Minute.
ESV End Systolic Volume
HMSR Haemodynamic Maximum Sensor Rate
HR Heart rate
LV Left Ventricle
SV Stroke Volume
TAT Total Active Time.
VDD Ventricular pacing dual chamber sensing.
VVI Fixed rate ventricular pacing.
VVIR Single chamber rate responsive ventricular pacing.
CHAPTER 1: INTRODUCTION AND OVERALL AIMS OF THE THESIS

1.1 INTRODUCTION

In the 1950s, the aim of pacemaker implantation was to improve prognosis in patients with severe bradycardias. More recently, there has been greater emphasis on pacemaker implantation for improvement in symptoms and quality of life, both at rest and on exercise. New pacing modes allow sophisticated adaptive responses to exercise but these advances have yet to be matched by demonstration of their relative benefits. To prescribe or program a pacemaker correctly it becomes increasingly necessary to have a detailed understanding of pacemaker effects on haemodynamics. Haemodynamics as studied in this thesis are assessed non invasively using the Capintec Vest which provides data on relative ejection fraction and cardiac output. This is a compromise as invasive techniques inhibit full evaluation of pacemaker patients during the activities of daily living. This chapter begins with a consideration of haemodynamics on exercise and a discussion of our current understanding of paced haemodynamics during the various pacing modes.

1.2 NOMENCLATURE

A standard method of naming modes of pacing has been devised where the first letter refers to the chamber paced (A = atria, V = ventricles, D = both) the second to the chamber sensed (A = atria, V = ventricles, D = both) and the third what happens when sensing occurs (I = Inhibition, T = Triggers, D = both). In addition the fourth letter (R) refers to the presence of rate adaption and the fifth to antitachycardia features. A summary of the common pacing modes is outlined in table 1.1.
Table 1:1 Explanation of the various pacing modes.

<table>
<thead>
<tr>
<th>Mode</th>
<th>Explanation</th>
<th>Current List Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>VVI/AAI</td>
<td>FIXED RATE VENTRICULAR / ATRIAL PACING</td>
<td>£1,350</td>
</tr>
<tr>
<td></td>
<td>Inhibition of pacing with higher spontaneous rates</td>
<td></td>
</tr>
<tr>
<td>AAIR/VVIR</td>
<td>SINGLE CHAMBER PACEMAKERS WITH SENSORS</td>
<td>£2,090</td>
</tr>
<tr>
<td></td>
<td>Pacing rate increases with exercise</td>
<td></td>
</tr>
<tr>
<td>DDD</td>
<td>DUAL CHAMBER SENSING AND PACING</td>
<td>£2,300</td>
</tr>
<tr>
<td></td>
<td>Atrial sensing or pacing with ventricular tracking.</td>
<td></td>
</tr>
<tr>
<td>VDD</td>
<td>VENTRICULAR PACING, DUAL CHAMBER SENSING NO ATRIAL PACING</td>
<td>£2,300</td>
</tr>
<tr>
<td></td>
<td>Specialised electrode with &quot;floating&quot; atrial sensor.</td>
<td></td>
</tr>
<tr>
<td>DDR</td>
<td>RATE RESPONSIVE DUAL CHAMBER PACING</td>
<td>£3,000</td>
</tr>
<tr>
<td></td>
<td>If sinus rate responses poor</td>
<td></td>
</tr>
</tbody>
</table>
1.3 RESPONSE TO EXERCISE

Before evaluating paced haemodynamics, it is first necessary to consider the normal cardiac responses to exercise. The mechanisms utilised to increase cardiac output during dynamic exercise vary, depending on the age, condition, posture and athletic training of the individual.

Cardiac output increases rapidly at the onset of exercise, then follows a slow exponential increase with half-time of 10 to 45 seconds, depending on the work intensity (Loeppky et al, 1981; Miyamoto, 1981). Thereafter, the increase in cardiac output is proportional to the increase in workload and oxygen consumption, at least within the limit of aerobic threshold (Loeppky et al, 1981; Miyamoto, 1981). At the termination of upright exercise there is a delay of 5 to 10 seconds before the fall in cardiac output and then an exponential fall with a half time of 25 to 60 seconds, (Miyamoto, 1981; Lau et al, 1990a).

In the upright position, at lower levels of exercise, the increase in cardiac output is accomplished both by an increase in stroke volume and heart rate (Chapman et al, 1960; Wang et al, 1960). However, at greater work loads the increase in stroke volume levels off (or only increases slightly) and the need for an increment in cardiac output is provided mainly by an increase in heart rate (Astrand et al, 1964; Epstein et al, 1967). Close to maximum exercise the heart rate increase is slowed until the maximal heart rate is approached asymptotically (Davis, 1968).
The physiological mechanisms involved in heart rate response to exercise are complex, but for the most part are mediated via the autonomic nervous system. During exercise there is an increase in sympathetic nervous activity in proportion to the intensity of the exercise and a decrease in the parasympathetic efferent stimuli to the heart (Robinson et al, 1966). The systolic blood pressure usually increases by 50-60 mmHg during moderately severe exercise, although the mean increases much less. The diastolic blood pressure may increase slightly, stay the same or decrease. Mechanical factors such as increased venous return to the atria (Bainbridge reflex) may also play a role (Folkow, 1971).

Physical training is associated with a lower heart rate at rest and a decreased rate of change in heart rate as exercise increases. The trained subject develops myocardial hypertrophy and an increased end-diastolic ventricular volume (Morganroth et al, 1975). Both of these provide the myocardial reserve that enables the trained subject to maintain a normal cardiac output in the presence of bradycardia. At any given work load the trained subject will therefore have lower heart rate than his untrained counterpart (Astrand et al, 1964). In severe exercise in both untrained and trained groups it is possible for an increase of between 30-100 % in stroke volume to be achieved despite considerable shortening in the systolic ejection period.

1.4 FIXED RATE VENTRICULAR PACING (VVI)

The first pacing systems developed were VVI pacemakers and today worldwide they are the commonest system implanted. This is related to their simplicity in terms of
implantation and follow up. The disadvantages of VVI pacing relate to its failure to provide a chronotropic response and thus a requirement for a single rate for both exercise and rest. Several haemodynamic studies have been performed to determine this optimal single rate (Sowton, 1964; Benchimol et al, 1965a) which concluded that rates of 70-90 bpm produced the maximal increase in cardiac output both at rest and on exercise.

During exercise increases in cardiac output with VVI pacing result from an increased stroke volume (Ausbel et al, 1985a). This occurs rapidly in patients with normal ventricular function (Koyama et al, 1976) and is brought about by two factors. Firstly, there is an increased venous return on exercise which causes an increase in ventricular filling pressure and end diastolic volume to augment cardiac output by the Frank-Starling mechanism (Baig et al, 1991). Secondly, and quantitatively more important, is the neurohumoral response to exercise, dominated by the activation of the sympathetic nervous system to cause increased ventricular contractility and a smaller end systolic volume. This can bring about a mean increase in cardiac output in patients with complete heart block of between 34% (Eimer et al, 1974) to 260% (Bevecgard et al, 1967) the wide range being accounted for by differences in ventricular function. When compared with the fivefold increase seen in normal subjects on maximal exercise (Epstein et al, 1967), it can be seen that VVI pacing imposes significant limitations on the cardiovascular reserve. An additional problem with VVI pacing is the potential for developing "pacemaker syndrome".
1.5 PACEMAKER SYNDROME

Pacemaker syndrome is a poorly defined condition which produces a constellation of symptoms, many of which are common in an elderly population. These symptoms vary from severe hypotension, syncope and overt congestive cardiac failure to intermittent and relatively mild symptoms e.g. dizziness, memory impairment and poor concentration. That may not even be appreciated as a problem to the patient if there is no basis for comparison.

1.5.1 Mechanisms

Mechanisms that have been implicated in the aetiology of pacemaker syndrome include loss of atrioventricular synchrony and inappropriate circulatory reflexes (Alicandri et al, 1978). Atrioventricular asynchrony leads to atrial contraction against closed valves may produce palpable cannon waves and cause elevations in right atrial, pulmonary artery, pulmonary capillary wedge and left ventricular end-diastolic pressures (Mitchell et al, 1962; Samet et al, 1968; Greenberg et al, 1979). Cases of pulmonary venous regurgitation and valvular regurgitation due to asynchronous atrial contractions have also been reported (Naito et al, 1983).

The circulatory reflexes involved have been shown to inhibit vasoconstriction during ventricular pacing. This could be mediated via inappropriate release of atrial natriuretic peptide, which is both a vasodilator and a diuretic (Stangl et al, 1988). Several studies have documented increases in this hormone when AV synchrony is lost (Ellenbogen et
Pacemaker syndrome is almost entirely limited to VVI and VVIR pacemakers, although it has been described in patients with DDI systems, (Cunningham, 1988) and AAIR systems (Clarke, 1987), where asynchronous pacing has occurred due to incorrect programming. Inadequate increase in heart rate during activity may be a factor in other patients with fixed rate VVI pacemakers (Ausubel et al, 1985a).

1.5.2 Incidence

The non specific nature of the symptoms of pacemaker syndrome and their high prevalence amongst the elderly, who form the majority of the paced population, all mean its precise incidence is unknown. In addition, it may occur immediately after implantation or any time post implant (Ausbel et al, 1985b). Its incidence is thought to be between 7-25 % of the VVI paced population. A recent study (Sulke et al, 1992) has suggested a subclinical form of the syndrome exists in up to 64% of VVI patients.

1.5.3 Treatment

Pacemaker syndrome is usually alleviated by upgrading to a DDD system although no controlled trials have been performed. Retrospective data (Santini et al, 1990) surprisingly suggests upgrading is only necessary in 1-2 % of patients. This low number probably relates to the clinicians' lack of enthusiasm in searching for the symptoms.
1.5.4 Risk factors

As the incidence of pacemaker syndrome is by no means universal. Studies have investigated patient characteristics distinguishing patients at low risk from those at high risk of developing the syndrome. Retrograde conduction occurs in almost 40% of pacemaker recipients (Hayes et al, 1983; Klementowicz et al, 1986) and its presence is a major determinant of the risk of developing the syndrome (Nishimura et al, 1982). However, retrograde conduction is variable in its presence and cannot be consistently demonstrated. Another sign is a large left atrium as, presumably, retrograde flow is increased in these patients. No rigorous selection criteria have emerged although avoidance of VVI pacing in patients with overt retrograde VA conduction seems appropriate.

1.6 COMPARISONS OF DUAL CHAMBER (DDD) AND FIXED RATE VENTRICULAR PACING (VVI)

DDD devices permit the restoration of atrioventricular (AV) synchrony which allows a prompt physiological increase in heart rate in response to physiological stress. Even though the haemodynamic advantages of AV synchrony were appreciated before the advent of DDD pacing, (Folkman et al, 1958; Nathan et al, 1964) controversy still continues today about which pacing mode should be implanted with editorials suggesting VVI pacing is outmoded (Nathan et al, 1992) on one hand and "who needs dual chamber pacing ?" expressed by others (Petch, 1993). The British Pacing and Electrophysiology Group has produced guidelines advocating atrial pacing for all (Clarke et al, 1991).
However the cost implications of following these guidelines are considerable, amounting to a 75% increase in budget (de Belder et al, 1992; Ray et al, 1992).

Many comparisons of VVI pacing against AV synchronous pacing at rest have been performed, using both invasive and non invasive methods (see table 1.2). These suggest that the restoration of AV synchrony can bring about a 4-43 % improvement in cardiac output at rest. This improvement has been attributed to better ventricular filling because of the atrial contraction at the end of diastole and avoidance of mitral and pulmonary venous regurgitation, (Nolan et al, 1969; Ruskin et al, 1970; Reiter et al, 1982; Kosowsky et al, 1968; Naito et al, 1983). This benefit is especially important in those patients with poor left ventricular function (Reiter et al, 1982; Mitchell et al, 1965).

Several studies using a randomised cross-over design have been undertaken to compare VVI with DDD during exercise (see table 1.3). However, the assessments have mostly been in terms of exercise tolerance rather than quantitative increases in cardiac outputs. Almost all of these demonstrated a significant improvement in exercise capability with DDD over VVI pacing.
### TABLE 1:2 Summary of haemodynamic studies comparing VVI and DDD pacing at rest.

<table>
<thead>
<tr>
<th>Author</th>
<th>Haemodynamic Method</th>
<th>REST CO VVI L/Min</th>
<th>REST CO DDD L/Min</th>
<th>% better</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stewart et al, 1984</td>
<td>Echodoppler (n=29)</td>
<td>4.3±0.3</td>
<td>5.0±0.3</td>
<td>16</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Rediker et al, 1988</td>
<td>Echodoppler (n=19)</td>
<td>4.4±2.2</td>
<td>6.3±2.6</td>
<td>43</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Menozzi et al, 1990</td>
<td>Echodoppler (n=14)</td>
<td>4.7±1.4</td>
<td>5.7±1.6</td>
<td>17</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Jutzy et al, 1990</td>
<td>Echodoppler (n=14)</td>
<td>3.19</td>
<td>4.83</td>
<td>34</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Suike et al, 1991</td>
<td>Echodoppler (n=22)</td>
<td>3.6±0.7</td>
<td>4.4±1.0</td>
<td>22.5</td>
<td>P&lt;0.006</td>
</tr>
<tr>
<td>Procter et al, 1991</td>
<td>Echodoppler (n=20)</td>
<td>4.49±0.3</td>
<td>4.68±0.3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Lascault et al, 1992</td>
<td>Echodoppler (n=12)</td>
<td>6</td>
<td>6.58</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Fananapazir et al, 1983a</td>
<td>Thermodilution (n=14)</td>
<td>3.7±0.8</td>
<td>4.5±1.2</td>
<td>22</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Kristensson et al, 1985a</td>
<td>Dye-dilution (n=10)</td>
<td>4.5±1.0</td>
<td>5.0±1.0</td>
<td>11</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Otsuji et al, 1992</td>
<td>Thermodilution (n=40)</td>
<td>3.9±0.9</td>
<td>4.6±1.0</td>
<td>18</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>L-Edelstam et al, 1992a</td>
<td>Thermodilution (n=16)</td>
<td>4.2±1.2</td>
<td>4.7±1.4</td>
<td>12</td>
<td>P&lt;0.04</td>
</tr>
<tr>
<td>Nitsch et al, 1984</td>
<td>Radionuclide (n=55)</td>
<td>4.86±1.5</td>
<td>5.12±1.4</td>
<td>5</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Ausubel et al, 1985b</td>
<td>Radionuclide (n=17)</td>
<td>4.51±0.7</td>
<td>4.47±0.7</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>McMeechin et al, 1990</td>
<td>Radionuclide (n=10)</td>
<td>4.1±1.1</td>
<td>5.7±1.1</td>
<td>39</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Rosenqvist et al, 1991</td>
<td>Radionuclide (n=12)</td>
<td>5.3±1.0</td>
<td>5.6±1.0</td>
<td>6</td>
<td>P&lt;0.08</td>
</tr>
</tbody>
</table>
Table 1.3 Summary of comparative studies of VVI and DDD pacing on exercise.

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>PARAMETER Description (Study size)</th>
<th>Peak Ex VVI</th>
<th>Peak Ex DDD</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kruse et al, 1981</td>
<td>Maximum Work Load (n=16)</td>
<td>94±26 Watts</td>
<td>113±33 Watts</td>
<td>20 P&lt;0.001</td>
</tr>
<tr>
<td>Kruse et al, 1982</td>
<td>Maximum Work load (n=16)</td>
<td>88±22 Watts</td>
<td>109±32 Watts</td>
<td>24 P&lt;0.001</td>
</tr>
<tr>
<td>Fananapazir et al, 1983a</td>
<td>Distance walked (n=14)</td>
<td>436±128 Metres</td>
<td>610±152 Metres</td>
<td>40 P&lt;0.001</td>
</tr>
<tr>
<td>Perrins et al, 1983</td>
<td>Distance walked (n=13)</td>
<td>2542±1269 kpm</td>
<td>3250±1676 kpm</td>
<td>27 P&lt;0.01</td>
</tr>
<tr>
<td>Rediker et al, 1988</td>
<td>Exercise Tolerance (n=19)</td>
<td>10.1±3.7 Mins</td>
<td>11.3±3.7 Mins</td>
<td>12 P&lt;0.006</td>
</tr>
<tr>
<td>Haskell et al, 1989</td>
<td>VO2 Anaerobic Threshold (n=7)</td>
<td>11.4±3.9 mL/Kg/Min</td>
<td>13.0±5.1 mL/Kg/Min</td>
<td>14 P&lt;0.025</td>
</tr>
<tr>
<td>Theodorakis et al, 1990</td>
<td>Exercise Tolerance (n=9)</td>
<td>10.8±4.2 Mins</td>
<td>14.0±4.0 Mins</td>
<td>30 P&lt;0.06</td>
</tr>
<tr>
<td>McMickin et al, 1990</td>
<td>CO Radionuclide (n=10)</td>
<td>6.30±1.09 L/min</td>
<td>7.6±1.9 L/min</td>
<td>21 NS</td>
</tr>
</tbody>
</table>

Comparisons of VVI and DDD pacing on exercise CO = cardiac output, NS = non significant
1.6.1 Prevention of Atrial Fibrillation

Several studies, although retrospective and non randomised, suggest DDD pacing can prevent atrial fibrillation, stroke, heart failure and reduce deaths (Alpert et al, 1987; Hesselson et al, 1992; Santini et al, 1990; Rosenqvist et al, 1988). However, the VVI patients in these studies were older with significantly more cardiovascular disease. Atrial fibrillation is a well known risk factor for stroke (Cairns et al, 1991) leading to an annual risk of stroke of 4-8% which can be reduced to 2-3% with anticoagulation. Pacemaker patients often do not receive anticoagulation because of their age and conduction abnormalities make the diagnosis of atrial fibrillation more difficult.

1.6.2 Prevention of Heart Failure

DDD pacing may also prevent heart failure. The initial compensating mechanism of the failing heart is increased sarcomere length, which optimises the (Frank-Starling) relationship between end-diastolic volume and contractile force. When this mechanism fails to provide adequate cardiac output, myocardial hypertrophy occurs, which leads ultimately to reduction in contractility of the individual cell (Pinsky et al, 1979). Physiologic pacing results in synchronised atrial contractions which augment left ventricular filling by up to 15% and which optimises the sarcomere length. It is hypothesised that by operating on a more favourable part of the Frank Starling curve, the stimulus for cardiac hypertrophy is lessened and its deleterious consequences on contractility may be reduced. Asynchronous pacing on the other hand results in reduced ventricular filling both directly and indirectly by causing atrial fibrillation which abolishes
the atrial contribution to ventricular filling.

In addition, circulating concentrations of atrial natriuretic peptide are abnormally elevated in patients with VVI pacing compared to dual chamber pacing (Stangl et al, 1988). These vasoactive substances have been associated with a poor prognosis in patients with congestive cardiac failure (Gottlieb et al, 1989; Lemke et al, 1992a).

1.6.3 Problems with Dual Chamber Pacing

Despite the haemodynamic advantages of DDD pacemakers, single chamber pacemakers remain the most widely implanted system. This is because they are easier and cheaper to implant than DDD pacemakers and they avoid the problems of atrial lead displacement, atrial malsensing and crosstalk. There is disparity in the literature regarding the additional complexity of a DDD implant over a single chamber one. With some centres reporting complication rates for DDD pacing of 8.7% compared with 2.9% for VVI (Chauhan et al, 1994) whereas others have reported similar complication rates for the two pacing modes (5% versus 4% for VVI implants)(Aggarwal et al, 1995). However, there is no doubt that atrial leads do displace more frequently than ventricular ones (Chauhan et al, 1994: Aggarwal et al, 1995).

DDD pacemakers are also harder to program than their VVI counterparts (Heinz et al, 1990) with problems which could not be corrected by reprogramming, due to poor atrial signals (Byrd et al, 1988). It is well known that atrial sensing can be lost on exertion even in the presence of what appears to be an adequate sensing threshold at rest (Bricker

1.7 VENTRICULAR RATE RESPONSIVE PACING (VVIR)

In the past ten years rate responsive pacemakers have become widely available (Benditt et al, 1987a; Lau, 1992). This allows even a VVI pacemaker to increase and decrease heart rate in response to physiologic demand. The response of a VVIR pacemaker is dictated by the implanted sensor incorporated in the pacing system, with the ultimate aim being to simulate physiological rate changes not only on exertion but also in response to other metabolic changes e.g. fever, mental stress and sleep.

By design, all sensors react to changes induced by exercise, although they may differ in terms of the speed and proportionality of the rate response to the external workloads. Other relevant characteristic include the sensitivity to detect non exercise related stimuli on one hand, but specific enough not to be falsely started by non physiological changes. There are two components of any rate responsive system, the sensor to detect the physiological change and the algorithm to respond to this change with an appropriate rate response. As the amount of physiological change varies from patient to patient it is often necessary to reprogram the rate responsive slope or algorithm to suit each individual to achieve the optimal rate response.

Sensors can be divided into two main types, activity and metabolic. The sensors which have found the widest application are those which can be used with standard leads, as specialist leads for some metabolic sensors have been unreliable.
1.7.1 Activity sensors

There are two main types: piezoelectric crystals which detect vibration and accelerometers which as the name suggest detect acceleration. The accelerometer has some advantages over the piezoelectric sensor (Lau et al, 1988a), as the piezoelectric crystal is limited to the detection of vibrations between 10-50 Hz because of problems with interference. The dominant frequencies during walking are under 4 Hz band and it is possible to detect these using an accelerometer while reducing the influence of unwanted external vibrations (Alt et al, 1992; Lau et al, 1988a). The accelerometer has been shown to be clinically superior to conventional vibration activity pacemakers (Alt et al, 1989; Müllerhagen et al, 1991; Bacharach et al, 1992). The main advantage of the piezoelectric crystal over the accelerometer is that the crystal requires no additional energy to run the sensor. Both these activity sensors give a prompt response to isotonic exercise.

A disadvantage of both sensors is that the response is to activity and not metabolic demand (Lau et al, 1988b), therefore on prolonged constant exercise there will be no further increase in heart rate. Paradoxically, if the work rate drops due to fatigue, there will be a drop in paced rate (Lau et al, 1988b). After exercise, activity sensing will reduce dramatically and the pacemaker rate decreases in response to a preprogrammed curve rather than the metabolic debt. Activity sensors do not respond well to isometric exercise or exercise involving little upper body movement eg cycling (Lau et al, 1988b). Thus, both devices will tend to under-respond to staircase ascent while over responding to the subsequent descent (Lau et al, 1988b). In addition, the piezoelectric devices tend
to respond to environmental vibrations such as those found when driving a car (Stangl et al, 1986; Toff et al, 1987) and they also respond to direct pressure and it is possible to get a tachycardia if the patient lies on their generator (Wilkoff et al, 1987).

1.7.2 Metabolic Sensors,

There are two main types developed: QT sensors which detect shortening in the paced QT interval and those which respond to changes in respiratory rate or minute ventilation. These sensors respond very well to prolonged isometric and isotonic exercise. However, as metabolic changes are not instantaneous their responses are often slow, up to 30-45 seconds in the minute ventilation devices (Lau et al, 1988c; Lau et al, 1989a). Although this has been improved with more recent devices.

1.7.2.1 Respiratory sensors

Minute ventilation is theoretically better correlated with heart rate and oxygen consumption than respiratory rate (Wasserman et al, 1973; Cummin et al, 1986; Alt et al, 1987; Vai et al, 1988). However, both are detected using impedance sensing which is affected by electrode motion artifacts (Webb et al, 1988). This is inversely related to the number of electrode pairs used in sensing (Sahakian et al, 1985). As respiratory rate sensing uses a bipolar electrode and minute ventilation a tripolar system, the respiratory sensor is more susceptible to electrode motion, which is normally produced by arm swinging. This gives a higher sensitivity to detect body movement and enhances rate response (Webb et al, 1988) and reduces the effects of phonation on the rate response which has been shown to reduce the rate response of the minute ventilation sensor (Lau
In addition to having a slow onset to their rate response, minute ventilation sensors often reach the peak response earlier during exercise (Kay et al, 1989) than the sinus rate and often the rate can remain elevated for up to 2 minutes after the cessation of exercise (Mond et al, 1988). An inappropriate tachycardia has been reported during Cheyne-Stokes respiration (Scanu et al, 1989).

1.7.2.2 QT Sensor

The QT interval shortens during exercise and mental stress (Rickards et al, 1981). Half of this change is brought about by increasing heart rate and the rest by the catecholamine direct effect on myocardial recovery and repolarization (Rickards et al, 1979; Fananapazir et al, 1983b). Thus the QT sensor will respond to non exercise increase in catecholamines. However, it is also influenced by drugs, myocardial ischaemia and electrolyte changes which effect the heart rate (Fananapazir et al, 1985b). There have also been problems with T wave malsensing (Fananapazir et al, 1985b), failure of the QT interval to shorten on exercise (Fyfe et al, 1986) and spontaneous rate accelerations at rest, possibly due to positive feedback loop (Winter et al, 1985).

1.7.3 Sensor Combination

From the above it can be seen that most sensors are still imperfect and no sensor responds optimally under all circumstances. Thus the idea of sensor combinations evolved in order to make the rate response more physiological and reduce inappropriate
rate responses by sensor cross checking. The best proposed combination is an activity sensor in conjunction with any of the slower but more physiologic metabolic ones. At least as important as sensor selection is the algorithm translating the information from the sensors into a rate response such that the optimal rate is determined for every situation.

The main disadvantages of combination sensors are their increased complexity and additional battery drain. Also there is a risk that if not weighted correctly, disadvantages of both sensors will predominate. Although these sensors produce a "cosmetically" better rate response, it has been hard to demonstrate the potential benefits of the sensor combination. This is because the quality of life of the usual pacemaker recipients is quite close to age matched normal individuals (Lau et al, 1989c) and the overall improvement in symptoms brought about by the sensor combination is probably small.

1.8 VENTRICULAR RATE RESPONSIVE PACING COMPARED WITH FIXED RATE VENTRICULAR PACING

The addition of a rate response overcomes one of the theoretical disadvantages of VVI pacing, that is the increase in heart rate with exercise. Several studies have demonstrated a significant rate response on exercise, improving both maximal oxygen consumption and anaerobic threshold and a general sense of well being (Beyersdorf et al, 1980; Humen et al, 1985; Lindemans et al, 1986; Benditt et al, 1987b). This improvement has been quantified by haemodynamic studies, which have shown that there is between 19-57% improvement in exercise capacity (Smedgard et al, 1987; Donaldson et al, 1983) and a 45% improvement in cardiac output at peak exercise (Donaldson et al, 1983).
figures are comparable to the improvements demonstrated with dual chamber pacing and was not related to age (Lau et al, 1988d).

1.9 ATRIAL SYSTOLIC FUNCTION

The benefits of both VVIR (Beyeradorf et al, 1980; Humen et al, 1985; Lindemans et al, 1986; Benditt et al, 1987b) and DDD pacing (Perrins et al, 1983; Kristensson et al, 1985; Rediker et al, 1988) over VVI have been previously described. Thus the addition of a rate response confers significant haemodynamic advantage over fixed rate pacing. VVIR systems are easier and cheaper to implant than their DDD counterparts therefore it is important to quantify the additional benefit of atrial systole.

The importance of atrial systole was appreciated by Gesells' studies in 1919 which showed enhancement of stroke volume by 50% with an appropriately timed atrial stimulus. The atrial contribution is both passive and active and has been divided into three distinct phases (Payne et al, 1971), fast filling, slow filling and atrial systole. The factors that modulate the haemodynamic events have been studied invasively in dogs. These have shown that the force of atrial contraction (Mitchell et al, 1962; Williams et al, 1965) and the compliance (Suga, 1974) of these chambers greatly influences ventricular filling and contractility. The atrial contraction is influenced by the autonomic nervous system (Mitchell et al, 1962) and by the level of atrial filling pressure (Williams et al, 1965). These studies indicate that the "atrial kick" has an influence over a wide range of heart rates, which is relevant to rate adaptive ventricular pacing, as well as atrial filling pressure (Samet et al, 1963).
As passive ventricular filling occupies more than half of ventricular diastole, (Nolan et al, 1969) therefore atrial compliance is an important factor. Low atrial compliance impedes the venous return, restricts both the increase in the peak and the mean levels of atrial pressure during ventricular filling, hence a reduced volume of blood is transferred and producing a smaller end diastolic ventricular volume (Baig et al, 1991). Early studies have examined haemodynamic indices in patients without heart failure (Samet et al, 1963; Samet et al, 1968; Samet et al, 1965; Samet et al, 1965; Benchimol et al, 1965b; Benchimol et al, 1969; Leinbach et al, 1969; Mitchell et al, 1965; Karlod et al, 1975) and all have shown that restoration of AV synchrony lowers pulmonary capillary wedge pressure (Mitchell et al, 1965) and improves the resting cardiac index by 10-22% by virtue of increasing the stroke volume (Kappenberger et al, 1982; Pehersson et al, 1983). The increase in end diastolic ventricular volume engendered by a correctly timed atrial contraction augments stroke volume according to the Frank-Starling mechanism (Linden et al, 1960; Linderer et al, 1983; Sarnoff et al, 1960).

1.9.1 Importance of the timing of atrial systole.

The critical effect of timing of the atrial systole was deduced by Wiggers and Katz, 1922, who noted the magnitude of the effect of atrial systole depended on its timing during ventricular diastole, as well as its force of contraction. This has been confirmed by several others (Leinbach et al, 1969; Braunwald et al, 1961; Carleton et al, 1966; Bashour et al, 1973), whereas incorrect timing can result in mitral regurgitation (Skinner et al, 1963). Corroboration of the importance of AV timing comes from a study (Von Bibra et al, 1986) of the effects of varying AV delays on mitral valve closure and
demonstrated, that if the atrioventricular delay is too long, the mitral valve closes prematurely with no alteration in the onset of ventricular systole or the timing of mitral valve opening. The net effect is a decrease in ventricular filling time. Merely mimicking the PR intervals in normal individuals is not suitable in paced subjects as pacing produces alterations in both left ventricular contraction and conduction times within the heart as discussed below.

1.9.2 Optimal AV Delay

An optimal AV delay means that for each and every cardiac cycle, the programmed electrical AV interval produces exactly the delay required for the left atrial systole to make its maximum contribution to stroke volume. Unfortunately, there is no correlation between the electrical interval applied at the pacing sites (usually in the right heart) and the optimal mechanical delay that concerns the left heart. This variation results from significant individual differences in electrical and electromechanical intervals both in the atria (electromechanical delay within the right atrium, interatrial conduction time [IACT], electromechanical delay within the left atrium) and in the ventricles (especially, the interventricular conduction time (Chirife et al, 1991; Daubert et al, 1992)).

This explains the wide variation in optimal AV delays, not only for the basic AV delay but also for the differences in AV delay between a paced or sensed cycle. This is because the IACT is longer after a paced right atrial event (Ausubel et al, 1986) as a consequence of right sided intra-atrial prolongation of the pacing stimulus. This has been measured (Ausubel et al, 1986) with a mean intrapatient difference of 27 ms between paced and sensed atrial beats.
In everyday clinical practice it is relatively straightforward to determine these different optimal delays with Doppler echocardiography (Faerstrand et al, 1985; Lascault et al, 1989). The optimal atrioventricular delay has been studied by several groups producing variable results between 150 msec and 200 msec, (Mehta et al, 1989; Leinbach et al, 1969; Nitsch et al, 1984; Leman et al, 1985; Faerestrand et al, 1985; Haskell et al, 1985). This variability may be due to patients with normal and abnormal left ventricular function being grouped together. Videen et al, 1986, using radionuclide ventriculography, showed that long AV delays are beneficial in patients with low ejection fractions, whereas a shorter AV delay was beneficial in patients with acute myocardial infarctions, (Chamberlain et al, 1970; Leinbach et al, 1969). Hartzler et al, 1977, also showed that a short AV delay was beneficial in patients immediately after surgery in whom complete heart block (CHB) had developed during the surgery. In addition, individual values for the amount of AV delay hysteresis varies between studies (Rey et al, 1990; Wish et al, 1987; Ritter et al, 1992).

1.9.3 Rate Adaptive AV Delay

This optimised AV delay must be maintained not only at rest but also on exercise. It has been shown in normal subjects that there is a decrease in the PR interval during exercise (Luceri et al, 1990), this is predominantly noticed during the early phases of exercise and less pronounced in patients with heart failure. Others (Shaldach, 1987) have suggested a linear relation between heart rate and PR interval, but this is probably an over simplification (Barbieri et al, 1990).
Most DDD pacemakers incorporate an algorithm to shorten the AV delay with increasing heart rate in an effort to maximise the atrial contraction. Haemodynamic studies have shown both improvement (Ritter et al, 1989; Igawa et al, 1990; Mehta et al, 1989) and detriment (Ryden et al, 1988; Haskell et al, 1989) on exercise from a rate adaptive AV delay when compared with a fixed one.

These algorithms also has the advantage of permitting a higher upper rate limit by raising the 2:1 point corresponding to the total atrial refractory period (sum of the AV delay and of the post ventricular refractory period).

1.9.4 Pacing Induced Alterations in Contraction

The normal activation sequence is distorted by pacing, as this is largely performed from the right side of the heart which causes aberrant depolarisation pathways resulting in less synchronous ventricular contraction (Askenazi et al, 1984). This can be compared with the global abnormalities induced by left bundle branch block which produces a delayed left ventricular contraction compared with the right ventricle. Thus alterations in diastolic filling time, left ventricular regional ejection fraction and septal motion can be seen on the M mode echocardiogram (Grines et al, 1989).

Studies comparing AAI pacing (maintaining a normal ventricular activation sequence) and DDD pacing with ventricular capture have shown that the AAI mode produced significant benefit over DDD pacing, both at rest and on exercise (Rosenqvist et al, 1991; Harper et al, 1991; Leclercq et al, 1992). This was observed for all parameters measured:
cardiac output and pulmonary pressures, global and regional LV ejection fractions and VO2 and O2 pulse at peak exercise. This has been confirmed by comparisons of His bundle pacing with standard right ventricular pacing, which showed that at any AV interval ventricular function was better with normal depolarisation (Kosowosky et al, 1968).

These observations suggest that a normal activation sequence should be preserved as often as possible. Thus, in patients with moderately long PR intervals, it will become necessary to perform individual assessments by echo-Doppler and exercise testing to determine whether intrinsic conduction or ventricular pacing produces the best haemodynamics.

1.10 CLINICAL COMPARISON OF VVIR AND DDD

Several short term crossover studies comparing DDD and VVIR pacing have been performed (tables 1:4 and 1:5). Most have shown no significant difference in exercise tolerance or peak cardiac output. In some studies it could be argued that the comparison was not valid as the rate response during VVIR pacing was achieved by matching the sinus rate (Pehrsson, 1983; Fananapazir et al, 1983c; Kristensson et al, 1985; Linde-Edelstam et al, 1992a), which may not be achieved in real life using biosensors (Sulke et al, 1990). However, comparisons using a biosensor (Menozzi et al, 1990; Oldroyd et al, 1991; Linde-Edelstam et al, 1992b) have showed that even in spite of reaching lower maximum heart rates in VVIR than DDD, comparable levels of exercise performance and symptoms were reached in VVIR. It may be that adaptive mechanisms
permit the maintenance of tissue oxygen levels despite lower heart rates. These mechanisms remain speculative, but could involve neuroendocrine mediated alterations in cardiac loading and/or contractile function leading to increases in stroke volume. One group has shown an increased exercise tolerance with VVIR pacing (Batey et al, 1990) but this was in chronotropically incompetent patients and has not been confirmed by others (Sulke et al, 1991; Lemke et al, 1992).

More longer term studies (Menozzi et al, 1990; Linde-Edelstam et al, 1992c) have demonstrated significant differences in symptomatology between the two pacing modes with a preference for DDD pacing, despite no demonstrable difference in exercise tolerance. These findings imply subtle differences in well being may well be present, although there is no apparent haemodynamic difference between VVIR and DDD pacing.

Having previously described the importance of a well timed atrial contraction it is surprising that no demonstrable benefit of DDD over VVIR has been shown. Why should this be? Several possible solutions arise. First, these studies concentrate on peak exercise. Physiologically it is known that the contribution to cardiac output of a well timed atrial contraction diminishes with increasing heart rate (Karlof, 1975; Fananapazir et al, 1983c; Kristensson et al, 1985; Pethrson, 1983) and DDD has been shown to be superior to VVIR during low levels of exercise (Lau et al, 1990; Lascault et al, 1992). Second, it is possible that the full benefit of the atrial contraction is not being realised. This could be due to an inappropriately timed atrial contribution as little attention has been paid in these studies to optimisation of the AV delay or to the influence of rate adaptive AV delay.
Table 1.4 Summary of quantitative haemodynamic data at peak exercise comparing VVIR and DDD pacing.

<table>
<thead>
<tr>
<th>Author</th>
<th>Haemodynamic method (Study size)</th>
<th>Peak CO VVIR</th>
<th>Peak CO DDD</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kristensson et al, 1985 *</td>
<td>dye dilution (n=10)</td>
<td>12.8±4.1</td>
<td>12.3±3.5</td>
<td>NS</td>
</tr>
<tr>
<td>Ausubel et al, 1985a. *</td>
<td>radionuclide (n=12)</td>
<td>7.65±1</td>
<td>7.97±2</td>
<td>NS</td>
</tr>
<tr>
<td>McMeekin et al, 1990 *</td>
<td>radionuclide (n=10)</td>
<td>8.1±1.5</td>
<td>7.6±1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Procter et al, 1991 **,#</td>
<td>echodoppler (n=20)</td>
<td>6.33±0.6</td>
<td>5.07±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Sulke et al, 1991 #, ***</td>
<td>echodoppler (n=22)</td>
<td>4.7±0.9</td>
<td>4.95±0.96</td>
<td>NS</td>
</tr>
<tr>
<td>Lascault et al, 1992 *,##</td>
<td>echodoppler (n=12)</td>
<td>8.01</td>
<td>9.24</td>
<td>15 P&lt;0.001</td>
</tr>
</tbody>
</table>

Comparisons of cardiac outputs during DDD and VVIR pacing on exercise in chronotropically competent and incompetent patients. NS = not significant

# Chronotropic incompetent patients

## Sub maximal exercise

* Rate matched VVI to sinus rate

** Rate matched to externally strapped piezoelectric crystal device

*** Rate increased externally to 120 bpm, no exercise

41
Table 1.5 Summary of comparative studies of VVIR and DDD pacing on exercise.

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>PARAMETER (Study Size)</th>
<th>VVIR</th>
<th>DDD</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fananapazir et al, 1983*</td>
<td>Distance walked</td>
<td>613±198 Metres</td>
<td>610±152 Metres</td>
<td>NS</td>
</tr>
<tr>
<td>Batey et al 1990 # **</td>
<td>Exercise tolerance</td>
<td>7.25±3.12 mins</td>
<td>6.01±2.27 mins</td>
<td>-21 P&lt;0.05</td>
</tr>
<tr>
<td>Menozzi et al, 1990</td>
<td>Exercise capacity</td>
<td>68±15 Watts/min</td>
<td>70±18 Watts/min</td>
<td>NS</td>
</tr>
<tr>
<td>Sulke et al 1991 # ***</td>
<td>Exercise Tolerance</td>
<td>10.2±3.6 mins</td>
<td>10.0±3.2 mins</td>
<td>NS</td>
</tr>
<tr>
<td>Oldroyd et al, 1991</td>
<td>VO2 Anaerobic Threshold</td>
<td>16.7±0.9 ml/kg/min</td>
<td>16.8±0.9 ml/kg/min</td>
<td>NS</td>
</tr>
<tr>
<td>L- Edelstam et al, 1992b</td>
<td>Exercise tolerance</td>
<td>10.5±4.7 mins</td>
<td>10.1±5.5 mins</td>
<td>NS</td>
</tr>
<tr>
<td>Lemke et al, 1992 #</td>
<td>VO2 anaerobic Threshold</td>
<td>7.4±0.3 ml/kg/min</td>
<td>7.4±0.3 ml/kg/min</td>
<td>NS</td>
</tr>
</tbody>
</table>

Comparative studies of DDD and VVIR pacing on exercise in both chronotropic competent and incompetent patients.

#  Chronotropic incompetence
*  Rate matched VVI pacing to sinus rate
** Rate matched to externally strapped piezo-crystal device
*** Rate increase to 120 bpm, no exercise
Much of this research was performed in younger more ambulant patients with normal cardiac function, and has involved short term studies which have focused almost exclusively on dynamic exercise. Little consideration has been given to non exercise stimuli that provoke a reflex increase in heart rate such as emotional responses or mental stress although sensitivity to these stimuli will depend on the sensor.

Sensors are also harder to program and this often requires multiple exercise tests with reprogramming often necessary 6 weeks post implant (Ahern et al, 1992), although it is still not known what is the "optimal rate" for a given level of exercise. A further limitation to the wider application of VVIR pacemakers is problems with pacemaker syndrome (Wish et al, 1988).

1.11 CHRONOTROPIC INCOMPETENCE

Studies (Astrand 1958, 1960) on the normal heart rate response to exercise in healthy individuals showed that the maximum heart rate decreased with age. As a reduced cardiac chronotropic response has also been observed in elderly patients in response to isoprenaline, it may be that alterations in catecholamine-adrenergic receptor interactions are responsible for this change (Bhuler, 1985; Vestal, 1979; Van Brummelen, 1981).

Sinoatrial disease can present in a number of different forms including persistent bradycardia, sinoatrial arrest and bradycardia-tachycardia. "Lazy sinus syndrome" was probably first documented by Erant et al, 1971, who noted that on exercise 27 patients
had an "abnormally small" rate increase. Further work (Holden et al, 1978) documented that a group of patients with sinoatrial disease had a significantly lower heart rate for a similar level of activity as age matched controls although the maximal oxygen consumption (VO2 max) was the same. This suggests that they performed the same level of exercise at a reduced heart rate. When compared with trained subjects, their level of maximum oxygen consumption was, as expected, much lower. However, their rate of change of heart rate was the same, suggesting that they have made similar adaptations as trained individuals to exercise;

- increasing stroke volume,
- widening of the arteriovenous oxygen difference
- or increased efficiency of distribution of cardiac output to exercising muscles.

This could lead to the speculation that these patients may not require rate responsive pacing at all, as they appear to be already optimally adapted. In fact, studies by Vardas et al, 1991 and Tresch et al, 1986 found that non syncopal patients with chronotropic incompetence actually exercised longer than age matched controls although not significantly so.

In contrast, people with impaired cardiac function have limited ability to increase stroke volume with exercise and the stroke volume may even decrease on increasing exercise (Epstein et al, 1967). Under these circumstances the ability to increase heart rate and provide the needed increment in cardiac output is very important. Therefore, in general patients with significant heart disease have a higher heart rate for a given work load than a normal subject. Ellestad (1975) has described an apparent exception to this point in a group of patients with ischaemic heart disease who show an inappropriately low heart rate.
increase with exercise a pattern he considers a poor prognostic sign. Chronotropic incompetence is also common in patients with heart failure whether this is caused by ischaemic heart disease (Yambe, 1987) or cardiomyopathy either dilated or hypertrophic (Keeling, 1992). Studies are currently running to determine the true incidence of chronotropic incompetence in these patients and the impact of restoring their rate response on their health. Hinkle et al (1972) found that middle aged or older men with low mean heart rates and a low heart rate response to exercise had a higher than expected rate of sudden death. It is also known that the 'intrinsic heart rate', the heart rate after sympathetic and parasympathetic blockade is lower in patients with heart disease (Jose et al, 1969; Jose et al, 1970). Since it is also known that the sick sinus syndrome is associated with a number of types of heart disease, it is possible that some patients cited by Ellestad and Hinkle may have mild forms of sinus node disease.

An alternative theory for some patients with chronotropic incompetence is that they are mechanically incompetent. Their ventricles being too stiff to respond to increasing heart rates with increasing cardiac outputs, due to decreased filling. Thus increasing their heart rate will result in detrimental haemodynamics.

1.11.1 Progression

The work of Vardas et al, 1991 has looked into the progression of sinus node disease. This has shown patients with bradycardia and a normal corrected sinus recovery time (cSNRT) although they had a low peak exercise rate, they showed no deterioration over a period of four and a half years. In contrast those with an abnormal cSNRT had a
statistically significant reduction in sinus node chronotropic response initially with further deterioration on re-examination. These patients also had a decreased exercise tolerance when compared with those with a normal cSNRT. This suggests that the cSNRT has more predictive value than the impaired chronotropic response alone.

Vardas and colleagues, also studied the reliability of chronotropic competence in patients with CHB and demonstrated that there was a small increase in cSNRT over the four and half year follow up but no change in chronotropic competence. Interestingly, one of their patients had a poor chronotropic response when first tested but normal cSNRT. When retested a prolonged cSNRT was reported suggesting failure of the chronotropic response is the first abnormality.

1.11.2 Diagnosis

To date, no universally accepted definition of chronotropic incompetence exists. The term implies the inability of the heart to increase its rate in proportion to metabolic demand. This can apply to CHB where an inability of the lower escape mechanism to respond exists but more usually refers to an inadequacy of the sinus node. Current definitions rely on the heart rate response to maximal exercise. The expression which was formulated by Astrand 1960 to predict the age dependant maximum sinus rate response to exercise (maximum predicted heart rate, MPHR) was \( \text{MPHR} = 220 - \text{age} \) beats/min.

Chronotropic incompetence has been defined as a maximum exercise heart rate achieved
during exercise testing that is < 75% (Isaef, 1989) or < 80% (Gwinn, 1990) of the predicted MPHR. Other arbitrary definitions such as maximum exercise heart rate < 100 beats/min (Batey, 1990) or < 120 beats/min (Rosenqvist, 1990) have also been used. However, the achievement of maximal exercise is not always possible. Elderly cardiac patients, especially those disabled with chronotropic incompetence, are unable to perform sufficient exercise on the treadmill. Furthermore, everyday life activities of these patients usually correspond to less than 6 metabolic equivalents corresponding to the first stage of a Bruce protocol. In addition, not much is known about the patterns of heart rate acceleration and deceleration in chronotropic incompetence.

A method to assess chronotropic response during sub maximal exercise was developed by Wilkoff et al, 1989, using gas analysis and the Chronotropic Assessment Exercise protocol (CAEP). This was achieved by comparing relative metabolic levels with relative heart rates, that is, by normalising the change in heart rate from rest to maximal function as a linear function of the change in metabolic work load. The normal predicted heart rate regardless of protocol is given by the formula:

$$HR\text{ (stage)} = \left\{\frac{[220-\text{age} - \text{HR (rest)}]}{\text{METS(peak)-1}}\right\} + HR\text{ (rest)}$$

where

$$\text{METS} = \frac{V02 \text{ (ml/kg/min)/3.5,}}{3.5},$$

$$\text{METS(peak)} = \text{the peak functional capacity.}$$

This formula only applies to patients able to exercise to maximum workload, but gives no indication for those patients unable to exercise to their anaerobic threshold. In such patients the level of chronotropic incompetence will be exaggerated as METS (peak) is the denominator of the equation.
1.11.3 Prevalence

This is not known, partly because of the inconsistency in defining chronotropic incompetence. It has been suggested (McBride et al, 1990) that approximately 40% of the pacemaker population exhibit some degree of chronotropic incompetence and might benefit from rate adaptive pacing. This percentage increases with time after implantation (Gwinn, 1990). The prevalence using the definition of <120 beats/min at maximum exercise has been reported to be between 28% to 57% (Rosenqvist, 1990). Characteristically the definition of chronotropic incompetence in the published series is not always clear (Ryden, 1989). In atrial fibrillation, where the impaired chronotropic response is due to the inadequacies of the atrioventricular node, up to 60% of the patients (Corbelli, 1990) may be chronotropically incompetent.

For the purpose of this thesis, patients have been defined as chronotropic incompetent if they fail to reach greater than 60% of their predicted optimal rate by the Astrand formula (220-age in years). The interest in these patients arises from the ability to be able to restore a physiological rate response in these patients on exertion. Thus, more needs to be known about the long term effects of this syndrome (Kappenberger et al, 1986). The relationship between chronotropic response and exercise performance, with the aim of identifying the optimal pacing mode, will be explored in this thesis.
1.12 DUAL CHAMBER (DDD) COMPARED AND DUAL CHAMBER RATE RESPONSIVE (DDDR) PACING IN PATIENTS WITH AND WITHOUT CHRONOTROPIC INCOMPETENCE

The development of DDDR pacemakers provides the clinician with the ability not only to programme the pacemaker in accordance with today's requirements, but the future status of the patient. In patients with an intact sinus node response no significant difference in symptoms, exercise tolerance (Capucci et al, 1992) or oxygen consumption (Weinhold et al, 1992; Lemke et al, 1992) have been demonstrated been DDD and DDDR pacing (table 1.6).

However, a higher VO2 at anaerobic threshold and increased exercise times have been shown in patients with chronotropic incompetence (Capucci et al, 1992; Lemke et al, 1992; Sulek et al, 1991). The amount of improvement seen with DDDR pacing varies from group to group. The META DDDR (Clinical study group 1992) showed a 27% increase in anaerobic threshold during rate responsive pacing, although others have only seen 12% improvement (Lemke et al, 1992). This difference may be due to Lemke et al, 1992 including more patients with hypertensive heart disease and those with only AV block and may have included several patients who are mechanically incompetent. In addition, the work was done in the supine position. Equally, the variation could be due to the heterogeneity of the condition with some patients already being at their optimal rate haemodynamics.
TABLE 1.6: Summary of comparative studies of DDD versus DDDR pacing.

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>PARAMETER (Study size)</th>
<th>DDD</th>
<th>DDDR</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cappucci et al, 1992</td>
<td>Exercise tolerance (n=8)</td>
<td>472±216 Secs</td>
<td>526±196 Secs</td>
<td>NS</td>
</tr>
<tr>
<td>Cappucci et al, 1992</td>
<td>Exercise Tolerance (n=5)</td>
<td>352±150 Secs</td>
<td>438±132 Secs</td>
<td>24 P &lt; 0.03</td>
</tr>
<tr>
<td>Lemke et al, 1992 #</td>
<td>VO2 Anaerobic Threshold (n=16)</td>
<td>7.4±0.3 ml/Kg/min</td>
<td>8.3±0.4 ml/Kg/min</td>
<td>11 P &lt; 0.001</td>
</tr>
<tr>
<td>Proctor et al, 1991 # *</td>
<td>CO Echodoppler (n=20)</td>
<td>5.07±0.5 L/Min</td>
<td>7.41±0.7 L/Min</td>
<td>46 P &lt; 0.05</td>
</tr>
<tr>
<td>Sulke et al 1991 # **</td>
<td>Exercise tolerance (n=22)</td>
<td>10.0±3.2 Mins</td>
<td>11.3±3.4 Mins</td>
<td>22 P &lt; 0.001</td>
</tr>
</tbody>
</table>

Comparative data on exercise in DDD and DDDR in chronotropically competent and incompetent patients, CO = cardiac output

# Chronotropically incompetent

* Rate matched DDD to externally strapped piezo-crystal device

** Rate increased to 120 bpm, no exercise
1.13 AIMS

It is the aim of the work reported in this thesis to explore the area of pacing haemodynamics in ambulatory during sub maximal exercise. This topic has previously been under investigated, mainly because of an inability to gain accurate ambulatory haemodynamic data owing to the limitations of the equipment utilised.

Specific aims are to;
1) Define techniques utilised (chapter 2).
2) Compare dual chamber and fixed rate pacing during the activities of daily living, rather than just at peak exercise (chapter 3).
3) Compare dual chamber and ventricular rate responsive pacing with an optimised AV delay and with a fixed or rate adaptive AV delay (chapter 4 and 5).
4) Determine the "optimal pacing rate" for a given level of exercise, thus at constant exercise the effect of increasing the pacing rate is studied. Then simple mechanisms for predicting this "optimal rate" are assessed (chapter 6).
5) To determine whether it is possible for a sensor driven pacemaker to determine an "optimal heart rate" (chapter 7).
4) To evaluate patients who are currently defined as chronotropically incompetent and those who are chronotropically competent. Comparing their exercise times and peak cardiac outputs during sinus rhythm and rate responsive pacing. In addition, predicted rate response curves will be drawn using the "activity time" to assess the response with the theoretical sensor and to see how the curves vary between the two modes of pacing (chapter 8).
CHAPTER 2: TECHNIQUES

2.1 INTRODUCTION

This chapter is a discussion of methodologies used in this thesis and their limitations. A description of the Capintec Vest, how it is used to measure ejection fraction, validation of measurement and previous research performed using this method is given. In addition, a description of the shuttle walking test and an analysis of its reproducibility is given.

2.2 CAPINTEC VEST

The major investigatory method presented in this thesis has been performed using an ambulatory monitoring system known as the Vest (Capintec Inc Rhode Island USA). This permits continuous collection of data relating to left ventricular function and stored on tape for further analysis. The Vest was originally designed as a battery powered device (Strauss et al, 1979) to determine the influences of daily living on cardiac function in patients with ischaemic heart disease. It consists of radionuclide detectors and a Holter electrocardiogram recorder carried on a vest like garment hence the name Vest. Technical improvements have increased sensitivity, decreased weight and increased stability of the device over the left ventricle.

Several clinical investigators have compared the validity and reproducibility of ejection fraction data obtained at rest and during exercise. When compared with conventional gamma camera blood pool imaging the Vest (Wilson et al, 1983) gave a correlation coefficient of 0.95
for supine and standing studies. Tamaki et al, 1988 made a similar comparison in "normal"
subjects and patients with ischaemic heart disease a correlation coefficient of 0.92 at baseline
and 0.86 on exercise was reported. Breisblatt et al, 1988 studied the correlation of ejection
fraction obtained by the vest with radionuclide angiography. A figure of 0.98 in post
myocardial infarction patients was reported. Ishibashi et al, 1991 showed the Vest to be an
excellent device to perform ambulatory assessment during the activities of daily living. Recent
studies by De Yang et al, 1991 thoroughly investigated the accuracy and reproducibility of
ejection fraction measured using the Vest compared with gated blood pool imaging at each
stage of exercise. The author concluded without reservation that the vest produced or
about perfect reproducibility in both normals and patients.

Fundamentally the Vest records two major parameters simultaneously, the left ventricular time
activity curve (permitting the calculation of relative changes in end-diastolic and end systolic
volumes, ejection fraction, relative cardiac output and ejection and filling rates) and two
channels of electrocardiographic information in analog form.

The Vest is composed of three modules (figures 2.1, 2.2);

2.1) a radionuclide detector.

2.2) a moulded plastic garment to hold the detector in place (from which the detector gets
its name).

2.3) data detection devices, batteries and recorder.

The complete apparatus weighs 3.1 kg. In addition to its ability to record the ECG and the
radionuclide data, the recorder contains an event marker and a real time clock. The recorded
radionuclide and electrocardiographic data are analyzed offline at an IBM workstation using
The radionuclide detector is shown on the far right of the picture. The supporting garment (Vest) is shown with the targeting device in position on the left of the picture. The data detection devices, batteries and recorder are shown towards the right of the picture and are usually carried in a shoulder bag.
This Vest is shown in position during one of the studies. The data collection devices are contained in the black shoulder bag over the handlebars of the cycle ergometer.
Figure 2.3 The IBM Workstation
software provided by the manufacturer (figure 2.3).

2.2.1 Detector

This consists of a 5.6 cm - diameter sodium iodide crystal mated to two phototubes. This detector views the left ventricle through a parallel-hole collimator. Energy discrimination is achieved with a thresholding circuit set to accept all events of more than 120 KeV. The digital data from the thresholding circuit are averaged for 31.25 msec, converted to an analog signal and recorded simultaneously with the electrocardiogram.

2.2.2 Detector positioning

The ambulatory ventricular function monitor is positioned over the left ventricle, after a conventional multi-gated (MUGA) blood pool scan with technetium 99-labelled red blood cells is used to assess global and regional ventricular functions. At the conclusion of the gated scan the patient was positioned upright in the left anterior oblique position that best demonstrated the septum and thus the best separation of the right and left ventricular blood pools could be achieved. The ECG electrodes were then positioned in a modified CM5 and CC5 position.

The plastic support garment for the Vest was placed on the patients chest and tightened into place. A targeting device was used to achieve optimal placement of the detector over the left ventricular blood pool. This consists of a replica of the probe with a three inch square of perspex attached. There are five markers attached to the perspex, four positioned round the
edge of the probe and one in the centre. The targeting device is positioned so that the markers cover most of the left ventricular blood pool (figure 2.1 shows the targeting device in position). The detector itself cannot be used as the shielding surrounding the detector casts a silhouette on the gamma camera larger than the sensitive area of the detector, approximately two thirds of the silhouette. The targeting device is then replaced with the probe and the image checked to ensure that it is still in the correct position. At the conclusion of the test the position of the detector was rechecked to ensure no movement of the Vest had occurred.

The statistical variation in the Vest derived ejection fraction has previously been calculated using serial measurements (15 second or 15 cycles averaged data) in several subjects while in the supine position. The ejection fraction variation ranged from 1.1% to 3.5% (mean 2.1%) (Tamaki et al, 1987,1988). Based on these data changes in the left ventricular ejection fraction of more than 6% persisting longer than 60 seconds are considered indicative of a change in left ventricular function.

2.2.3 Data Analysis and Quality Control

Before the Vest data was analyzed the ECG and nuclear data was reviewed for technical adequacy. The average count rate during the entire recording interval was displayed. If the detector and left ventricular blood pool remained in constant relation, the decay corrected curve had a 10% deviation from a straight line. Sudden shifts in the slope of the line are indicative of detector movement or instrument malfunction and were a reason to discount the rest of the data. When the data passed the screening tests, the radionuclide data were then
"manually" gated to the ECG data. There were problems with automatic gating of the paced ECG due to maldetection of pacing spikes as R waves, particularly in patients with unipolar pacing electrodes. It was necessary to view the data at 10 seconds intervals to ensure correct gating and that only accurate nuclide data were included. New detection systems for automatic gating could have been developed but this was not a priority in this research.

Radionuclide and ECG data were then summed for 30 second intervals to measure heart rate, ejection fraction, end systolic and end diastolic counts and relative cardiac output (heart rate times stroke volume in counts) for the full duration of the test period. The effects of different time averaging for the Vest have been studied (Pace et al, 1993; 1992), by comparing the Vest data with conventional radionuclide angiography (RNA). This has shown that the limits of agreement for ejection fraction and peak filling rate between the two methods are clinically acceptable. These were calculated as 1.96 times the standard deviation of the mean differences between the two methods for each time averaging. The limits of agreement for ejection fraction measurements by the Vest were;

-10.4:8.8 (single beat analysis),
-11.2:9.9 (5 sec averaging),
-5.4:4.8 (10 sec averaging),
-4.9:4.5 (15 sec averaging),
-6.2:5.6 (30 sec averaging),
-6.9:4.5 (60 sec averaging).

These results indicate agreement for time averaging ≥ 10 seconds. Differences between the two methods were plotted against their mean, to investigate any potential relationship between measurement error and the true value (whose best estimate is the mean of the two methods).
No such error was demonstrated. The authors also calculated the accuracy for the beginning of the study compared with the end, the limits of agreement for the ejection fraction were -1%:2% at the beginning of the Vest study and -4%:4% at the end. The authors report that the Vest slightly underestimates the EF as compared to RNA. This is not surprising as RNA calculates the EF using a multiple region of interest method whereas the Vest only uses a single region.

The background counts were estimated using the ejection fraction obtained from the initial MUGA scan. The Vest software then compared the MUGA ejection fraction with the Vest data and calculated the background counts from the lungs etc. Relative end-diastolic volume was expressed as 100% at time zero. Relative cardiac output was calculated as relative stroke volume multiplied by heart rate.

2.2.4 POTENTIAL ERRORS

Several potential sources of error should be considered in the evaluation of Vest radionuclide data.

2.2.4.1) Position

The left ventricular radionuclide detector must be kept over the left ventricular blood pool during the whole acquisition. Although the Vest garment is tightly fixed over the chest wall, the detector or the heart may move during vigorous activities. The position of the detector
for sudden changes of greater than 10% in the acquired data. The detector only moved once during the series of studies in this thesis in a lady wearing a silk blouse. Subsequent patients participating in the study were provided with a cotton shirt to wear while performing the studies.

2.2.4.2) Cardiac Motion

A constant position of the detector relative to the heart does not consider cardiac motion. Cardiac rotation with changes in posture, such as lying down may move the heart out of the field of the detector. Some motion can be tolerated, however, because the relative isosensitive field of view of the detector permits movement of ±1.2 cm without a significant change in calculated ejection fraction. Motion of the cardiac blood pool of greater than 1.2 cm will cause a fall in the overall count rate and should be picked up during the post exercise review. In addition, the detector was positioned while the patients were standing as this is the position during which most measurements were made.

2.2.4.3) Region of Interest

A fixed region of interest is used for data acquisition and analysis with the Vest, whereas with blood pool scans recorded with a gamma camera use a variable region of interest. Although a fixed region of interest may over estimate end systolic volume and underestimate ejection fraction it provides good correlation with that calculated by contrast ventriculography (Green et al, 1978).

2.2.4.4) Background Activity

The background activity used to calculate the ejection fraction during the study period was
calculated from the actual ejection fraction obtained during the MUGA scan performed pre-test instead of from a second detector positioned over the lung fields. This is because changes in counts caused by respiratory movement are reduced by the 15 to 30 second averaging and any error induced would be the same for each study and did not justify the additional inconvenience to the patients of the second detector.

2.2.5 LIMITATIONS OF THE VEST

The Vest is by no means the ideal instrument for studying pacing haemodynamics as it necessitates the use of isotopes. Pregnant and breast feeding women are necessarily excluded as well as those with young children. This is not a large problem in the pacemaker population as a whole as their mean age is 75 (BPEG data), but could be a minor problem in those ambulant enough to carry out the study protocols.

The reliance of the Vest on short half-life isotopes means the study period is reasonably limited to 3 hours although meaningful data can be collected for 18 hours. The cost and potential for damage of the probe means that it is not suitable for use out of hospital although this is the application it was designed for. The intrinsic difficulties of repositioning the Vest in exactly the same place means it does not lend itself to sequential studies. Thus all the studies have been performed on one day and if a patient has volunteered to participate in a second study, no comparisons have been made between the two investigations.
2.2.6 SETTING FOR THE STUDY

All parts of the study were performed in the Gamma camera suite of either Groby Road Hospital, Leicester (March 1992 - January 1994) or the Glenfield General Hospital, Groby Road, Leicester (February 1994 - January 1995). All studies were performed by the author, usually with the assistance of a Medical Physics technician, Staff nurse and a physiological measurement technician (see acknowledgments).

2.2.7 ETHICAL APPROVAL

Ethical committee approval was obtained from the Leicester Ethical Committee for a series of Vest studies to investigate pacing haemodynamics. Repeat studies could be performed on the same patient providing they were six months apart. As isotopes were involved permission was also obtained from ARSAC and as the radiation is no more than a routine MUGA scan it was given approval to be used as a routine investigation. Written informed consent was obtained from all patients prior to inclusion in the study.

2.3 LIMITATIONS OF OTHER HAEMODYNAMIC METHODS

Several methods have been used for the acquisition of haemodynamic data from paced subjects. These broadly divide into invasive and non invasive. The advantage of invasive methods are that direct measurement of haemodynamic variables is possible but studies are restricted to the vicinity of the monitoring equipment. It is difficult to study exercise responses reproducibly, as exercise will be limited to the supine position which has been
shown to have varying effects on peak work loads, with studies showing higher (Poliner et al, 1980; Holmgren et al, 1960), equal (Bevegard et al, 1960) and lower (Astrand et al, 1961) peak work loads than in the upright position.

Non invasive methods that have been previously used are echocardiography particularly echo-Doppler, and nuclear ventriculography. The problems with the former are that it is not possible to obtain continuous data. The measurements, even in expert hands, can take several minutes to obtain, and there are also considerable inter and intra operator variability. The major limitation of nuclear ventriculography is that the camera is static. Although possible to obtain continuous data, data collection are limited to the proximity of the camera with subjects required to maintain their chest wall against the camera.

2.4 DOPPLER ECHOCARDIOGRAPHY

In the studies involving the optimisation of the atrioventricular delay the Doppler left ventricular diastolic flow velocity waveform has been used. This method has been validated as non invasive, reliable and easily obtained method for assessment of left ventricular diastolic function (Sprito et al, 1986). They may be recorded by pulsed Doppler echocardiography by placing the sample flow in the inflow region of the left ventricle (Rokey et al, 1985; Hatle et al, 1982; Dabestani et al, 1984; Gardin et al, 1984; Maron et al, 1984). A normal Doppler waveform shows a rapid increase in flow velocity early in diastole, followed by a period of diastasis (during which velocity returns to zero baseline) and finally a second smaller rise concomitant with atrial systole. It is however important to ensure that there is no change in left ventricular filling pressure and heart rate as these have been shown to alter the doppler...
mitral flow velocity pattern (Choong et al, 1987).

In the studies reported in this thesis Doppler measurements of transmitral flow were obtained using a 2.5 MHz transducer and a Hewlett Packard 77030A monitor. The patients were rotated 30° into a left lateral decubitus position. The AV delay was studied at 75, 100, 125, 150, 175, and 200 msec and the waveform was studied approximately 5 minutes after programming. Characteristics of the optimal AV delay occurred when the E and A waves were separate and distinct.

All the studies were performed by the author so no error could be introduced from interobserver variation. To make sure there was no intraobserver variation the author repeated the study blinded to the AV delay on three patients on three separated occasions producing identical results on each occasion.

2.5 STATISTICAL METHODS

In this thesis all data are presented as the mean ± one standard deviation (SD). Demonstrations of statistical significance have been calculated using a two tailed paired Students 't' test. Results showing a $P<0.05$ have been taken to be significant.

2.6 EXERCISE METHODS

The standard exercise test protocol used in this thesis, to compare the different pacing modes, has to be reproducible, easy to perform and mimic normal activity so as to stimulate
the activity sensors as in "normal" life. Previous investigators have used both cycle ergometry and incremental treadmill exercise. However, the age and underlying disease of the paced population often precludes this type of exercise test (Langenfeld et al, 1990).

More importantly, the standard treadmill or cycle ergometry are both poor stimuli for the activity sensors (both the piezoelectric crystal and the accelerometer) as upper body movement is minimal. The stimulus can be improved on the treadmill, if the arm on the same side as the pacemaker is swung. However, this becomes difficult with increasing treadmill inclines and speeds. The overall result of this is a reduced rate response in a non physiological condition which would not have permitted a true comparison of the activity sensors.

An assessment of day to day activities has shown that they are usually of an irregular nature and steady state condition are rarely achieved (Spiro, 1977). Consequently, patient symptoms are probably more likely to be revealed or identified during an incremental test rather than a self paced exercise test. A simple corridor walk was not used as the patient may or may not be stressed maximally depending on how the test is conducted and the amount of motivation and encouragement offered which would make a valid comparison difficult (Guyatt et al, 1984). It has been suggested that the habitual nature of walking may prevent a self paced test from showing any benefits from changing treatments (Swinburn et al, 1985). As patients who have completed the same distance on a corridor walk have not necessarily experienced the same work rate / stress and therefore comparisons may not be valid.

A step test was excluded as this shows a pronounced learning effect (Swinburn et al, 1985) with a 96% improvement over the first four tests. This probably relates to the fact that it is
an unfamiliar activity for many and requires a degree of coordination and muscle fatigue becomes one of the factors assessed.

The shuttle walking test was originally developed for the assessment of patients with chronic airways disease (Singh et al, 1992) as a replacement for the more commonly used six minute walking test and is highly suitable for the purposes of this thesis as well. It is a standardised incremental field walking test that provokes a maximal performance and allows a direct comparison of patients performance. Its reproducibility has been demonstrated in patients with chronic obstructive airways disease by (Singh et al, 1992).

The shuttle walking test has several feature which lend itself to the study of paced patients;

i) It has a very slow start which permits low levels of exercise to be studied. Relevant in pacing haemodynamic studies as the patients are generally elderly.

ii) It is based on a familiar activity. Therefore as repeat exercise testing is necessary, it reduces the effects of muscle fatigue and coordination.

iii) Its external speed control helps reduce operator bias. In addition, the operator walking with the patient during the first minute prevents more ambulant patients starting off too quickly.

iv) The instructions are taped so each patient will receive the same instructions everytime they perform the test.

2.6.1 METHOD

The shuttle walking test requires the patients to walk up and down a 10 metre course marked
out by two cones inset 0.5 m from either end to reduce the need for sudden changes in
direction (figure 2.4). The speed at which the patient walks is controlled by an audio signal
played on a tape cassette originally generated from a BBC microcomputer. The accuracy of
the timed signal is maintained by inclusion of a calibration period of one minute at the start
of the tape.

At the start of the test a standardised explanation is given which advises the patients to walk
at a steady pace aiming to turn around the cones when they hear the signal. They should
continue to walk until they are unable to maintain the speed without becoming unduly
breathless. The start of the test is indicated by a triple bleep. Thereafter the tape emits a
single bleep at regular intervals, at which point the subject should attempt to be at the
opposite end of the course, hence by the time the patient heard the signal he should be turning
around the cone to proceed back down the course. Each minute the speed increased by 0.17
m/s so the subject was required to walk progressively faster. A change of speed to the next
level was indicated by a triple bleep from the tape recorder.

In all there are 12 levels with the final speed being 2.37 m/s. The number of shuttles at each
level is determined by the speed (Table 2.1). To help the subject establish a routine, the
operator walked alongside for the first minute. The patient has 20 seconds to complete each
shuttle leg in the first minute. After this the subjects paced themselves. If the subjects
reached the cones before the bleep, they were instructed to remain until the signal indicated
they could proceed with the test. No encouragement was provided during the test. The only
verbal contact was the advice given at the end of each minute to increase their speed slightly.
The end of the test was determined either by the subject being too breathless to maintain the
Figure 2.4 Diagram of the Shuttle Walking Test Course

10 metres

Audio Cassette

Timed Tone
required speed or by failure to complete a shuttle in the time allowed (that is, was more than 0.5 m away from the cone when the bleep sounded).
<table>
<thead>
<tr>
<th>LEVEL</th>
<th>SPEED M/S</th>
<th>SPEED MPH</th>
<th>NO OF SHUTTLES PER LEVEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.50</td>
<td>1.12</td>
<td>3</td>
</tr>
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<td>2</td>
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<td>12</td>
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</tbody>
</table>
2.6.2 VALIDATION

For the purposes of this thesis accurate measurements of absolute cardiac output are not required. However, what is necessary is that the vest produces a reproducible measurement during the course of the normal investigating conditions. Therefore validation of the method is required for reproducibility only. Ten patients performed three shuttle walking tests with twenty minutes rest between each, to determine if a significant difference existed. The shuttle walks were carried out on the same day in order to mimic the test regime used during further studies reported in the remainder of this thesis. Patients had the Vest positioned in the usual way.

To assess the reproducibility of the vest data the peak relative cardiac outputs were recorded at the start of the final minute of exercise, so the level of exercise would be the same. The reproducibility of the shuttle walking test was calculated by recording the total exercise duration and these data compared.

As the same person analysed the data for each patient. There was no need to assess interobserver variation. Intraobserver variation was assessed on the above 10 patients. Each tape being analysed three times and no difference in relative cardiac output data were found.

2.6.3 RESULTS

All subjects found it easy to pace themselves and no difficulties were encountered in administering the test. The Vest data are recorded in table 2.2 and the shuttle walking times in table 2.3.
Table 2.2 Vest reproducibility data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Peak CO Ex 1 (EDV/M)</th>
<th>Peak CO Ex 2 (EDV/M)</th>
<th>Peak CO Ex 3 (EDV/M)</th>
<th>Range (EDV/M)</th>
</tr>
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<tbody>
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<td>10</td>
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<td>72</td>
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CO = cardiac output (EDV/M)
Table 2.3 Shuttle walking test reproducibility data

<table>
<thead>
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<td>7.4</td>
<td>7.3</td>
<td>6.9</td>
<td>0.5</td>
</tr>
</tbody>
</table>

min = minutes
When comparing either the relative cardiac output data or the shuttle walking test times there was no significant difference between test 1 and test 3. The largest range in relative cardiac outputs between tests was 3 EDV/M suggesting a change greater than this value on exercise is significant.

2.6.4 DISCUSSION

These data show the shuttle walk and the Vest methodology to be very reproducible and therefore both are suitable tools for the study of different pacing modes on exercise.

2.6.5 CONCLUSION

The Vest permits haemodynamics to be measured non invasively and gives a reproducible measurement of relative cardiac output during consecutive exercise tests. The shuttle test has been shown to produce a symptom limited maximal exercise, is easy for the patients to perform, reproducible and permits a fair comparison of sensors and other pacing modes.

Both will now be used to form comparisons between different modes and modalities of pacing.
CHAPTER 3: A COMPARISON OF VVI AND DDD DURING THE ACTIVITIES OF DAILY LIVING

3.1 AIMS

The aim of this chapter is to demonstrate that the Vest can be used effectively to evaluate pacemaker patients and produces quantitatively similar results when compared with more traditional methods. A comparison of relative cardiac output during fixed rate ventricular and dual chamber pacing has been performed both at rest and during the activities of daily living. Similar evaluations have been executed by several groups using other methods and these data are presented for comparison.

3.2 INTRODUCTION

As discussed in chapter one, several comparisons of VVI and DDD pacing have been made both at rest and on exercise (table 1.2 and 1.3) using invasive and non invasive methods. The studies at rest have shown a 4-43% improvement in cardiac output between VVI and DDD pacing. The assessments during exercise however have concentrated on indirect measurements of exercise capability rather than cardiac output and have shown between a 12-40% improvement in exercise capacity with dual chamber pacing. Interestingly one of the few studies to measure cardiac output on exercise failed to demonstrate a significant improvement in cardiac output with AV synchronous pacing, although it did show improvement in other parameters (McMeekin et al, 1990). It was the intention of this study to show that the Vest is a useful tool for the investigation of
pacemaker patients, using previous comparative data as a baseline.

3.3 METHODS

3.3.1 Patient Selection

All patients who had a dual chamber pacemaker for chronic complete heart block, no intrinsic atrio-ventricular conduction, and an intact sinus rate were considered eligible providing they were fit enough to complete the exercise protocol. Eleven patients, 7 male, were recruited with mean age 56 years (range 34-75) patient details are recorded in table 3.1. Included in this group were 6 patients who had been upgraded to DDD pacing from VVI due to pacemaker syndrome.
<table>
<thead>
<tr>
<th>MINIETTER</th>
<th>CHB</th>
<th>HDP</th>
<th>CTB</th>
<th>EF</th>
<th>SEX</th>
<th>AGE</th>
<th>SYNDROME</th>
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<td>HDP</td>
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<td>EF</td>
<td>SEX</td>
<td>AGE</td>
<td>SYNDROME</td>
</tr>
</tbody>
</table>

**TABLE 3.1 PATIENT CHARACTERISTICS**
3.3.2 Study Design

The study was a within patient double blind prospective study of cardiac output and ejection fraction between the two pacing modes, VVI and DDD. On the day of assessment the patients were randomised to one of the two pacing modes. They were then programmed by an independent physical measurement technician without either the patient or the investigator being aware of the selected mode.

A MUGA scan was performed and the Vest was positioned over the left ventricle (see methods chapter two). An activities protocol was then undertaken. A twenty minute rest separated each activity and the order of activities altered for each subject, i.e. the first performed them in the order shown, the second start with item 2 and the third subject with item 3 and so on.

Item 1) Corridor walk for 10 minutes. The subjects were instructed to walk back and forth along a 25 metre stretch of corridor at their own speed taking as many rests as they wanted. During the test the patients were informed of the time remaining to walk but no further instructions. After 10 minutes the total distance walked was recorded.

Item 2) Mental stress. The subjects were either requested to subtract 7 (or 8) from 1000 until less than zero.

Item 3) Staircase Climbing. Subjects were asked to ascend and descend a flight of 15 stairs three times as quickly as they could. Unfortunately the Vest is not sensitive enough to distinguish between a single ascent or descent.

Item 4) A shuttle walking test was performed and the total distance walked was recorded.
The patients were then reprogrammed to the opposite mode and the series of exercises repeated. At the completion of the test the patient was questioned to determine the preferred mode.

3.4 RESULTS

Eleven patients were studied and the relative cardiac output was calculated at rest and was on average 15% higher at 36.9±8 EDV/M in DDD pacing compared with 32±9 EDV/M pacing in VVI (P < 0.004) (figure 3.1). Seven patients expressed a preference for DDD pacing and none preferred VVI pacing. This included all of the six patients who had previously been upgraded for pacemaker syndrome and patient 10.

3.4.1 Corridor walk

All patients were able to complete both walks, the peak cardiac output was 66±14 EDV/M with DDD pacing and 51±9 EDV/M in VVI pacing, P < 0.0001 (figure 3.2) an increase in 29%. The total distance walked was 765±30 M and 680±25 M respectively an increase of 12.5% and the peak mean heart rate in DDD was 109±21 bpm.
FIGURE 1  CARDIAC OUTPUT AT REST IN VVI AND DDD

P < 0.004

FIGURE 3.2  PEAK CARDIAC OUTPUT DURING CORRIDOR WALK

P < 0.0001
3.4.2 Mental stress

All patients completed both tests with a mean heart rate rise to 102±8 bpm in DDD pacing and peak mean cardiac output of 53±9 EDV/M compared to 46±7 EDV/M in VVI (P < 0.0002) (Figure 3.3) an increase of 15%. Mistakes were similar in both groups with a mean of 7.

3.4.3 Staircase climbing

All patients were able to complete all three climbs peak cardiac output during DDD pacing was 58±9 EDV/M compared with 49±8 EDV/M in VVI pacing (P < 0.0001) (Figure 3.4).

3.4.4 Shuttle walk

All patients completed both walks, the peak cardiac output being 71±17 EDV/M for the DDD group and 53±11 EDV/M for the VVI group, (P < 0.0002) representing a 34% increment for DDD pacing (figure 3.5). The total exercise time was increased from 7.4±1.5 minutes in VVI mode to 8.1 minutes in DDD (P < 0.02) a 9% increase in exercise tolerance (figure 3.6). The mean peak heart rate in DDD pacing was 125±12 bpm.
FIGURE 3.3 PEAK CARDIAC OUTPUT DURING MENTAL STRESS

PACING MODE

FIGURE 3.4 PEAK CARDIAC OUTPUT AFTER STAIRCASE CLIMBING

PACING MODE
FIGURE 3.5 PEAK CARDIAC OUTPUT DURING THE SHUTTLE WALK

![Graph showing peak cardiac output for VVI and DDD pacing modes. The graph indicates a significant difference (P < 0.0002) between the two modes.]

FIGURE 3.6 TOTAL EXERCISE TIME FOR SHUTTLE WALK

![Graph showing total exercise time for VVI and DDD pacing modes. The graph indicates a significant difference (P < 0.02) between the two modes.]

81
3.4.5 Pacemaker Syndrome Patients

In patients with pacemaker syndrome the mean increase in peak cardiac output between VVI and DDD during the shuttle walk compared with the non pacemaker syndrome patients was $23.5 \pm 11$ EDV/M and $11.2 \pm 6$ EDV/M respectively, $P < 0.035$. Representing a mean increase in the peak VVI cardiac output of $20.6 \pm 8.6\%$ for the unselected group and $44 \pm 16\%$ for the pacemaker syndrome patients. This indicates that the pacemaker syndrome patients gained more benefit from the change which is in agreement with the findings of Stewart et al (1984). In addition, if preference is plotted against increase in cardiac output (figure 3.7) it can be seen that a difference in cardiac output of greater than $14$ EDV/M is detectable by the patients. The patients in both groups were similar for age and ejection fraction.
FIGURE 3.7 INCREASE IN PEAK CARDIAC OUTPUT VERSUS PREFERENCE FOR DDD PACING

Increase in peak cardiac output between VVI and DDD pacing plotted against preference for DDD pacing.
3.5 DISCUSSION

These results demonstrate that left ventricular haemodynamics are significantly improved by the restoration of AV synchrony at rest and on exercise. The improvement is individually variable, however an overall 15% increase could be shown with DDD pacing at rest and is in accord with more conventional methods (table 1.2).

In contrast, most previous studies comparing DDD and VVI pacing on exercise have used qualitative rather than quantitative assessment and have relied on comparisons between exercise tolerance (Kruse et al, 1981; Kruse et al, 1982; Fananapazir et al, 1983c) and questionnaires (Perrins et al, 1983) to assess the benefits. Whilst these end point investigations are valid and interesting, they do not carry detailed haemodynamic data which are of potential value for more refined pacing studies. Using the Vest not only is it possible to demonstrate improvements in symptoms and exercise tolerance but also a mean increase of 34% in peak cardiac output between VVI and DDD pacing during the shuttle walk with an impressive demonstration of almost doubling of cardiac output during exercise with dual chamber pacing. In addition, it was also feasible to show significant improvements with DDD pacing during the activities of daily living such as staircase climbing and mental stress, not previously investigated.

The luxury of using the Vest is that data can be assessed during the whole of exercise period. A typical plot of relative cardiac output in the two pacing modes is shown (figure 3.8). This indicates that as the exercise progresses the benefit from the restoration of atrioventricular synchrony is increased. It is not clear whether this is due to the
FIGURE 3.8 CARDIAC OUTPUT DURING DDD AND VVI PACING

CARDIAC OUTPUT (EDV/mL)

TIME

VVI
DDD
increasing heart rate or the atrial contribution. From preliminary work and that of others (Smedgard et al., 1987; Lau et al., 1988) it is more likely to be due to the increase in rate as similar results have been noted when comparing fixed rate ventricular pacing with ventricular rate responsive pacing.

Six of these patients had been upgraded due to pacemaker syndrome - interestingly these patients gained significantly from atrioventricular synchronous pacing both subjectively and quantitatively, with a substantial 44±16% increase in peak cardiac output between single and dual chamber pacing, when compared with the normal group. Only one of the non-upgraded group was able to express a preference and he also had a large increase from VVI to DDD pacing. Similar results have been found by others (Stewart et al., 1984) where a 14.4±3.4% improvement in cardiac output was demonstrated between VVI and DDD pacing in the group as a whole. Whereas those patients with pacemaker syndrome or VA conduction had a 30.4±8.6% increase. This is not simply related to ejection fraction as the subject with the lowest ejection fraction was unable to differentiate between the two modes.

Of the fifteen patients who volunteered to participate in more than one study, three (had pacemaker upgrades for pacemaker syndrome) had significant improvements in their ejection fraction as measured by MUGA scan. The MUGA scans having been performed at approximately 3 months post upgrade and then 12 months later. This was by 10% in one patient, whereas those patients in dual chamber mode throughout had constant or decreasing ejection fractions due to coincident cardiovascular disease. This improvement is presumably related to remodelling changes in the left ventricle which means that
improvements following upgrade may continue for long after the procedure has been performed.

The limitations of this study design and others of its type are that it is of short duration and in a small group of younger more ambulant patients, who are not truly representative of the pacemaker population as a whole. Whilst providing powerful support for implantation of DDD pacemakers for AV block, the extra costs are considerable. Larger prospective clinical studies in a more representative sample of elderly patients need to be performed to confirm the prospects of enhanced pacing performance.

3.6 CONCLUSION

The Vest is shown to be a powerful tool for investigation of pacemaker haemodynamics. Dual chamber pacing was found to be superior to fixed rate ventricular pacing throughout a spectrum of different exercises which represent the activities of daily living and selection of dual chamber devices should not be limited to assessments of patients mobility. More sophisticated investigations are subsequently described in chapter 4-8.
CHAPTER 4: CARDIAC OUTPUT DURING SUBMAXIMAL AND MAXIMAL EXERCISE; COMPARISON BETWEEN DDD AND VVIR

4.1 AIMS

The aim of work described in this chapter was to compare ventricular rate responsive pacing with dual chamber pacing to assess the relative importance of rate response and AV synchrony during exercise.

4.2 INTRODUCTION

Despite the inability to create a sensor which is capable of exactly mimicking the behaviour of the sinus node, previous comparisons of ventricular rate responsive pacing (VVIR) against dual chamber (DDD) pacing have failed to demonstrate the presumed superiority of DDD pacing on exercise. No improvement in exercise tolerance or cardiac output was shown between DDD pacing and either rate matched VVI pacing (Pehrsson, 1983; Fananapazir et al, 1983c; Kristensson et al, 1985; Linde-Edelstam et al, 1992a) or sensor driven pacemakers (Oldroyd et al, 1991; Linde-Edelstam et al, 1992b).

At rest, with equal rates, atrial synchronisation provides a higher stroke volume and cardiac output than ventricular pacing (Kristensson et al, 1985; Kruse et al, 1982). It could therefore be claimed that the 10-20% increase in cardiac output at rest is relatively small considering the increase of 100-300% required during heavy exercise (Goldreyer et al, 1982). This has led to the conclusion that the atrial contribution to cardiac output
maybe relatively unimportant and that restoration of a rate response is the more important factor, even if it does not accurately represent the sinus node.

The studies quoted have limitations. In particular, most of the comparisons (Pehrsson, 1983; Fananapazir et al, 1983c; Kristensson et al, 1985; Linde-Edelstam et al, 1992a) have compared peak cardiac outputs at peak exercise and maximal exercise tolerance between the two groups when the atrial contribution is known to be diminished (Karlov I, 1975; Ogawa et al, 1978; Fananapazir L, 1983c). In addition, the clinical relevance is questionable as most people rarely exercise above modest levels (6 metabolic equivalents) and this is mostly done in bursts. Low level exercise has been investigated using invasive techniques (Karlov, 1975; Kristensson et al, 1985) at constant workloads. Kristensson et al showed no significant difference between the two pacing modes but found that in general at the lower work level the atrioventricular synchronous haemodynamics were better. Whereas Karlov, 1975, who used lower exercise levels with a mean rate of 100 bpm found an 8% increase with atrioventricular synchronous pacing. This concurs with the work of Lau 1990 who demonstrated the superiority of DDD pacing at low work loads. As the shuttle walking test starts at low exercise levels it will be possible to compare the two pacing modes during the whole range of exercise.

Another criticism of most of the studies performed is that no attempt has been made to select the optimal AV delay. If inappropriately timed, atrial contraction will be wasted and a DDD pacemaker will work essentially as a VVIR system. The comparison therefore becomes one of two rate responsive pacemakers, sinus node tracking versus activity sensor, and not of AV synchrony versus VVIR pacing. This study compared
DDD and VVIR pacing during the whole of exercise using an optimal AV delay.

4.3 METHODS

This study was a prospective double blind comparison of VVIR against DDD with each patient acting as their own control. The differences in heart rate and cardiac outputs were analyzed during the whole exercise period.

4.3.1 Patients

Eight pre-implant patients were selected to participate, all had a DDDR pacemaker. Seven had activity sensors, five had piezoelectric crystals (Medtronic Elite,) and two had an accelerometer (CPI Vigor). The remaining patient had a minute ventilation sensor (ELA Chorus RM). Patients were all chronotropically competent defined as being able to achieve a rate of greater than 80% of predicted peak heart rate [Astrands formula (220 - age bpm)]. None had competition due to intrinsic conduction, atrial flutter, atrial fibrillation, recent myocardial infarction, angina or respiratory disease.

4.3.2 Protocol

Prior to the day of study, patients practiced the shuttle walk once to reduce the learning effect. As well as ensuring that the rate responsive sensor produced a rate response of an equivalent rate to the sinus rate. An echocardiogram was performed to ensure optimisation of the AV delay as described in chapter two. All pacemakers were programmed so that the maximum upper rate limit could be achieved through the use of the rate adaptive AV delay. This operates differently depending on the pacemaker
implanted. The CHORUS RM and VIGOR dual chamber pacemakers have a dynamic AV delay which shortens gradually from the programmed maximum AV delay to the programmed minimum AV delay as the cycle length decreases. The Elite and the Minuet have a rate adaptive AV delay which suddenly shortens at any AA interval which is less than 500 msec (120 bpm) to 65 msec. This concurs with the work of some (Mehta et al, 1989; Ritter et al, 1989) but in conflict with that of others (Ryden et al, 1988; Haskell et al, 1988). It was decided to adopt this approach as the lowering of the 2:1 point was likely to be more of a limitation to exercise than the reduction in the AV delay. The impact on cardiac output of a patient reaching their 2:1 blocking point is shown in figure 4.1.

On the day of study the patients were randomised to either DDD or VVIR by an independent assistant and programmed to the pre determined settings. They then performed a shuttle walk in each mode with 20 minutes rest in between.
FIGURE 4.1 EFFECT OF REACHING THE 2:1 POINT ON CARDIAC OUTPUT
4.4 RESULTS

Eight patients were studied, 4 male with a mean age of 51 years (range 35-66 years) with a mean ejection fraction of 49% (range 34-64%) patient characteristics are shown in table 4.1. All patients completed both exercise programmes. Resting cardiac output was higher in DDD, mean 36±9 EDV/M than VVIR, mean 32±6 EDV/M (P < 0.02) despite comparable rates 74 bpm and 72 bpm (P < 0.4) respectively. At peak exercise there was no significant difference between cardiac outputs 72±14 EDV/M and 74±16 EDV/M (P < 0.2) (figure 4.2), exercise times 8.8±1.0 minutes and 8.9±1.0 minutes (P < 0.2) (figure 4.3), or peak heart rates 127±14 bpm and 124±10 bpm (P<0.5), in DDD and VVIR pacing. Graphs of individual exercise tests are shown at the end of the chapter figure 4.6-4.13.

If the whole of exercisers examined, despite no difference in the peak mean heart rates, it can be seen during earlier exercise the mean heart rate was significantly higher in VVIR than DDD (figure 4.4) from 3-6 minutes, although there was no difference in cardiac output (figure 4.5). Only two patients expressed a preference for a particular mode and they preferred dual chamber pacing.
<table>
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<th>ECG</th>
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<td>64%</td>
<td>CHB</td>
<td>F/51</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Disease: SND = Sine Node Disease, EF = Ejection Fraction, TPG = Tissue Propensity.

CHB = Complete Heart Block, CTP = Conduction Tissue Propensity, HSD = Hyperactive Heart.

TABLE 4:1: PATIENT CHARACTERISTICS
FIGURE 4.2 PEAK CARDIAC OUTPUT IN VVIR AND DDD

CARDIAC OUTPUT (EDV/M)

VVIR       DDD

P < 0.4

FIGURE 4.3 TOTAL EXERCISE TIMES IN VVIR AND DDD

TIME (MINS)

VVIR       DDD

P < 0.2

95
FIGURE 4.4 MEAN HEART RATE IN DDD AND VVIR

![Heart Rate Graph]

**FIGURE 4.5 MEAN CARDIAC OUTPUT IN VVIR AND DDD**

![Cardiac Output Graph]

NS = NOT SIGNIFICANT
Table 4.2 MEAN HEART RATES IN DDD AND VVIR

<table>
<thead>
<tr>
<th>TIME (MINUTES)</th>
<th>MEAN HEART RATE VVIR</th>
<th>MEAN HEART RATE DDD</th>
<th>% INCREASE FROM DDD TO VVIR</th>
<th>SIGNIFICANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>72.5</td>
<td>74.5</td>
<td>-3</td>
<td>P&lt;0.4</td>
</tr>
<tr>
<td>1</td>
<td>80.5</td>
<td>77.5</td>
<td>4</td>
<td>P&lt;0.36</td>
</tr>
<tr>
<td>2</td>
<td>86</td>
<td>80</td>
<td>7.5</td>
<td>P&lt;0.1</td>
</tr>
<tr>
<td>3</td>
<td>94.5</td>
<td>83</td>
<td>14</td>
<td>P&lt;0.025</td>
</tr>
<tr>
<td>4</td>
<td>102</td>
<td>88</td>
<td>16</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td>5</td>
<td>107</td>
<td>93</td>
<td>15</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td>6</td>
<td>112</td>
<td>100</td>
<td>12</td>
<td>P&lt;0.045</td>
</tr>
<tr>
<td>7</td>
<td>116</td>
<td>114</td>
<td>2</td>
<td>P&lt;0.67</td>
</tr>
<tr>
<td>8</td>
<td>117</td>
<td>127</td>
<td>-8</td>
<td>P&lt;0.57</td>
</tr>
</tbody>
</table>
4.5 DISCUSSION

In this study the addition of AV synchrony has produced no significant difference in exercise times or peak cardiac output. This concurs with the results of others (Pehrsson, 1983; Fananapazir et al, 1983c; Kristensson et al, 1985; Linde-Edelstam et al, 1992a).

Cardiac output at rest was significantly higher during dual chamber pacing, this suggests the atrial contribution diminishes with increasing heart rate in agreement with others (Karlof, 1975; Ogawa et al, 1978; Fananapazir et al, 1983c). Thus, it could be expected that the dual chamber pacemakers may have higher cardiac outputs during the early phase of exercise (Kalof, 1975; Krisstensson et al, 1985; Lau 1990).

Unfortunately, the plots of mean cardiac output (figure 4.4) obtained during this study are virtually superimposed during the whole phase of exercise. Thus, the expected benefit from DDD pacing during the early phase of exercise was not shown. Although, if individual plots are examined (figure 4.6-4.13) then some patients (patients one, two, three, four and six) do have a higher cardiac outputs with DDD pacing during the first few minutes of exercise. Therefore, success or failure in demonstrating the advantage of DDD pacing at low exercise levels could reflect the small patient numbers involved in pacing studies. Interestingly, these patients were the older patients in the group. The clinical implications for pacemaker implantation in children and implies they have less reliance on their atrial contribution. Therefore, providing they do not develop pacemaker syndrome their is little detriment from VVIR pacing until they are of sufficient size to implant an atrial lead.
One possible reason for the failure of this study to demonstrate a haemodynamic advantage can be seen from the mean heart rate plots (figure 4.5). These show a more aggressive rate response during VVIR pacing, particularly during the early phase of exercise which may offset any advantage from the atrial contribution. Although, it could be argued that these higher heart rates would require more energy to maintain which may cause problems with more prolonged exercise. This would not have occurred in the studies by Karlof, 1975 and Krisstensson et al, 1985 as they used rate matched VVI pacing.

In addition, little is known about the influence of exercise on the optimal AV delay. It has been presumed because the PR interval shortens on exercise that the AV delay should too, though haemodynamic data remains in conflict (Mehta et al, 1989; Ritter et al, 1989; Ryden et al, 1988; Haskell et al, 1988). A rate adaptive AV delay has advantages as it permits an increase in the 2:1 point and thus allows a higher upper rate limit to be programmed, therefore it was used in this study. However, this may mean that, what was an optimal delay at rest became unphysiological on exercise and thus some of the atrial contribution lost.

The fact that some patients did gain an increase in cardiac output from dual chamber pacing may mean that a search should be made for these patients. It is well known that the haemodynamic effect of a correctly timed atrial contraction has a greater effect in the presence of mitral stenosis and myocardial hypertrophy than in normal hearts (Stott et al, 1970; Benchimol et al, 1965c). The situation is not quite so clear in patients with failing hearts where the atrial contribution was initially felt to be significant, but data from
Greenberg et al, 1979 contradicted this, having shown greater effects in hearts with normal filling pressures. Therefore two patient groups to further investigate are hypertensives and patients with heart failure. In this study only one of the patients who gained some benefit from the atrial contribution had a low ejection fraction.

4.6 CONCLUSION

There appears to be no difference in cardiac output between dual chamber pacing and ventricular rate responsive pacing at peak exercise or at low levels of exercise equivalent to normal daily activities. The main criticism that might be levelled at this study is the use of rate adaptive AV delay which could diminish the atrial contraction at higher heart rates. Further investigations will need to be undertaken to exclude these factors and to determine whether particular patient groups benefit from AV synchrony.
FIGURE 4.6.1 PATIENT 1 CARDIAC OUTPUT IN DDD AND VVIR

FIGURE 4.6.2 PATIENT 1 HEART RATE IN DDD AND VVIR
FIGURE 4.7.1 PATIENT 2 CARDIAC OUTPUT IN DDD AND VVIR

FIGURE 4.7.2 PATIENT 2 HEART RATE IN DDD AND VVIR
FIGURE 4.8.1 PATIENT 3 CARDIAC OUTPUT IN DDD AND VVIR

FIGURE 4.8.2 PATIENT 3 HEART RATE IN DDD AND VVIR
FIGURE 4.9.1 PATIENT 4 CARDIAC OUTPUT IN DDD AND VVIR

FIGURE 4.9.2 PATIENT 4 HEART RATE IN DDD AND VVIR
FIGURE 4.10.1 PATIENT 5 CARDIAC OUTPUT IN DDD AND VVIR

FIGURE 4.10.2 PATIENT 5 HEART RATE IN DDD AND VVIR
FIGURE 4.11.1 PATIENT 6 CARDIAC OUTPUT DDD AND VVIR

![Cardiac Output Graph]

FIGURE 4.11.2 PATIENT 6 HEART RATE DDD VVIR

![Heart Rate Graph]
FIGURE 4.12.1 PATIENT 7 CARDIAC OUTPUT DDD AND VVIR

FIGURE 4.12.2 PATIENT 7 HEART RATE IN DDD AND VVIR
FIGURE 4.13.1 PATIENT 8 CARDIAC OUTPUT DDD AND VVIR

FIGURE 4.13.2 PATIENT 8 HEART RATE DDD AND VVIR
CHAPTER 5: THE IMPORTANCE OF MAINTAINING ATRIOVENTRICULAR SYNCHRONY DURING EXERCISE; SHOULD THE AV DELAY BE FIXED OR RATE ADAPTIVE?

5.1 AIMS

The purpose of this chapter is to explore the role of an optimally timed atrial contraction during exercise, in normal and impaired left ventricles and address the deficiencies of chapter four.

5.2 INTRODUCTION

In normal subjects the PR interval usually decreases with increasing heart rate brought on by exercise (Luceri et al, 1990). From the literature, the optimal AV delay at rest is 150 ms (Sowton, 1965) but is this the optimal AV delay on exercise?

Whether the paced AV delay should shorten (Mehta et al, 1989; Ritter et al, 1989; Igawa et al, 1990) on exercise or remain fixed (Ryden et al, 1988; Haskell et al, 1988) is a matter for debate with work supporting either. However, none of these studies attempted to individually optimise the AV delay and compared cardiac outputs and exercise times at each AV delay which may have been optimal only for some of the patients. In practice, the rate adaptive AV delay is switched on to ensure a sufficient margin between the upper rate limit and the 2:1 point.
From chapter 4 it has been seen that except for at rest, VVIR pacing is equal to atrioventricular pacing in normal hearts using a rate adaptive AV delay, optimised at rest. However, the heart rate during the early phase of exercise was significantly higher in the VVIR pacing mode and this could have offset the advantage of AV synchrony.

It was the purpose of work described in this chapter to evaluate a correctly timed atrial contraction throughout the whole of exercise in patients with a normal myocardium and those with left ventricular impairment. The haemodynamic contribution of an optimised AV delay was assessed by comparing it with a very short AV delay which effectively eliminates the atrial contraction. To permit a comparison between the best and worst case scenarios. In addition, a study has been made between a fixed and a rate adaptive AV delay.

5.3 METHODS

5.3.1 PATIENTS

Patients were recruited providing they had first degree heart block or higher, with no evidence of atrial flutter/fibrillation and were chronotropically competent. All were able to complete a maximal exercise programme and had to have pacemakers with an AV delay which was programmable down to 31 msec.

Prior to the day of study the AV delay was optimised using the echoDoppler as described in chapter two. Patients with an optimal AV delay of less than 75 msec were excluded from the study as this would be too close to the minimum delay of the pacemakers. They also practised
the shuttle walk to reduce the training effect.

5.3.2 PROTOCOL

On the day of study a MUGA scan was performed to determine the ejection fraction, left ventricular function was considered normal if the ejection fraction was greater than 40%. The Vest was positioned over the left ventricle as in chapter two and the patients underwent three shuttle walking tests with three options for AV delay synchronisation selected at random;

i) Rate adaptive AV delay activated (AV delay optimised at rest).

ii) Fixed A-V delay (optimised at rest).

iii) Short AV delay (31 msec) "Simultaneous AV pacing".

The rate adaptive AV delays used vary depending upon the pacemakers implanted (see chapter 4). Twenty minutes rest was allowed between each test.

Graphs of cardiac output of heart rate against time were then plotted looking for the point where the cardiac outputs crossed and the heart rate at which this point occurred.

5.4 RESULTS

Eight patients were studied, 5 male and 3 female, mean age 56 years (range 27-74) with a mean ejection fraction of 49 % (range 34-64%). Patient characteristics are shown in table 5.1.
**TABLE 5: PATIENT CHARACTERISTICS**

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>AGE</th>
<th>SEX</th>
<th>ECG</th>
<th>AETIOLOGY</th>
<th>PACEMAKER</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>F</td>
<td>47%</td>
<td>CHB</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>M</td>
<td>39%</td>
<td>CHB</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>M</td>
<td>33%</td>
<td>CHB</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>M</td>
<td>39%</td>
<td>CHB</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>M</td>
<td>34%</td>
<td>CHB</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>M</td>
<td>44%</td>
<td>HIB</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>33</td>
<td>M</td>
<td>55%</td>
<td>CHB</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>F</td>
<td>64%</td>
<td>CHB</td>
<td></td>
</tr>
</tbody>
</table>

**IHD = Ischemic Heart Disease, CHB = Complete Heart Block, CTP = Conductance Tissue Property, EF = Ejection Fraction**
Only patient 1 had a history of hypertension with left ventricular hypertrophy on echocardiography. At rest, as expected, the relative cardiac output was higher in DDD than simultaneous AV pacing, 43±12 EDV/M to 38±11 EDV/M (P<0.007). No significant difference at peak exercise was found between simultaneous AV and DDD pacing in total exercise time (7.8±1.5 minutes versus 7.7±1.5 minutes - P<0.47) or in peak relative cardiac output (67.8±18 EDV/M versus 72±18 EDV/M - P<0.2) or peak heart rate (132±12 bpm versus 127±17 bpm - P<0.1) respectively.

When the whole of exercise is examined it can be seen that the heart rates are significantly higher during simultaneous AV pacing than in DDD, although not significantly higher at peak exercise (Table 5.2 and Figure 5.4). If cardiac output is examined it can be seen that cardiac output is higher during the first 5 minutes of exercise although not significantly so.

Of particular interest is the point where the cardiac output plots for the two pacing modes intersect. This indicates the point where the atrial contribution loses significance. For three of the patients (6 and 4) who have relatively low ejection fractions (34% and 35%) and in the patient with hypertension (patient 1), DDD pacing with an optimal AV delay is superior throughout the whole of exercise. In another two (patient 5 and 8), as expected, there is a crossover point at heart rates of approximately 100 bpm. In another two patients (2 and 3), the atrial contribution assumed greater significance after the first few minutes of exercise, the reasons for this are unclear. In the remaining patient (7) the atrial contribution was not significant during the whole phase of exercise, in fact simultaneous AV pacing was superior as peak exercise was approached.
FIGURE 5.1 CARDIAC OUTPUT IN DDD AND AV.SIMULTANEOUS PACING

FIGURE 5.2 TOTAL EXERCISE TIME IN DDD AND AV.SIMULTANEOUS PACING
FIGURE 5.3 MEAN HEART RATE IN DDD AND AV SIMULTANEOUS PACING

* = P < 0.05

FIGURE 5.4 MEAN CARDIAC OUTPUT IN DDD AND AV SIMULTANEOUS PACING

NS = NOT SIGNIFICANT
<table>
<thead>
<tr>
<th>TIME (MINS)</th>
<th>MEAN HEART RATE Simultaneous AV</th>
<th>MEAN HEART RATE DDD</th>
<th>% INCREASE WITH Simultaneous AV STATISTICAL SIGNIFICANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>REST</td>
<td>84±7</td>
<td>84±6</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.6</td>
</tr>
<tr>
<td>1</td>
<td>92±10</td>
<td>87±8</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.08</td>
</tr>
<tr>
<td>2</td>
<td>95±9</td>
<td>90±8</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>3</td>
<td>98±10</td>
<td>93±9</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>4</td>
<td>102±12</td>
<td>97±9</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.1</td>
</tr>
<tr>
<td>5</td>
<td>108±10</td>
<td>102±8</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.02</td>
</tr>
<tr>
<td>6</td>
<td>115±12</td>
<td>109±9</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.1</td>
</tr>
<tr>
<td>7</td>
<td>120±14</td>
<td>120±9</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.8</td>
</tr>
<tr>
<td>8</td>
<td>129±13</td>
<td>130±13</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.3</td>
</tr>
<tr>
<td>TIME (MINS)</td>
<td>MEAN CARDIAC OUTPUT (EDV/M) Simultaneous AV</td>
<td>MEAN CARDIAC OUTPUT (EDV/M) DDD</td>
<td>% INCREASE WITH DDD</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------</td>
<td>---------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>REST</td>
<td>40±10</td>
<td>44±10</td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td>46±11</td>
<td>51±11</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>50±11</td>
<td>53±11</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>51±9</td>
<td>56±10</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>57±10</td>
<td>59±10</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>59±14</td>
<td>61±10</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>63±12</td>
<td>62±13</td>
<td>-1.5</td>
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<tr>
<td>7</td>
<td>69±18</td>
<td>66±19</td>
<td>-4</td>
</tr>
<tr>
<td>8</td>
<td>74±21</td>
<td>73±20</td>
<td>-1.3</td>
</tr>
</tbody>
</table>
It has been demonstrated that the atrial contribution to left ventricular contraction is maximal at rest and diminishes with increasing heart rates on exercise. This study has investigated the value of a correctly timed atrial contraction in patients with normal and abnormal left ventricular function, particularly looking for the point where the atrial contraction ceased to be important and what rate this typically occurs. It can be seen that in most patients the atrial contribution improved cardiac output for at least some of the exercise period and this significance was individually variable. The point where it usually ceased to be of value depended on the individual but was usually at a rate of less than 100 bpm. However, in patients with ejection fractions less than 40%, its contribution to cardiac output was notable throughout the whole of the exercise period.

As most patients studied had a Minuet pacemaker, whose AV delay is fixed until heart rates greater than 120 bpm, it was not possible to fully evaluate the rate adaptive AV delay. However, in patient 1 (who had a chorus RM) the rate adaptive AV delay can be seen to be detrimental, initially the cardiac output is comparable to the fixed AV delay but as exercise progresses and the AV delay shortens there is a deterioration in cardiac output.

In the patients with impaired left ventricular function, the cardiac output was greater during the whole exercise period, where DDD was compared with simultaneous AV pacing. This demonstrates the importance of AV synchrony in these patients and confirms the need for AV delay optimisation. As such patients rarely need a high upper rate, a fixed AV delay which will constrain the upper rate limit is probably ideal. This is in agreement with normal
responses in subjects with heart failure (Luceri et al, 1990) who were shown to have no statistically significant shortening of the PR interval.

It is of interest that heart rates during simultaneous AV pacing are approximately 6% higher. This suggests the heart is attempting to compensate for the reduced cardiac output due to suboptimal AV delay programming, possibly by neurohumoral mechanisms. If the percentage increase in heart rate during simultaneous AV pacing is combined with the increase in cardiac output during DDD pacing. Then this gives an implied value for the atrial contribution to cardiac output of 10% at rest increasing to a maximum of 17% during the first minute of exercise. This value then gradually decreases until of no significance at rates of greater than 110 bpm. This confirms that the atrial contraction is significant at low work loads and this is of the order of 10-20% as anticipated. However, when compared with the almost 100 percent increase in cardiac output at peak exercise this is of little overall significance in patients with good left ventricular function.

These findings have implications for programming of rate adaptive AV delays. Current algorithms for rate adaptive AV delay shortening achieve this in two different ways. Either they adopt a linear decrease between the maximum and minimum value (Chorus, ELA) or they have a sudden shortening at higher rates (Minuet, Medtronic). In view of the above, an improvement could be a fixed AV delay until rates of 110 bpm and then rapidly shorten to a lower value to maximise the upper tracking limit.

The main criticism of the study is that the simultaneous AV pacing is obviously a very extreme form of pacemaker programming and would not be done in clinical practice. It is difficult to
assess the haemodynamic effects of programming the AV delay 25 msec shorter or longer than the optimal and whether this has a clinical implication. However, it can be used to highlight the need for AV delay optimisation in certain patient subgroups.

5.6 CONCLUSION

The atrial contribution to overall cardiac output decreases with increasing heart rate in those with normal myocardial function. Maintenance of a fixed optimal AV delay up to heart rates of 110 bpm with sudden shortening at higher rates, offers the best haemodynamic option in rate adaptive AV delay programming to support a higher upper tracking limit. When cardiac function is impaired, the value of the atrial contraction is maintained throughout the whole of exercise. Thus, extra care should be taken with the programming of AV delays in this group, echoDoppler is recommended.
FIGURE 5.5.1 PATIENT 1 CARDIAC OUTPUT IN DDD AND AV SIMULTANEOUS PACING

- VVIR LIKE
- DDD FIXED AV

FIGURE 5.5.2 PATIENT 1 HEART RATE IN DDD AND AV SIMULTANEOUS PACING

- DDD
- VVIR

FIGURE 5.5.3 EFFECT OF RATE ADAPTIVE AV DELAY

- DDD RATE ADAPTIVE
- "VVIR LIKE"
- DDD FIXED AV
FIGURE 5.6.1 PATIENT 2 CARDIAC OUTPUT IN DDD AND AV SIMULTANEOUS PACING

![Cardiac Output Graph]

FIGURE 5.6.2 PATIENT 2 HEART RATE IN DDD AND AV SIMULTANEOUS PACING

![Heart Rate Graph]
FIGURE 5.7.1 PATIENT 3 CARDIAC OUTPUT IN DDD AND AV SIMULTANEOUS PACING

FIGURE 5.7.2 PATIENT 3 HEART RATE IN DDD AND AV SIMULTANEOUS PACING
FIGURE 5.8.1 PATIENT 4 CARDIAC OUTPUT IN DDD AND AV SIMULTANEOUS PACING

FIGURE 5.8.2 HEART RATE IN DDD AND AV SIMULTANEOUS PACING
FIGURE 5.9.1 PATIENT 5 CARDIAC OUTPUT IN DDD AND AV SIMULTANEOUS PACING

FIGURE 5.9.2 PATIENT 5 HEART RATE IN DDD AND AV SIMULTANEOUS PACING
FIGURE 5.10.1 PATIENT 6 CARDIAC OUTPUT IN DDD AND AV SIMULTANEOUS PACING

FIGURE 5.10.2 PATIENT 6 HEART RATE IN DDD AND AV SIMULTANEOUS PACING
FIGURE 5.11.1 PATIENT 7 CARDIAC OUTPUT IN DDD AND AV SIMULTANEOUS PACING

FIGURE 5.11.2 PATIENT 7 HEART RATE IN DDD AND AV SIMULTANEOUS PACING
FIGURE 5.12.1 PATIENT 8 CARDIAC OUTPUT IN DDD AND AV SIMULTANEOUS PACING

![Cardiac Output Graph]

FIGURE 5.12.2 PATIENT 8 HEART RATE IN DDD AND AV SIMULTANEOUS PACING

![Heart Rate Graph]
CHAPTER 6: OPTIMAL PACING RATES

6.1 AIMS

This chapter describes the effects of increasing pacing rate on cardiac output as measured by the Vest. An attempt is made to define the "optimal rate" for individual patients at different work loads and determine whether this is predictable by straightforward means i.e. related to age or predicted peak heart rate (Astrand formula [220-age]). This has considerable importance in the field of pacing haemodynamics as definitions of chronotropic incompetence are based around the predicted peak rate.

6.2 INTRODUCTION

Cardiac performance during pacing should ideally allow enhancement of myocardial efficiency. The importance of recognised factors such as maintenance of AV synchrony and appropriate AV delay are well established. However, no clear demonstration of the "ideal pacing rate" for any particular activity has yet been defined.

It is commonly assumed that an increase in heart rate will bring about greater cardiac output. This supposition is only correct if the following conditions are met. Firstly, the heart muscle is in a condition to support the increased work load (calcium availability, lack of ischaemia, etc) and secondly sufficient blood can return to the heart to maintain cardiac output. As rate responsive pacemakers are available, the choice of the correct exercise pacing rate is important. However, this cannot be considered in isolation.
FIGURE 6.1.1 RELATIONSHIP BETWEEN CO AND PACING RATE IN Normals

PERCENT CARDIAC OUTPUT

PACING RATE

1 2 3

P2

P2'
FIGURE 6.1.2 RELATIONSHIP IN PATIENTS WITH IMPAIRED VENTRICLES
Fujiyama et al, 1984). Phase II is also narrow or diminished in patients exercising vigorously.

To find the optimal heart rate, consideration has to be given to the fact that the higher the heart rate, the greater the energy consumption. Increasing heart rates not only decreases the efficiency of the heart but reduces the diastolic time. As coronary impedance is lower during diastole than during systole, its average value will increase if the diastolic time is decreased, especially in the endocardial tissue. Coronary blood flow occurs mainly during ventricular diastole, therefore maximising the diastolic interval is important. From this argument it follows that the optimum heart rate is the lowest rate which produces the maximum cardiac output on a treadmill or cycle ergometer, i.e., the end of phase I and the beginning of phase II. It has also been shown that cardiac efficiency decreases with heart rate, being maximum at the lowest heart rate (Nobuaki et al, 1990). It would also take into account changes in the myocardial force-velocity relationship and the Frank-Starling mechanism.

Previous studies in humans have mostly been limited due to invasive methods to the supine position and have not looked at the optimal rate and the effects of varying work loads on this value. It is the intention of this work to look at the effects on cardiac output of increasing pacing rate in the erect position at differing constant work loads.
6.3 METHODS

6.3.1 PATIENTS.

Patients were included if they had dual chamber pacemakers for chronic complete heart block and able to complete both sub maximal and maximal exercise programmes. The pulse generator had to be programmable to pace in VOO mode at rates greater than 200 bpm. Thus devices were restricted to either Medtronic (Elite DDDR or Minuet DDD) or ELA (Chorus I DDD). Patients who were "trained", had severe heart failure or with evidence of intrinsic conduction (to avoid competition between conducted and paced beats) were excluded.

6.3.2 STUDY DESIGN

Twenty patients were recruited. Seven were female with a mean age of 60 years (range 33-71) and mean ejection fraction of 51% (31-76). Patient characteristics are shown in table 6.1. Prior to the day of study a symptom limited maximal exercise stress test was performed on a treadmill, using a Bruce protocol to determine their maximum sinus rate. They practised on the cycle ergometer to determine which work loads could be comfortably managed for twelve minutes. It is recognised phase II is diminished if the subject is exercising maximally.
**TABLE 6.1 PATIENT CHARACTERISTICS**

<table>
<thead>
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*CHB = Complete Heart Block, CTF = Conduction Tissue Fibrosis, EF = Ejection Fraction, IHD = Ischeamic Heart Disease, MVD = Mitral Valve Disease.*
An echocardiogram was performed to measure the subjects' Doppler mitral flow profile paying particular attention to the relationship between the E wave and the pacing spike whilst paced VDD at rest. Superimposition of the E wave on the pacing spike suggests that the filling time is already at its upper limit. Any increase in the heart rate will reduce the diastolic period and will result in diminished ventricular filling time, a decreased cardiac output and under such circumstances a three phase relationship will not be demonstrated. This echo study is only an assumption as no account of the compensation mechanisms of the heart is made. Just one patient was excluded on these grounds.

On the day of study, all were programmed to VVI. A MUGA scan was performed and the Vest positioned over the left ventricle. The study population were then randomised to be exercised on a cycle ergometer against continuous work loads of either 0, 25, 50 or 75 Watts, depending on the individual fitness. A total of three exercise tests of twelve minutes duration were performed by each patient.

The subjects started with a baseline paced heart rate (VVI) of 60 bpm for three minutes to allow a steady state to be established. The paced heart rate was then reprogrammed at one minute intervals by increments of 10 bpm until a rate of 130 bpm was reached and then the rate was reprogrammed by 20 bpm increments to ensure that the maximum sinus rate was exceeded by at least twenty bpm. The overall aim was to give an exercise time of approximately 12 minutes. The number of beats averaged by the Gamma Vest processing software was decided empirically after analysing a subset of patients.
6.4 RESULTS

The end of phase I was defined as the point were 90% of the maximum cardiac output is reached and the end of phase II as the point when the cardiac output has dropped by more than 10%. The requirement for this is twofold and prevents the precise determination of the "optimal rate". Firstly, error intrinsic to the measurement of the cardiac output with the Vest which for a stable cardiac output is ± 2.1% (Tamaki et al, 1987; 1988). Secondly, even in the cases were cardiac output has previously been accurately measured (ie electromagnetic flowmeter) the physiological variations, particularly in exercise, are in the order of ± 10% (Spinelli et al, 1994).

The raw data were analyzed using a median filter varying the window depending on the number of data points. The data is shown in figures 6.11.1 to 6.30.3. Table 6.2 shows the limits of phase II, the optimal rate lying between these points (graphically figures 6.2-6.5). The mean range of these rate bands was 68-134 bpm at 0 Watts, 89-148 bpm at 25 Watts, 99-156 bpm at 50 Watts and 108-157 bpm at 75 Watts. The mean point for each band was calculated and was 96±20 bpm [95% Confidence Intervals (CI); 84-108 bpm] at 0 watts, 118±25 bpm [95% CI; 106-130 bpm] at 25 watts (P<0.01), 129±22 bpm [95% CI; 118-140 bpm] at 50 watts (P<0.008) and 134±21 bpm [95% CI; 115-153 bpm] at 75 watts (P<0.3) figure 6.6. To assess whether this mean rate was easy to predict by straightforward means a correlation with age and predicted peak heart rate (Astrand formula 220-age) was performed (figures 6.7-6.10).
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FIGURE 6.2 OPTIMAL RATE BANDS AT 0 WATTS

OPTIMAL RATE BAND

PATIENT
FIGURE 6.3 OPTIMAL RATE BANDS AT 25 WATTS
FIGURE 6.4 OPTIMAL RATE BANDS AT 50 WATTS
FIGURE 6.5 OPTIMAL RATE BANDS AT 75 WATTS
FIGURE 6.6 MEAN OPTIMAL RATE AT EACH WORK LOAD

MEAN OPTIMAL RATE

P<0.01  P<0.008  NS

WORK LOAD (WATTS)

0  25  50  75
Figure 6.7 Correlation at 0 Watts between Age and Predicted Peak Heart Rate

\[ y = -0.146x + 105.341, \text{ R-squared: } 0.004 \]

\[ y = 0.146x + 73.18, \text{ R-squared: } 0.004 \]
Figure 6.8 Correlation at 25 Watts between Age and Predicted Peak Heart Rate

\[ y = 1.396x + 35.512, \text{ R-squared: .336} \]

\[ y = -1.396x + 342.724, \text{ R-squared: .336} \]
SURE 6.9 CORRELATION AT 50 WATTS BETWEEN AGE AND PREDICTED PEAK HEART RATE

\[ y = 0.06x + 125.926, \text{ R-squared: .001} \]

\[ y = -0.06x + 139.145, \text{ R-squared: .001} \]
Figure 6.10 Correlation at 75 watts between age and predicted peak heart rate

\[ y = 0.196x + 123.657, \text{ R-squared: 0.01} \]

\[ y = -0.196x + 166.74, \text{ R-squared: 0.01} \]
6.5 DISCUSSION

The curves generated above confirm the three phase relation between increasing heart rate and cardiac output at constant exercise. The curves can be seen to vary individually with some patients producing a typical three phase relationship at all work loads. However, in some patients the pacing rate does not start sufficiently low, particularly at low work loads, or alternatively go high enough to demonstrate the three phase relationship.

The "optimal rate" has been defined as the lowest rate at which maximum cardiac output is achieved ie the onset of phase II. However, inaccuracies in the data mean that calculation of this exact point was unrealistic. It has been possible to determine the boundaries of phase II and the true "optimal rate" will lie within this rate band. The mean of the optimal rate bands, which it can be seen from the plots of cardiac output and heart rate (figure 6.11-6.30) is higher than the optimal rate, has been calculated at each work load. This mean rate has been shown to vary both individually and also with the work load, increasing at greater work loads in a non linear fashion. Of more clinical concern, is the lack of correlation between optimal pacing rate and age or predicted peak heart rate (Astrand's formula). Prediction of upper heart rates by straightforward means, as used extensively in the programming of rate responsive pacemakers have considerable inaccuracy.

The variability of this mean rate demonstrates that the "optimal rate" for one individual will be sub optimal in another. With current methods rate responsive pacing could produce a cardiac output which may be in phase I or alternatively well into phase II.
This latter rate will require more energy to sustain but the cardiac output will be maintained providing the patient has sufficient cardiac reserve. However, in patients with heart failure where phase II may be reduced or absent, an elevated rate will push them into phase III. This gives rise to the concept that it can be detrimental to over pace a person for a given level of exercise. Indeed, some patients with impaired ventricles, their resting rate may already be optimal and giving them a rate responsive pacemaker would lead to a deterioration in their performance rather than an improvement.

There are many factors that would potentially influence the dynamics of ventricular filling and emptying. These include atrioventricular synchrony, diastolic compliance and variations in the AV and ventriculo-atrial intervals as the heart rate changes (Greenberg et al, 1979; Haskell et al, 1986). Certainly as filling time diminishes, random AV synchrony or well sequenced AV systole can appropriately enhance or detract from stroke volume. This will change not only the stroke volume, but also the stroke work, since filling pressure and ventricular diameter is altered by variations in AV dynamics.

6.6 LIMITATIONS OF THE STUDY

This work applies to single chamber rate responsive pacing and is the first step towards understanding the more complex interrelationships between preload, afterload, electromechanical delays and pacing rate which occur with DDDR pacing. Further work needs to be done during DDD pacing although this is technically harder because the extra timing cycles necessary to permit correct dual chamber function (atrial refractory period, ventricular refractory period, post ventricular atrial refractory period) will reduce the
upper rate limit. In addition, to difficulties determining the correct AV delay and the degree of shortening which should occur on exercise.

The "optimal rate" is defined in relation to cardiac parameters and fails to take into account the whole body and whether the cardiac output at the "optimal rate" is sufficient to meet metabolic requirements of the entire subject or any component organ systems. Thus a critical organ failure that will cause dysfunction can be present when the subject is otherwise optimised. This method of defining "optimal rate" however means that cardiac function should never be compromised for instance in the midst of cardiac ischaemia, hypoxia or arrhythmias. The need for increased cardiac output may not be available, indeed, in the heart's effort to meet these requirements, further myocardial damage or arrhythmias may be produced. Therefore, although the "optimal rate" may not be optimal for the whole body, it is likely to provide a guide to the optimisation of cardiac function and a safety mechanism to prevent a potentially catastrophic pacemaker mediated tachycardia. To establish the correlation between this "optimal rate" and clinical benefit to the patient it will be necessary to perform chronic quality of life surveys.

6.7 POTENTIAL FOR CLINICAL APPLICATION

In a clinical context the optimal pacing rate is at the onset of phase II and under ideal circumstances the aim should be to maintain the pacing rate at this level. Recognition of this limit by a sensor driven pacemaker would theoretically maximise the pacing
performance without compromising the patient.

The right ventricular stroke volume can be determined by continuous measurement of intracardiac impedance (Rushmer et al, 1963; Geddes et al, 1966; Baan et al 1984; McKaye et al, 1984; Salo et al, 1986), at end-diastole the right ventricle is full of blood and thus impedance is low. As systolic ejection occurs the blood volume decreases and thus impedance increases. Initially, this impedance signal was measured from the distal electrode to the pacemaker can but adaptations by Chirife 1987 mean that it can be measured using a standard bipolar pacing electrode. This principle offers possibilities for a servo mechanism and self optimisation of pacing rate.

6.8 CONCLUSION

A three phase relation exists between increasing heart rate on exercise as well as at rest. The "optimal rate" is defined as the lowest heart rate at which maximum cardiac output is reached ie onset of phase II. However, inaccuracies in the data prevents the calculation of this point. Thus phase II has been defined and this can be seen to be individually variable and not predictable by straightforward measures. This has considerable implications both for patient selection for rate responsive pacemakers as well as programming and the setting of upper rate limits. The self optimisation of the rate by a rate responsive pacemaker being the ultimate aim.

The right ventricular stroke volume waveforms produced from the standard bipolar electrode are similar to the activity curves generated by the Vest. In chapter 7 a method
of using this data to control a pacemaker sensor so that it is always at the "optimal rate"
is evaluated.
FIGURE 6.12.1 PATIENT 2 OPTIMAL RATE BAND 50 WATTS

FIGURE 6.12.2. PATIENT 2 OPTIMAL RATE BAND 25 WATTS

FIGURE 6.12.3 PATIENT 2 OPTIMAL RATE BAND AT 0 WATTS
FIGURE 6.13.1 PATIENT 3 OPTIMAL RATE BAND AT 25 WATTS

FIGURE 6.13.2 PATIENT 3 OPTIMAL RATE BAND AT 0 WATTS
FIGURE 6.15.1 PATIENT 5 OPTIMAL RATE BAND AT 50 WATTS

FIGURE 6.15.2 PATIENT 5 OPTIMAL RATE BAND 25 WATTS

FIGURE 6.15.3 PATIENT 5 OPTIMAL RATE BAND 0 WATTS
FIGURE 6.17.1 PATIENT 7 OPTIMAL RATE BAND AT 50 WATTS

FIGURE 6.17.2 PATIENT 7 OPTIMAL RATE BAND AT 25 WATTS

FIGURE 6.17.3 PATIENT 7 OPTIMAL RATE BAND AT 0 WATTS
FIGURE 6.18.1 PATIENT 8 OPTIMAL RATE BAND AT 50 WATTS

FIGURE 6.18.2 PATIENT 8 OPTIMAL RATE BAND AT 25 WATTS

FIGURE 6.18.3 PATIENT 8 OPTIMAL RATE BAND AT 0 WATTS
FIGURE 6.19.1 PATIENT 9 OPTIMAL RATE BAND AT 50 WATTS

FIGURE 6.19.2 PATIENT 9 OPTIMAL RATE BAND 25 WATTS

FIGURE 6.19.3 PATIENT 9 OPTIMAL RATE BAND AT 0 WATTS
FIGURE 6.20.1 PATIENT 10 OPTIMAL RATE 50 WATTS

FIGURE 6.20.2 PATIENT 10 OPTIMAL RATE BAND AT 25 WATTS

FIGURE 6.20.3 PATIENT 10 OPTIMAL RATE BAND AT 0 WATTS
FIGURE 6.21.1 PATIENT 11 OPTIMAL RATE BAND 75 WATTS

Mean Optimal Rate

90% Cardiac Output

Phase I Phase II Phase III

HEART RATE

FIGURE 6.21.2 PATIENT 11 OPTIMAL RATE BAND AT 50 WATTS

Mean Optimal Rate

90% Cardiac Output

Phase I Phase II Phase III

HEART RATE

FIGURE 6.21.3 PATIENT 11 OPTIMAL RATE BAND AT 25 WATTS

Mean Optimal Rate

90% Cardiac Output

Phase II Phase III

HEART RATE
FIGURE 6.22.1 PATIENT 12 OPTIMAL RATE BAND 50 WATTS

![Graph showing cardiac output vs heart rate for 50 watts with phase I and phase II markers.]

FIGURE 6.22.1 PATIENT 12 OPTIMAL RATE BAND 25 WATTS

![Graph showing cardiac output vs heart rate for 25 watts with phase I and phase II markers.]

FIGURE 6.22.3 PATIENT 12 OPTIMAL RATE BAND 0 WATTS

![Graph showing cardiac output vs heart rate for 0 watts with phase I and phase II markers.]

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FIGURE 6.24.1 PATIENT 14 OPTIMAL RATE BAND 75 WATTS

![Graph showing cardiac output vs heart rate for Phase I, II, and III, with 90% cardiac output and mean optimal rate marked.]

FIGURE 6.24.2 PATIENT 14 OPTIMAL RATE BAND 50 WATTS

![Graph showing cardiac output vs heart rate for Phase I, II, and III, with 90% cardiac output and mean optimal rate marked.]

FIGURE 6.24.3 PATIENT 14 OPTIMAL RATE BAND 25 WATTS

![Graph showing cardiac output vs heart rate for Phase I, II, and III, with 90% cardiac output and mean optimal rate marked.]

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**FIGURE 6.26.1 PATIENT 16 OPTIMAL RATE 25 WATTS**

Mean Optimal Rate

90% Cardiac Output

**FIGURE 6.26.2 PATIENT 16 OPTIMAL RATE 0 WATTS**

Mean Optimal Rate

90% Cardiac Output

Phase I  Phase II  Phase III

Heart Rate

Cardiac Output (EDV/mL)
FIGURE 6.27.1 PATIENT 17 OPTIMAL RATE BAND 50 WATTS

FIGURE 6.27.2 PATIENT 17 OPTIMAL RATE BAND 25 WATTS

FIGURE 6.27.3 PATIENT 17 OPTIMAL RATE BAND 0 WATTS
FIGURE 6.28.1 PATIENT 18 OPTIMAL RATE 50 WATTS

Mean Optimal Rate

90% Cardiac Output

Phase I  Phase II  Phase III

HEART RATE

FIGURE 6.28.2 PATIENT 18 OPTIMAL RATE BAND 25 WATTS

Mean Optimal Rate

90% cardiac Output

Phase II  Phase III

HEART RATE

FIGURE 6.28.3 PATIENT 18 OPTIMAL RATE BAND 0 WATTS

Mean Optimal Rate

90% Cardiac Output

Phase I  Phase II  Phase III

HEART RATE
FIGURE 6.29.1 PATIENT 19 OPTIMAL RATE BAND 50 WATTS

FIGURE 6.29.2 PATIENT 19 OPTIMAL RATE BAND 25 WATTS

FIGURE 6.29.3 PATIENT 19 OPTIMAL RATE BAND 0 WATTS
CHAPTER 7: "ACTIVE TIME": A METHOD FOR OPTIMAL RATE DETERMINATION?

7.1 AIMS
This chapter intends to expand the concepts of "optimal rate" developed in chapter 6 by creating a method for a sensor driven pacemaker to dynamically control its upper rate limit. The pacing rate will then never enter phase III and hence detrimental haemodynamics are avoided. The concept of "total active time" will be introduced.

7.2 INTRODUCTION
As shown in chapter 6, a three phase relation exists between increasing heart rate and cardiac output. The "optimal rate" was defined as being the lowest rate at which peak cardiac output is reached. Unfortunately, it was not possible to calculate this rate precisely but an optimal rate band could be defined. The mean of this "optimal rate" band varied with each individual and work load and is not correlated to age or peak heart rate as predicted by the Astrand formula (220-age). How can clinicians set up an appropriate rate on a rate responsive pacemaker in the light of this?

In a normal person, exercise results in increased circulating catecholamines, reduced pre-ejection interval, increased dp/dt max, decreased ejection time and decreased -dp/dt max. All these decrease the time when the ventricle could be described as active, that is from the pacing spike (or the peak R wave in intrinsic conduction) to the period of isovolumic relaxation (Active Time). The changes that occur with exercise are associated with an
increase in heart rate, which in turn decrease the passive time (the diastolic phase). At maximum load (peak exercise) the passive time is very small with only fast filling phase in evidence. This effect manifests itself in the Doppler mitral velocity profile as a superimposition of the E wave on the A wave at peak exercise. If the fast filling phase is included as part of the active time and this is called the Total Active Time (TAT). It can be seen that the maximum heart rate at peak exercise is primarily determined by the resting TAT and the heart's capacity to reduce this with exercise. This rate is determined by systolic function, the diastolic function and the ability of the venous system to refill the right and left ventricles during the fast filling phase (atrial-ventricular pressure gradient).

The parameter it is proposed to extract from the output of the haemodynamic sensor is TOTAL ACTIVE TIME; the total time that would elapse from the beginning of the cardiac contraction (pacing spike or peak of the R wave for intrinsic beats) to the end of the filling phase, provided that the ventricles are refilled at the fast filling rate.

Figure 7.1 illustrates how the TAT is obtained from the intraventricular volume waveform. It shows an ECG synchronised with an intraventricular volume waveform. TAT (dashed line in figure 7.1) is calculated as the time between pacing spike (or the peak of the R wave during sinus rhythm) and the intersection between the linear regression line (using the least squares errors technique) of the fast filling phase points and the end-diastolic volume from the previous beat (solid straight line in figure 7.1). The points that belong to the fast filling phase are defined as the points that lie between the end systolic volume (ESV) plus 5% of the stroke volume (SV) and the ESV plus 30% of the SV. To maintain haemodynamic stability, pacing must be prevented from
encroaching on the patient's TAT. It is clear that if insufficient time is allowed (after the pacing spike or the peak of the R wave in an intrinsic beat) before another pacing spike is issued, the heart will not be able to fill to its previous volume and the cardiac output will not be sustained.

The TAT at rest in milliseconds can be transformed to bpm using the formula, and giving a prediction of the optimal pacing rate - the Active Time Heart Rate (ATHR).

\[
\text{ATHR} = \frac{60,000}{\text{TAT}} \text{ [bpm]}
\]

In patients with very depressed systolic function, the low stroke volume generated by these ventricles prompts homeostatic responses to increase the heart rate to maintain the cardiac output. However, filling occurs so late in the cardiac cycle due to impaired diastolic function, it is superimposed on the next deactivation cycle. At the same time depolarisation is not instantly followed by contraction (due to a long pre ejection phase) allowing part of the filling phase to take place during the electro-mechanical delay time. Therefore patients with systolic dysfunction have little or no heart rate reserve at rest and further increases in the electrical rate will only trigger a disadvantageous electro-mechanical pattern which compensatory mechanisms are unlikely to offset. In these patients the dynamic control of upper rate limit will be important with the real potential for detriment rather than benefit from current rate adaptive sensors.

The aim of this study is to calculate the ATHR from the data obtained in chapter 6. Then to determine the Haemodynamic Maximum Sensor Rate (HMSR) which will be defined as the intersection of the ATHR and the pacing rate. The objective being to use the
HMSR to dynamically limit the upper rate limit so that the pacing will always be within phase II and any increase in pacing rate will result in an increase in cardiac output. Ultimately these will be incorporated into a pacemaker sensor algorithm in order to achieve a closed loop control system.

7.2 METHODS

The patients have been exercised at three different work loads and the pacing rate increased until in excess of their peak heart rate and their ATHR max by at least 20 bpm. In addition, patients with no heart rate reserve were excluded. This was accomplished by looking at the mitral flow doppler velocities profile and if the peak of the E wave occurred very close to the next electrical deactivation while pacing VDD at rest. This assessment is only an approximation because it does not allow for the compensation capabilities of the heart during exercise. Another subset of patients to be excluded were those where the E/A ratio is < 1 which implies increased significance of the atrial contraction.

During the study, as well as collecting ejection fraction and cardiac output, the Vest also gives volume waveform data from which these calculations have been made. Similar to those which can be produced from a standard bipolar electrode. The ATHR can be calculated for these volume waveforms. These ATHR's can be plotted with the paced heart rate against time. The point of intersection of these two heart rates will be defined as the haemodynamic maximum sensor rate (HMSR). This will then be compared with the data obtained in chapter 6 and in order to demonstrate that the HMSR lies within the
lower rate of the optimal rate band and its mean.

7.4 RESULTS

Figure 7.2 - 7.21 show predicted ATHR from the waveform data collected by the Vest accompanied by the actual paced heart rates. Table 7.1 demonstrates how the H MSR varies with workload and individually. As expected the H MSR increases with increasing workload.

The mean H MSR at 0 Watts 90±6 bpm (95% confidence intervals 87-93), 25 Watts 97±9 bpm (95% confidence intervals 92-101 bpm) P<0.002, 50 Watts 106±11 bpm (95% confidence intervals 100-112 bpm) P<0.007 and 75 watts load is 115±12 bpm (95% confidence intervals 102-128 bpm) P<0.003.

The H MSR was then compared with the optimal rate bands obtained in chapter 6 for each workload. Table 7.2 and 7.3 present the data for comparison. Then to demonstrate the relationship between the optimal rate, which lies between the lower rate of the optimal rate band and its mean, and the H MSR. The three heart rates were given a number (optimal rate band lower rate = 1, mean optimal rate band = 3, H MSR = 2) and then ranked. The mean value of the middle heart rate was calculated and found at 0 Watts to be 2.2, 1.9 at 25 Watts, 1.9 at 50 Watts and 2 at 75 Watts. Showing that the H MSR usually lies within or slightly below the optimal rate band.
TABLE 7.1 Maximum Haemodynamic Sensor Rate at Each Work Load

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<th>75 Watts</th>
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Table 7.3 Comparison of the HMSR and Optimal Rate bands at 50 and 75 Watts

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7.5 DISCUSSION

From the volume waveforms provided by the Vest it has been possible to calculate both the ATHR at each heart rate and the HMSR. This has been shown to significantly increase with increasing work load in agreement with the "optimal rate" data (see chapter 6). In accord with this data the HMSR is individually variable and increases with increasing work load. The HMSR has been shown to lie within or just below phase II for each work load.

It is proposed initially to use the HMSR to dynamically limit the upper rate of activity sensing pacemakers. Therefore, the upper rate will vary depending on the haemodynamic circumstances of the individual patient. Currently, in order to correctly programme an activity sensing pacemaker, it is necessary to perform repeat exercise tests to ensure the rate response slope is appropriate. This can be time consuming and the arbitrary selection of a target heart rate may leave some patients in phase I or alternatively well into phase III. A pacemaker with the ability to determine an upper rate limit thus guaranteeing optimal haemodynamics, is very attractive. The activity sensor's response to prolonged constant exercise should also be improved because as exercise progresses there will be a changes in filling and contractility leading to changes in the HMSR. In addition, it will reduce the sensors over response to certain activities eg staircase descent or environmental stimuli. This will revolutionise rate responsive pacing today.

The author feels that this is the way forward in the development of rate responsive pacemakers, rather than complicating the issue further by developing dual or even triple
sensor devices. This is because although the dual sensors produce a cosmetically better rate response on exercise testing, there is no evidence that this is more physiological. In addition, their increased complexity requires sophisticated algorithms to ensure the rate response is appropriate. This is not failsafe and often the patient can be exposed to the drawbacks of both sensors. Furthermore, the extra technology causes increased battery drain reducing the longevity of the device.

The application of HMSR is not limited to rate responsive pacing but could also extend to dual chamber pacing. As already outlined in chapter 1, chronotropic incompetence is a common syndrome amongst paced patients affecting up to 40% (McBride et al, 1990). It is diagnosed as a failure to reach 60% of predicted peak rate (220-age) but little is known of the natural history of this disorder. Particularly how long it takes for the syndrome to evolve and which part of the chronotropic response is the first to be effected. Therefore, the HMSR could be used to check the rate response of patients thought to have a normal sinus node response. Consistent failure of the sinus rate to reach the HMSR could be used to activate a rate responsive sensor, to ensure an appropriate rate response. In addition, the HMSR could be used to distinguish between those patients diagnosed under current criteria as chronotropically incompetent who are already at their "optimal rate" and those which need rate responsive pacing. This subject is investigated further in chapter 8.

The HMSR's in general are quiet conservative with an average rate of 106 at 50 watts. This provides the clinical reassurance that the paced rate will not be too high. However, concern arises that the HMSR may adversely restrict the maximum heart rate. Although,
in comparisons between DDD and VVIR pacing where the paced rate was a little too slow (Oldroyd et al, 1992) there was no effect on exercise tolerance.

It was the original aim to be able to use the HMSR to determine the optimal rate and hopefully ensure optimal rate haemodynamics. It would appear this was too ambitious, as it has proved difficult to define the optimal rate more accurately than a rate band because of inaccuracies inherent in the data. In addition, even though a constant work load was used this does not mean that the haemodynamics are stable because as the exercise progressed there would be changes caused by fatigue and thus the "optimal rate" will change. The heart rate is held artificially low during the first phase of the exercise period, thus it is impossible to say how this influences the optimal rate haemodynamics. However, it may yet be shown that the optimal rate and the HMSR are correlated.

There also appears to be more to optimal rate than first thought as recent work by Fujimoto et al, 1994. This has shown that short filling times, as seen in patients with NYHA grade IV heart failure at rest or at high pacing rates in patients with normal ventricles, can create very narrow filling jets at high velocities. The filling pressure gradients under these conditions can match those seen during mitral stenosis. Therefore, cardiac output may be increased or maintained at higher pacing rates but at the expense of a pathological increase in preload, due to this pressure gradient.

Unfortunately, this sensor algorithm is not yet commercially available so it is not currently possible to evaluate the HMSR in a practical setting. The data does give strong support for attempting to incorporate this sensor in to a rate responsive pacemaker.
7.6 CONCLUSION

The Haemodynamic Maximum Sensor Rate can be calculated from volume waveform data derived from the Vest. Using impedance, this data can be calculated from a standard bipolar lead. The potential exists to incorporate this into a rate responsive pacemaker in order to provide dynamic control of the maximum heart rate. The maximum paced rate will be limited hence cardiac output will not enter phase III with the consequent detrimental haemodynamics. This will have a major impact on rate responsive pacing. Unfortunately, the clinical evaluation of such an algorithm is awaiting product development.
FIGURE 7.3.1 PATIENT 2 HMSR AT 50 WATTS

Optimal rate band 90-170

FIGURE 7.3.2 PATIENT 2 HMSR AT 25 WATTS

Optimal rate 60-120

FIGURE 7.3.3 PATIENT 2 HMSR AT 0 WATTS

Optimal rate band <60-100
FIGURE 7.4.1 HMSR PATIENT 3 AT 25 WATTS

HEART RATE

ATHR
PACED RATE

FIGURE 7.4.2 PATIENT 3 HMSR AT 0 WATTS

HEART RATE

ATHR
PACED RATE
FIGURE 7.5.1 PATIENT 4 HMSR AT 75 WATTS

FIGURE 7.5.2 PATIENT 4 HMSR AT 50 WATTS

FIGURE 7.5.3 PATIENT 4 HMSR AT 25 WATTS

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FIGURE 7.6.1 PATIENT 5 HMSR AT 50 WATTS

FIGURE 7.6.2 PATIENT 5 HMSR AT 25 WATTS

FIGURE 7.6.3 PATIENT 5 HMSR AT 0 WATTS
FIGURE 7.7.1 PATIENT 6 HMSR AT 75 WATTS

HEART RATE

optimal rate band 130-190

ATHR

PACED RATE

TIME

FIGURE 7.7.2 PATIENT 6 HMSR AT 50 WATTS

HEART RATE

optimal rate band 120-170

ATHR

PACED RATE

TIME

FIGURE 7.7.3 PATIENT 6 HMSR AT 25 WATTS

HEART RATE

optimal rate 90-160

ATHR

PACED RATE

TIME
FIGURE 7.8.1 PATIENT 7 HMSR AT 50 WATTS

optimal rate band 140-190

FIGURE 7.8.2 PATIENT 7 HMSR AT 25 WATTS

optimal rate band 130-150

FIGURE 7.8.3 PATIENT 7 HMSR AT 0 WATTS

optimal rate band 60-130
FIGURE 7.9.1 PATIENT 8 HMSR AT 50 WATTS

FIGURE 7.9.2 PATIENT 8 HMSR AT 25 WATTS

FIGURE 7.9.3 PATIENT 8 HMSR AT 0 WATTONS
FIGURE 7.10.1 PATIENT 9 HMSR AT 50 WATTS

FIGURE 7.10.2 PATIENT 9 HMSR AT 25 WATTS

FIGURE 7.10.3 PATIENT 9 HMSR AT 0 WATTS
FIGURE 7.11.1 PATIENT 10 HMSR AT 50 WATTS

HEART RATE

TIME

FIGURE 7.11.2 PATIENT 10 HMSR AT 25 WATTS

HEART RATE

TIME

FIGURE 7.11.3 PATIENT 10 HMSR AT 0 WATTONS

HEART RATE

TIME

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FIGURE 7.12.1 PATIENT 11 HMSR AT 75 WATTS

optimal rate band 90-190

FIGURE 7.12.2 PATIENT 11 HMSR AT 50 WATTS

optimal rate band 120-190

FIGURE 7.12.3 PATIENT 11 HMSR AT 25 WATTS

optimal rate band 60-140
FIGURE 7.14.1 PATIENT 13 HMSR AT 50 WATTS

FIGURE 7.14.2 PATIENT 13 HMSR AT 25 WATTS

FIGURE 7.14.3 PATIENT 13 HMSR AT 0 WATTS
FIGURE 7.15.1 PATIENT 14 HMSR AT 75 WATTS

Heart Rate vs Time

Optimal rate band 100-130

PACED RATE

ATHR

FIGURE 7.15.2 PATIENT 14 HMSR AT 50 WATTS

Heart Rate vs Time

Optimal rate band 90-140

PACED RATE

ATHR

FIGURE 7.15.3 PATIENT 14 HMSR AT 25 WATTS

Heart Rate vs Time

Optimal rate band 70-110

PACED RATE

ATHR

198
**FIGURE 7.17.1** PATIENT 16 HMSR AT 25 WATTS

- Optimal rate band: 110-180

**FIGURE 7.17.2** PATIENT 16 HMSR AT 0 WATTS

- Optimal rate band: 120-130
FIGURE 7.18.1 PATIENT 17 HMSR AT 50 WATTS

optimal rate band 100->190

FIGURE 7.18.2 PATIENT 17 HMSR AT 25 WATTS

optimal rate band 70-170

FIGURE 7.18.3 PATIENT 17 HMSR AT 0 WATTS

optimal rate band <60-60
FIGURE 7.19.1 PATIENT 18 HMSR AT 50 WATTS

Heart rate vs. time graph with optimal rate band 100-150.

FIGURE 7.19.2 PATIENT 18 HMSR AT 25 WATTS

Heart rate vs. time graph with optimal rate band 60-110.

FIGURE 7.19.3 PATIENT 18 HMSR AT 0 WATTS

Heart rate vs. time graph with optimal rate band 90-140.
FIGURE 7.21.1 PATIENT 20 HMSR AT 50 WATTS

FIGURE 7.21.2 PATIENT 20 HMSR AT 25 WATTS

FIGURE 7.21.3 PATIENT 20 HMSR AT 0 WATTS
CHAPTER 8: COMPARISON OF RATE RESPONSIVE PACING IN THE CHRONOTROPICALLY COMPETENT AND THOSE WITH AN IMPAIRED RATE RESPONSE.

8.1 AIMS

Investigating optimal pacing rate further, this chapter is a comparison of patients who are currently defined as chronotropically incompetent with those who are chronotropically competent. Exercise times and peak cardiac outputs during sinus rhythm and rate responsive pacing are compared. In addition, predicted rate response curves will be drawn using the TAT to assess how the rate response with the theoretical sensor differed between the two modes of pacing.

8.2 INTRODUCTION

The previous two chapters have dealt with the "optimal pacing rate" for a given level of exercise and the lack of correlation of this rate with the predicted peak heart rate (Astrand formula). Current definitions of chronotropic incompetence hinge around failure to reach 60% of this predicted peak heart rate. As already shown the optimal rate is individual. Therefore, failure to reach a set heart rate could represent a disease process and the requirement for a rate responsive pacemaker. Alternatively, the patient could already be at their optimal rate due to impaired ventricular filling and the addition of a rate response may lead to detrimental haemodynamics.
Several studies have been reported in chapter 1 comparing dual chamber rate responsive pacing with dual chamber pacing for both patient groups. These show no significant difference between the pacing modes in chronotropically competent patients (Capucci et al, 1992; Weinhold et al, 1992; Lemke et al, 1992) but increased exercise times in those with chronotropic incompetence (Capucci et al, 1992; Lemke et al, 1992; Sulke et al, 1991). Although the definition of chronotropic incompetence and the amount of improvement was highly variable.

In this chapter the effects of rate responsive pacing is assessed in these two groups of patients using the Vest. In addition, the ATHR was calculated to assess how the sensor would perform in these two patient groups.

8.3 METHODS

8.3.1 PATIENTS

The study was set up as a double blind prospective comparison of the effects of DDD and DDRR on symptoms, maximal exercise capacity and cardiac output in patients with and without chronotropic competence. The patients were recruited pre implant in two groups those who were chronotropically competent and able to reach approximately 70% of their predicted heart rate (Astrands formula 220-age), and those with an impaired rate response who were unable to reach a rate of greater than 100 bpm or 60% of their predicted peak heart rate. This was assessed by a maximal symptom limited exercise test prior to implant. Patients with recent myocardial infarction, significant angina or respiratory
disease, chronic atrial flutter and exercise induced arrhythmias were excluded.

8.3.2 STUDY PROTOCOL

All patients had a dual chamber rate responsive pacemaker. The rate response curves were programmed according to the manufacturer's instructions and correct programming was ascertained during a shuttle walk prior to the day of study. This was also done to reduce the learning effect. At the same time an echocardiogram was performed to establish the optimal AV delay during sensed and paced rhythm and to ensure that the E and the A waves were not superimposed.

On the day of study the patients had a MUGA scan and then the Vest was positioned over their left ventricle. They were then randomised to either DDD or DDDR and programmed by an independent person. They then performed two shuttle walking tests with twenty minutes rest in between.

8.4 RESULTS

Sixteen patients were studied nine chronotropically competent and seven chronotropically incompetent. Eight were male with a mean age 55 years (range 33 - 70 years) and a mean ejection fraction 50 % (range 34 - 64 %). Seven patients had activity sensors (five piezoelectric crystal (Elite), two Accelerometer (Vigor)) and nine had minute ventilation sensors (Chorus RM). Patient characteristics are shown on table 8.1.
## Table 8.1 Patient Characteristics

<table>
<thead>
<tr>
<th>Age Rate</th>
<th>Rate (25% of Predicted)</th>
<th>Rate (40% of Predicted)</th>
<th>Rate (50% of Predicted)</th>
<th>Rate (65% of Predicted)</th>
<th>Rate (80% of Predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>55%</td>
<td>157</td>
<td>18</td>
<td>18</td>
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</tr>
<tr>
<td>56%</td>
<td>160</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>60%</td>
<td>165</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
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<tr>
<td>66%</td>
<td>169</td>
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<td>30</td>
<td>30</td>
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<td>69%</td>
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<td>35</td>
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<tr>
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<td>172</td>
<td>40</td>
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<tr>
<td>74%</td>
<td>176</td>
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<td>181</td>
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<td>184</td>
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<td>75</td>
<td>75</td>
<td>75</td>
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<tr>
<td>87%</td>
<td>205</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
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<td>208</td>
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<tr>
<td>91%</td>
<td>212</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>93%</td>
<td>215</td>
<td>95</td>
<td>95</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>95%</td>
<td>219</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

**Heart Disease** = CHD = Complete Heart Block, CHP = Conduction Hype Reaction, HIB = Blackout

* = Pre Implant Rate, T = Tissue Failure
Two patients originally recruited as chronotropically incompetent were found at the time of study to be chronotropically competent. However, out of clinical interest they are still included in the chronotropically incompetent group. Unfortunately patient 6 had problems with P wave sensing on exercise he is still included as this did not significantly affect the data.

8.4.1 Symptoms

Six patients expressed a preference for one mode and that was for DDDR pacing, all were from the chronotropically incompetent group. None of the others was able to express a preference and this was confirmed by equal Borg scores for each exercise test.

8.4.2 Exercise performance

If all the patients are considered together the peak heart rate was significantly higher during DDDR mode 134 bpm (95% CI; 125-143 bpm) than during DDD pacing 113 bpm (95% CI; 104-122 bpm)(P <0.0006). The total exercise times were 8.7±1.0 mins (95% CI; 8.2-9.2 mins) and 8.8±1.2 mins (95% CI; 8.1-9.4 mins) (P<0.7) (figure 8.1) and the peak cardiac outputs 75±19 EDV/M (95% CI; 65-85 EDV/M) and 78±19 EDV/M (95% CI; 67-88 EDV/M) (P<0.3) (figure 8.2) for DDD and DDDR pacing respectively. Thus the increase in heart rate brought about no significant improvement in haemodynamic parameters when all patients are considered together.
FIGURE 8.1 TOTAL EXERCISE TIME IN DDD AND DDDR PACING

FIGURE 8.2 PEAK CARDIAC OUTPUT DURING DDD AND DDDR
8.4.2.1 Chronotropically Competent Patients

If the patients are then considered in their groups as originally defined then the peak heart rate for the chronotropically competent patients was $123 \pm 12$ bpm (95% CI; 115-133 bpm) and $134 \pm 20$ bpm (95% CI; 120-149 bpm) ($P < 0.02$), peak cardiac output $74 \pm 16$ EDV/M (95% CI; 61-86 EDV/M) and $75 \pm 17$ EDV/M (95% CI; 58-87 EDV/M) ($P < 0.9$) and total exercise time $8.7 \pm 1.3$ mins (95% CI; 7.8-9.8 mins) and $8.6 \pm 1.3$ mins (95% CI; 7.6-9.5) ($P < 0.1$) in DDD and DDDR pacing respectively.

8.4.2.2 Chronotropically Incompetent Patients

For the chronotropically incompetent patients the peak heart rate $99 \pm 14$ bpm (95% CI; 86-112) and $135 \pm 16$ bpm (95% CI; 120-148) ($P < 0.004$), cardiac output $77 \pm 24$ EDV/M (95% CI; 55-99) and $84 \pm 20$ EDV/M (95% CI; 65-102) ($P < 0.1$) and total exercise time $8.5 \pm 0.4$ mins (CI 95%; 8.2-8.9 mins) and $9.1 \pm 1.1$ mins (CI 95%; 8.0-10.2 mins) ($P < 0.2$) in DDD and DDDR respectively.
FIGURE 8.3 CARDIAC OUTPUT IN THE CHRONOTROPICALLY COMPETENT

![Cardiac Output in Chronotropically Competent Patients](image)

- Cardiac Output (EDV/mL)
- Pacing Mode: DDD, DDDR
- P < 0.9

FIGURE 8.4 CARDIAC OUTPUT IN CHRONOTROPICALLY INCOMPETENT PATIENTS

![Cardiac Output in Chronotropically Incompetent Patients](image)

- Cardiac Output (EDV/mL)
- Pacing Mode: DDD, DDDR
- P < 0.1
8.4.3 Activity time curves

The ATHR was calculated for the waveform curves for each individual during each mode of pacing and these were then plotted. Unfortunately problems with the ECG meant that this could not be performed for patient 1. The data are summarised in tables 8.2 and 8.3 and graphically at the end of the chapter.

In the chronotropically competent patients although the sensor rate is significantly higher than the sinus rate (P<0.02). There is no significant difference between the two sets of ATHR data (patients 1-9, table 8.2) or between the ATHR and the sinus rate. Implying that the sinus rate is the correct heart rate. Again in the chronotropic incompetent patients the sensor rate is significantly higher than the sinus rate (P<0.004) with no significant difference between the two sets of ATHR data. However, there is a significant difference P <0.03 between the sinus rate and the ATHR data derived from it. This suggests that the higher sensor driven rate is more acceptable than the sinus rate (patients 10-16, table 8.3).
Table 8.2 Comparison of peak sinus rate and peak ATHR in the chronotropically competent patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Peak Sinus Rate (bpm)</th>
<th>Peak ATHR during DDD</th>
<th>Peak sensor rate</th>
<th>Peak ATHR during DDDR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>126</td>
<td>NA</td>
<td>132</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>123</td>
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<tr>
<td>4</td>
<td>140</td>
<td>137</td>
<td>178</td>
<td>146</td>
</tr>
<tr>
<td>5</td>
<td>105</td>
<td>98</td>
<td>128</td>
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<td>126</td>
</tr>
<tr>
<td>9</td>
<td>113</td>
<td>142</td>
<td>115</td>
<td>135</td>
</tr>
</tbody>
</table>
Table 8.3 Comparison of peak sinus rate and ATHR in chronotropically incompetent patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Peak sinus rate DDD</th>
<th>ATHR during DDD</th>
<th>Peak sensor rate DDDR</th>
<th>Peak ATHR (DDDR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>116</td>
<td>125</td>
<td>117</td>
<td>128</td>
</tr>
<tr>
<td>11</td>
<td>117</td>
<td>125</td>
<td>155</td>
<td>138</td>
</tr>
<tr>
<td>12</td>
<td>107</td>
<td>107</td>
<td>123</td>
<td>122</td>
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<tr>
<td>13</td>
<td>94</td>
<td>134</td>
<td>136</td>
<td>118</td>
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<tr>
<td>14</td>
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<tr>
<td>16</td>
<td>82</td>
<td>138</td>
<td>146</td>
<td>146</td>
</tr>
</tbody>
</table>
8.5 DISCUSSION

If all the patients are considered together, although rate responsive pacing brings about a significantly increased heart rate, it effects no improvement in exercise times or peak cardiac output. This is to be expected in the chronotropically competent patients, as rate responsive pacing will lead to the cardiac output either moving further into phase II or worse slipping into phase III. Therefore an overall decrease in cardiac efficiency occurs. This is verified by a dramatic reduction in peak cardiac output in one patient, with a low ejection fraction, during rate responsive pacing (patient 5).

In chronotropically incompetent patients it could be expected that the increased rate response will lead to an improvement in cardiac output, as due to their impaired rate response they are in phase 1 and never reach phase II. As shown in figure 8.3 in general there was an improvement in cardiac output although, this was not significant and was by no means universal. Indeed an improvement in symptoms was not always associated with an increase in cardiac output. Thus, their haemodynamics must improve in other ways. If the rate response is impaired, then any increase in cardiac output can only be achieved through a larger stroke volume. It may be these large stroke volumes which the subjects find unpleasant, similar to VVI patients with pacemaker syndrome. In addition, this maintenance of cardiac output requires all their cardiac reserve and this could restrict exercise.

The ATHR plots show that in the chronotropically competent patients, there is very good agreement between the ATHR and the sinus rate. This is reassuring as one of the concerns about HMSR highlighted in chapter 7 was that they were conservative with an average rate
of 106 at 50 watts. The data demonstrates that during a shuttle walk there are no significant differences between the ATHR (from which the HMSR is derived) and the peak sinus rate.

However, in the chronotropically incompetent group the ATHR suggests a higher heart rate will lead to more optimal haemodynamics. This supports the need for further research into this new method for sensor control.

Several of the sensors are not set up correctly (patients 4, 5, 9, 10, 11, 13 and 14). Mostly these are minute ventilation sensors (5, 11, 13 and 14) which achieve their peak rate response before the end of exercise. This has previously been reported in association with this sensor type (Kay et al, 1989). In this particular model this problem is exacerbated by the automatic reprogramming of the sensor. This means that the sensor recalibrates after a period of maximum exercise if VE max is exceeded (there is a 6% tolerance) and if VE max is not achieved during a period of 24 hours then the VE max is reduced automatically by 3%. This means that care has to be taken with the selection of the upper rate limit taking into account not only the patients general condition but the patients level of exercise. One patient, a young thin women with a piezo-electric crystal device (patient 4), adopted a “rocking” walking posture after the Vest had been attached, leading to increased vibration stimulus to the pacemaker. A further point of interest is that although these high rates are sustainable in the short term after several minutes cardiac output is decreased (patient 1, and 4).

In patient 9 the sensor seems to dramatically under respond this data was sent to the manufacturers. They were unable to explain its behaviour and offered to replace the device!
This highlights the difficulties with programming rate responsive pacemakers even under these experimental conditions where time has been taken to try and ensure programming of the optimal rate response.

None of the patients defined as chronotropically incompetent were found to be mechanically incompetent. That is patients who appear to have an impaired rate response as a result of mechanical limitations of their heart eg diastolic failure and have a lower heart rate response as a direct result of this. Rate responsive pacing will lead to a deterioration in their haemodynamics. This may well relate to the small numbers studied.

8.6 LIMITATIONS OF THE STUDY

The ATHR has only been verified for single chamber rate responsive pacing, although it may apply to dual chamber pacing, but, this is yet to be fully evaluated.

8.7 CONCLUSION

Patients with chronotropic incompetence feel better during rate responsive pacing but this does not always reflect an increase in cardiac output but more favourable haemodynamics during exercise. Chronotropically competent patients may have subtle abnormalities of their rate response which may be predictors of future incompetent behaviour. The ATHR had good agreement with the sinus rate in the chronotropically competent group confirming that the ATHR may be a successful method of controlling a pacemaker sensor and further studies should be undertaken in this area.
FIGURE 8.5.1 CARDIAC OUTPUT PATIENT 1 IN DDD AND DDDR

FIGURE 8.5.2 PATIENT 1 HEART RATE IN DDD AND DDDR
FIGURE 8.6.1 CARDIAC OUTPUT PATIENT 2 IN DDD AND DDDR

FIGURE 8.6.2 ACTIVE TIME FROM DDD AND DDDR DATA
FIGURE 8.7.1 CARDIAC OUTPUT PATIENT 3 IN DDD AND DDDR

FIGURE 8.7.2 ACTIVE TIME HEART RATE FROM DDD AND DDDR
Figure 8.8.1 Patient 4 Cardiac Output in DDD and DDDR

Figure 8.8.2 Active Time Heart Rate from DDD and DDDR
FIGURE 8.9.1 PATIENT 5 CARDIAC OUTPUT IN DDD AND DDDR

FIGURE 8.9.2 ACTIVE TIME HEART RATE FROM DDD AND DDDR
FIGURE 8.10.1 PATIENT 6 CARDIAC OUTPUT IN DDD AND DDDR

- DDD
- DDDR

FIGURE 8.10.2 ACTIVE TIME HEART RATE IN DDD AND DDDR

- DDDR
- DDD
- ATHR DDDR
- ATHR DDD
FIGURE 8.11.1 PATIENT 7 CARDIAC OUTPUT IN DDD AND DDDR

FIGURE 8.11.2 ACTIVE TIME HEART RATE FROM DDD AND DDDR
FIGURE 8.12.1 PATIENT 8 CARDIAC OUTPUT IN DDD AND DDDR

![Cardiac Output Graph]

FIGURE 8.12.2 ACTIVE TIME HEART RATE FROM DDD AND DDDR

![Heart Rate Graph]
FIGURE 8.13.1 PATIENT 9 CARDIAC OUTPUT IN DDD AND DDDR

FIGURE 8.13.2 ACTIVE TIME HEART RATE IN DDD AND DDDR
FIGURE 8.14.1 PATIENT 10 CARDIAC OUTPUT IN DDD AND DDDR

FIGURE 8.14.2 ACTIVE TIME HEART RATE FROM DDD AND DDDR
**Figure 8.15.1 Cardiac Output Patient 11 in DDD and DDDR**

Cardiac output (EDV/m)

- DDD
- DDR

**Figure 8.15.2 Active Time Heart Rate from DDD and DDDR**

Heart rate (BPM)

- Heart rate DDDR
- ATHR DDDR
- Heart rate DDD
- ATHR DDD
Figure 8.16.1 Cardiac Output Patient 12 DDD and DDDR

Figure 8.16.2 Active Time Heart Rate from DDD and DDDR
FIGURE 8.17.1 PATIENT 13 CARDIAC OUTPUT IN DDD AND DDDR

![Graph showing Cardiac Output in DDD and DDDR](image)

FIGURE 8.17.2 ACTIVE TIME HEART RATE FROM DDD AND DDDR

![Graph showing Active Time Heart Rate](image)
FIGURE 8.18.1 CARDIAC OUTPUT PATIENT 14 IN DDD AND DDDR

FIGURE 8.18.2 ACTIVE TIME HEART RATE FROM DDD AND DDDR
FIGURE 8.19.1 CARDIAC OUTPUT PATIENT 15 IN DDD AND DDDR

![Cardiac Output Graph]

FIGURE 8.19.2 ACTIVE TIME FROM DDD AND DDDR DATA

![Active Time Graph]
FIGURE 8.20.1 CARDIAC OUTPUT PATIENT 16 IN DDD AND DDDR

CARDIAC OUTPUT (EDV/m)

TIME

FIGURE 8.20.2 ACTIVE TIME HEART RATE FROM DDD AND DDDR

HEART RATE (BPM)

TIME
CHAPTER 9 SUMMARY AND DISCUSSION

This thesis has set out to evaluate pacing haemodynamics during normal daily activities using the Capintec Vest. This has previously been poorly investigated because of the limitations of haemodynamic methods used. Most comparisons (chapter 1) have concentrated on peak exercise which is rarely reached during the normal activities of daily living (most around 6 metabolic equivalents). It has been shown by several investigators that DDD pacing is significantly better than VVI pacing on maximal exercise and at rest. The Vest was able to confirm these findings during submaximal exercise as well as mental stress (chapter 1, n=11). This suggests that the benefits of DDD pacemakers are not necessarily limited to patients with normal mobility.

Patients with pacemaker syndrome were able to detect the difference dual chamber and single chamber pacing. Most patients without pacemaker syndrome were unable to detect differences between the two pacing modes unless cardiac output improved by greater than 15 EDV/M. This implies patients will be unable to distinguish subtle differences between pacing modes if they only have a small impact on cardiac output. This may explain why it has not been possible to distinguish symptomatically between VVIR and DDD at peak exercise or between VVIR pacemakers using either a dual or single sensor.

Interestingly, three patients who had been upgraded from VVI to DDD pacing, for pacemaker syndrome who had participated in two studies a year apart demonstrated significant improvement in their ejection fractions. In one patient, the first study three months after upgrade, the ejection fraction was 51% improving to 61% a year later on MUGA scanning.
Whereas all other patients who had repeat scans demonstrated no improvement or in most cases deterioration due to ischaemic heart disease. This suggests that ventricular remodelling occurs after upgrade to dual chamber pacing and this can take at least a year to occur.

A comparison of VVIR and DDD pacing was performed (n=8). This showed, despite the use of an optimal AV delay at rest, there was no significant difference between the two pacing modes in either exercise tolerance or peak cardiac output. Although DDD pacing was superior to VVIR at rest. When the whole of exercise was assessed there was no significant difference in the mean cardiac output, but the mean heart rate during VVIR was significantly higher from minute 2 to minute 6, by up to 16%. This could have offset any advantage of AV synchrony over rate response alone. In addition, rate responsive AV delay was used and this could have diminished the atrial contribution as the exercise test progressed. Interestingly, from comparisons of individual cardiac outputs, the older patients gained more benefit from DDD pacing than their younger counterparts. This has clinical implications for pacing in children and implies that their will be no haemodynamic disadvantage from VVIR until they are old enough to implant an atrial lead.

Further studies (chapter 5) were performed comparing dual chamber pacing with a short AV delay (the worst possible AV programming) versus DDD pacing using an optimal AV delay at rest (n=8). Assessments of cardiac output in patients with normal LV function showed the atrial contribution was limited to rates below 110 or below the rate at which the exercise started. However, in those patients with impaired left ventricular function and hypertension, the optimal AV delay was superior to simultaneous AV pacing during the whole of exercise. Thus showing the value of AV delay optimisation particularly in these groups.
During simultaneous AV pacing the mean heart rate was significantly higher during the first five minutes of exercise (by approximately 6%) until the heart rate during DDD pacing was greater than 110 bpm. Suggesting that compensation has occurred for the lower ejection fraction due to sub optimal programming of the AV delay. As cardiac output was higher in DDD pacing, although not significantly so, this combined data implies a maximum value for the atrial contraction of up to 17%. These results confirm the relatively insignificant value for the atrial contribution when compared with the 100% overall increase in cardiac output at peak exercise. The value of atrial pacing in activities of daily living is likely to be of greater importance and explains the subtle benefits of DDD pacing reported on symptoms of well being.

In applying these results to clinical practise patients with normal LV function the rate adaptive AV delay should be programmed on to allow the maximum upper rate limit. The most effective algorithm for rate adaption would be to have the AV delay fixed to a rate of 110 bpm and then have more rapid shortening at higher rates. In patients with impaired LV function, the optimal AV delay should be fixed for the whole of exercise to ensure that the value of the atrial contribution is maintained. The peak heart rate is not as important in this group as their rate rarely exceed 120 bpm.

The universal adoption of VVIR pacing is limited by the lack of an ideal sensor and how should they be correctly programmed. What is the most appropriate rate for a given level of exercise? In view of this, a study of the "optimal rate" for a given level of exercise was performed with the intention of creating a pacemaker sensor algorithm capable of providing the patients with "optimal haemodynamics" at all times. A three phase relationship has been
demonstrated between cardiac output and increasing heart rate, with the cardiac output initially increasing, then a plateau phase and finally decreasing with further increases in heart rate. The "optimal rate" was defined as the lowest heart rate at which maximum cardiac output was achieved i.e. the onset of phase II. The optimal rate was shown to have great inter-patient variability with no correlates with age, predicted peak heart rate (Astrand formula 220 - age) or ejection fraction (chapter 6) (n=20). Thus, the optimal pacing rate cannot be predicted by straightforward means and therefore the commonplace selection of upper heart rates by age, may lead to detrimental haemodynamics. This study was using single chamber pacing and as such is the first step in our understanding of the more complex haemodynamics during dual chamber rate responsive pacing.

A sensor algorithm capable of predicting the "optimal rate" would therefore be highly desirable. The "total active time" (TAT) was defined as the time from the beginning of cardiac contraction to the end of the filling phase, provided that refilling occurs at the fastest rate. The TAT was calculated from the optimal rate data generated in chapter 6 and the Active Time Heart Rate (ATHR) calculated from this. The intersection of the ATHR and the actual paced rate was defined as the Haemodynamic Maximum Sensor Rate (HMSR) and this rate was shown to lie within phase II. It is proposed that this should be used to form a dynamic limitation for the upper rate in rate responsive pacemakers with the intention of ensuring that pacing is always within phase II and never enters phase III.

These observations may have a significant impact on rate responsive pacing today. Firstly there is a potential for reducing the need for repeat exercise tests to ensure programming of the best rate response slope. Secondly, it will improve the performance of currently used
activity sensors by reducing their response to false stimuli and thirdly it may improve their rate response to prolonged exercise because as the exercise progresses there will be changes in the HMSR leading to an increase in paced rate.

The author feels the issues outlined in this thesis represent the way forward in the development of rate responsive pacemakers rather than towards dual sensor devices. Currently such devices have an increased complexity which makes programming and initial setting up more complicated and can expose the patient to the worst aspects of both sensors. This is not offset by a significant improvement in haemodynamics.

The HMSR in general are conservative with a mean of 106±11 bpm at 50 watts providing the clinical reassurance that the paced rate will not be too high. Despite concern that this rate may restrict the maximum heart rate and thus limit exercise tolerance comparisons of DDD and VVIR pacing did not indicate an effect on exercise tolerance.

Although, the initial application of our proposed sensor system is in single chamber rate responsive pacemakers, this could be extended to dual chamber and dual chamber rate responsive pacemakers. As this data has shown that the HMSR will work as means of limiting the maximum heart rate. It will have to be incorporated into an implantable pacemaker sensor, for full clinical evaluation.

A study of optimal pacing rate would not be complete without an investigation of so called chronotropically incompetent patients. As some of these patients may already be at their optimal rate, this was assessed by a comparison of DDD and DDDR pacing in both
chronotropically competent and incompetent patients (n=16). This showed that in the chronotropically competent patients (as expected from earlier work) there was no improvement in peak cardiac output. In the chronotropically incompetent group there was an improvement in cardiac output although this was not statistically significant.

The ATHR and HMSR were also calculated. In the chronotropically competent patients the sensor gave good agreement with the sinus rate. This was reassuring as the work in chapter 7 suggests the mean HMSR are on the conservative side. The similarity of the HMSR and the sinus rate during the shuttle walk suggests this is not true. Whereas in the chronotropically incompetent patients as expected the HMSR predicted a higher rate than the sinus rate. This suggests that the incorporation of the HMSR into a sensor will be worthwhile.

FURTHER WORK

STUDIES OF THE "OPTIMAL RATE" DURING DUAL CHAMBER PACING
This work as already mention in chapter 6 is in VVIR patients and thus further studies need to be undertaken in these patients to investigate the more complex interrelationship between pacing rate and cardiac output during DDD and DDDR pacing.

CLINICAL EVALUATION OF THE HMSR
In theory the haemodynamic maximum sensor rate based on the calculation of the active time heart rate looks promising as a means of controlling more commonly used sensors. This should be the way forward in sensor development rather than dual sensors. Obviously full
clinical evaluation is necessary.

FURTHER EVALUATION OF CHRONOTROPICALLY INCOMPETENT PATIENTS

More needs to be known of the natural history of the disease from the work in this thesis it would appear that chronotropic incompetence can effect the initial phase of exercise rather than just being a failure to reach an upper rate. What are the phenomena which bring about this incompetence. Are there two groups of chronotropically incompetent patients the mechanically incompetent and those who really have an impaired rate response? How can these different groups be distinguished to ensure that detrimental haemodynamics do not occur.
PUBLICATIONS FROM THIS THESIS

PAPERS

1  A new method of investigating pacing haemodynamics using a nuclear probe (Capintec Vest): Comparison of VVI and DDD.
   GE Payne, H Williams & JD Skehan. (PACE In Press).

2  The shuttle walking test; A new approach for evaluating pacemaker patients?
   GE Payne, JD Skehan. (British Heart Journal In Press)

PAPERS SUBMITTED

3  Pacing Haemodynamics during the Activities of Daily Living using an Ambulatory Nuclear Vest.
   GE Payne, H Williams, JD Skehan.

4  The 'True Optimal Rate' an Individual Parameter.
   GE Payne, H Williams, J Spinelli, CJ Garratt and JD Skehan.

5  Automatic Optimisation of Pacing Rate
   GE Payne, H Williams, J Spinelli, CJ Garratt and JD Skehan.

6  Comparison of VVIR and DDD pacing; Implications for programming
Atrioventricular delays.

GE Payne, H Williams, CJ Garratt, and JD Skehan.

7 Does rate responsive pacing treat the Doctor or the patient?

GE Payne, H Williams, CJ Garratt, and JD Skehan.

ABSTRACTS

EUROPACE OSTEND JUNE 1993

1 A STUDY ON OPTIMAL PACING HAEMODYNAMICS


BRITISH CARDIAC SOCIETY TORQUAY MAY 1994

2 THE 'TRUE OPTIMAL RATE' AN INDIVIDUAL PARAMETER.

GE Payne, J Spinelli, CJ Garratt and JD Skehan

BR Heart J 1994;71 (suppl):89

CARDIOSTIM NICE JUNE 1994

3 DOES RATE RESPONSIVE PACING TREAT THE DOCTOR OR THE PATIENT?

GE Payne, CJ Garratt and JD Skehan

Eur J.C.P.E 1994;4 (suppl):77

4 THE 'TRUE OPTIMAL RATE' AN INDIVIDUAL PARAMETER.
BRITISH CARDIAC SOCIETY HARROGATE MAY 1995

5  OPTIMAL PACING HAEMODYNAMICS

GE Payne, J Spinelli, CJ Garratt and JD Skehan.
Br Heart J 1995;73:19

NASPE BOSTON MAY 1995

6  AUTOMATIC OPTIMISATION OF PACING HAEMODYNAMICS.

GE Payne, J Spinelli, CJ Garratt and JD Skehan.
PACE 1995;18:908
REFERENCES


Chirife R, Ortega DF, Salazar AI. Nonphysiological left heart AV intervals as a result of DDD and AAI "physiological" pacing. PACE 1991;14:1752-56.


Clarke M. Rate responsive atrial pacing resulting in pacemaker syndrome [abstract] PACE 1987;10:1209.


Davis CTM. Limitations to the prediction of maximum oxygen intake from cardiac frequency measurements. J Appl Physiol 1968;24:700-706.


Faerstrand S, Ohm O-J. A time related study of the haemodynamic benefit of atrioventricular synchronous pacing evaluated by doppler echocardiography. PACE 1985;8:838-848.


Fananapazir L, Rodemaker M, Bennett DH. Reliability of the evoked response in determining the paced ventricular rate and performance of the QT or rate responsive (TX) Pacemaker. PACE 1985;8:701-714.


Goldreyer BN. Physiological pacing: The role of AV synchrony. PACE 1982;5:613-5.


Kristensson B-E, Arman K and Ryden L. The haemodynamic importance of atrioventricular synchrony and the rate increase at rest and during exercise. Eur Heart J 1985b;6:773-778.


Lau CP. The range of sensors and algorithms used in rate adaptive cardiac pacing. PACE 1992;15:1177-1211.


Leman RB, Kratz JM. Radionuclide evaluation of dual chamber pacing: Comparison between variable AV intervals and ventricular pacing. PACE 1985;8:408-414.


Linden RJ, Mitchell JH: Relation between left ventricular diastolic pressure and myocardial segment length and observations on the contribution of the atrial systole. Circ Res Cardiol 1960;8:1092-99.


Miyamoto Y, Transient changes in ventilation and cardiac output at the start and end of exercise. Jpn J physiolo 1981;31:149-164.


Pace L, Cuocolo A, Nappi A et al. Accuracy and repeatability of left ventricular systolic and
diastolic function measurements using an ambulatory radionuclide monitor. Eur J Nuc Med

1971;31:326-331.

Pehrsson SK, Astrom H. Left ventricular function after long term treatment with ventricular

Pehrsson SK. Influence of heart rate and atrioventricular synchronisation on maximal work

Perrins EJ, Morley CA, Chan SL, Sutton R. Randomised controlled trial of physiological and


Pinsky WW, Lewis RM, Harley CJ et al. Permanent changes in ventricular contractility and

Poliner L, Dehmer GJ, Lewis SE et al. Left ventricular performance in normal subjects. Circ
1980;62:592-34.


Ritter P, Daubert C, Mabo P, et al. Haemodynamic benefit of a rate adapted AV delay in

Ritter P, Mabo Ph, Cereze P et al. Interest and assessment of the atrioventricular hysteresis
function in dual chamber pacing. Eur Heart J 1992;

Robinson BF, Epstein SE, Beiser GD et al. Control of heart rate by the autonomic nervous
system. Studies in man on interrelation between baroreceptor mechanism and exercise. Circ

Rokey R, Kuo LC, Zoghbi WA et al. Determination of parameters of left ventricular
diastolic filling with pulsed Doppler echocardiography: Comparison with cineangiography.


Rosenqvist M Brandt J, Schuller H. Long term pacing in sinus node disease; the effects of

Rosenqvist M, Isaa K, Botvinick EH et al. Relative importance of activation sequence
compared to atrioventricular synchrony in left ventricular function. Am J Cardiol


Wilkoff BL, Shimokochi DD, Schaal SF. Pacing rate increase due to application of steady external pressure on an activity sensing pacemaker. [abstract] PACE 1987;10:423.


Wish M, Fletcher RD, Gottdiener JS et al. Importance of left atrial timing in the programming of dual chamber pacing. Am J Cardiol 1987;60:566-571.
