Double blind crossover comparison of the effects of dual chamber pacing (DDD) and ventricular rate adaptive (VVIR) pacing on neuroendocrine variables, exercise performance, and symptoms in complete heart block

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Abstract

Objective—To compare the effects of dual chamber pacing (DDD) and ventricular rate adaptive pacing (activity sensing) (VVIR) in patients with complete heart block.

Design—Double blind crossover comparison with one month in each pacing mode.

Patients—10 consecutive patients aged 23–74 presenting with complete anterograde atrioventricular block at rest and on exercise and with an intact atrial rate response received Synergyist I (Medtronic) pacemakers.

Main outcome measures—Symptom scores, maximal exercise performance on a treadmill, and the plasma concentrations of atrial natriuretic peptide, adrenaline, and noradrenaline.

Results—No significant differences were identified between pacing modes in symptom scores for dyspnoea, fatigue, and mood disturbance; exercise time; and maximal oxygen consumption. One patient with intact ventriculoatrial conduction developed pacemaker syndrome during VVIR pacing. Resting plasma concentrations of atrial natriuretic peptide were raised in complete heart block and were restored to normal by DDD pacing but not by VVIR pacing. Resting plasma catecholamine concentrations were normal in complete heart block and in both pacing modes. During exercise the increase in the concentrations of all three hormones was similar in both pacing modes.

Conclusions—In patients with complete anterograde and retrograde atrioventricular block, symptoms and maximal exercise performance were no better during DDD than during VVIR pacing.

However, it is not clear whether either of these rate responsive modes is better than the other. Because the Synergyist I (Medtronic) pacemaker can operate in the DDD and activity sensing VVIR pacing modes we were able to compare the effects of these two modes in the same patient.

Patients and methods

The study was designed as a double blind prospective crossover comparison of the effects of DDD and VVIR pacing on symptoms, maximal exercise capacity, and plasma concentrations of adrenaline, noradrenaline, and atrial natriuretic peptide in complete heart block. It was approved by the ethics committee of Glasgow Royal Infirmary and all patients gave written informed consent before entry. There were seven men and three women (mean age 56 years (range 23–74)). The underlying cardiac diagnoses were ischaemic heart disease (two), hypertension (two), congenital heart block (two), and idiopathic fibrosis of the conducting tissue (four). Only two patients were receiving cardiovascular drugs and treatment was not changed during the course of the study. The mean ejection fraction was 58% (range 40–74) and none of the patients had any clinical evidence of cardiac failure.

STUDY PROTOCOL

We implanted a Synergyist I (Medtronic) pacemaker in 10 consecutive patients presenting with complete anterograde atrioventricular block at rest who were capable of completing an exercise protocol. We excluded patients with recent myocardial infarction, appreciable angina or respiratory disease, chronic atrial flutter/fibrillation, and exercise induced arrhythmias.

Patients performed exercise tests before permanent pacing to confirm an intact atrial rate response, before randomisation to facilitate programming of rate response in the VVIR mode, and after each treatment period. The preliminary tests also served to familiarise patients with the exercise apparatus. Program settings were chosen with the aim of allowing similar maximum ventricular rates in both modes. Patients were then randomised to either the DDD or VVIR mode for one month.
Double blind crossover comparison of DDD and VVIR pacing in complete heart block

SYMPTOM SCORES
Symptoms were assessed at the end of each one month period by a self-administered questionnaire. This questionnaire was developed at McMaster University and has been used in a previous study to compare different pacing modes. Three sets of eight questions related to dyspnoea, fatigue, and mood disturbance were answered by marking an ungraded 100 mm linear visual analogue scale cued with "very much" and "not at all". The distances of all the marks for each category of questions were summed: a maximum score of 800 was possible.

EXERCISE PROTOCOL
Maximal symptom limited treadmill exercise tests with concurrent measurement of respiratory gas exchange were used. In our laboratory the limb of the breathing circuit for inspiration is fitted with a turbine ventilometer and the limb for expiration includes a mixing chamber from which mixed expiratory gases are measured by polarographic oxygen and infrared carbon analysers. The output of the ventilometer and gas analysers are processed by an on line microcomputer (PK Morgan Exercise Test System) to allow continuous measurement of gas exchange and inspired minute ventilation. For the exercise protocol patients were monitored at rest for two minutes to establish a steady state, then they performed incremental treadmill exercise at a fixed gradient of 10 degrees starting at one mile per hour and increasing by 0·5 miles per hour every minute. Maximal oxygen consumption and the respiratory anaerobic threshold were determined by standard criteria. We used a fixed gradient because activity sensing pacemakers respond in treadmill speed rather than incline.

EJECTION FRACTION
This was calculated from cross sectional echocardiographic images obtained in DDD mode. We used an area × length formula.

ASSAYS
Atrial natriuretic peptide was measured by radioimmunoassay (normal range 5–50 pg/ml). Catecholamines were measured by radioenzymatic assay (normal values adrenaline <1·0 nmol/l and noradrenaline <5·0 nmol/l).

STATISTICAL ANALYSIS
To assess the distribution of the data derived from this study we calculated the standardised skewness and kurtosis of each of the variables. Normally distributed values were expressed as mean (SEM) and skewed values as the median (interquartile range). Paired two tailed group comparisons were made with Student’s t (parametric) or Wilcoxon signed rank (non-parametric) tests as appropriate. p Values of <0·05 were regarded as significant.

Results
SYMPTOMS
Only one patient requested early crossover

Figure 1 Individual values and means (SEM) of symptom scores during VVIR (ventricular rate adaptive pacing) and DDD (dual chamber pacing).
Table 1  Results (mean (SEM)) of maximal symptom limited cardiopulmonary exercise testing

<table>
<thead>
<tr>
<th>Variable</th>
<th>VVIR</th>
<th>DDD</th>
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<tbody>
<tr>
<td>Exercise time (s)</td>
<td>477 (32)</td>
<td>489 (31)</td>
</tr>
<tr>
<td>Maximal oxygen consumption (ml/min/kg)</td>
<td>22.9 (1.4)</td>
<td>22.1 (1.2)</td>
</tr>
<tr>
<td>Peak ventilation (l/min)</td>
<td>62.7 (1.5)</td>
<td>59.5 (1.1)</td>
</tr>
<tr>
<td>Oxygen consumption at anaerobic threshold (ml/min/kg)</td>
<td>16.7 (0.9)</td>
<td>16.8 (0.9)</td>
</tr>
<tr>
<td>Maximal carbon dioxide production (ml/min/kg)</td>
<td>24.8 (1.8)</td>
<td>23.6 (1.4)</td>
</tr>
<tr>
<td>Basal respiratory quotient</td>
<td>0.84 (0.03)</td>
<td>0.86 (0.04)</td>
</tr>
<tr>
<td>Peak respiratory quotient</td>
<td>1.06 (0.05)</td>
<td>1.06 (0.05)</td>
</tr>
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VVIR, ventricular rate adaptive pacing; DDD, dual chamber pacing.

from VVIR back to DDD for symptoms consistent with pacemaker syndrome. This was the only patient with evidence of intact ventriculoatrial (VA) conduction. Nine patients expressed no overall preference for either pacing mode. In keeping with this, there were no significant differences in any of the three symptom scores between VVIR and DDD pacing (fig 1).

EXERCISE PERFORMANCE (TABLE 1)

Though the program settings were aimed at allowing a similar maximum heart rate in both pacing modes, the maximum heart rate achieved was significantly higher in the DDD mode than in the VVIR mode: 136 (4) vs 117 (3) (fig 2). Seven of the 10 patients actually reached their programmed upper tracking rate during exercise in DDD mode and reverted to a Wenckebach pattern of atroventricular conduction. In six this upper tracking rate was 144 beats per minute. There was no significant difference between the modes in exercise time (fig 2), maximal oxygen consumption, or peak ventilation (fig 3). Oxygen consumption at anaerobic threshold, maximal carbon dioxide production, and the mean resting and peak respiratory quotients were also similar in both modes. The resting values were close to the expected normal values of around 0.85, indicating that a reasonable steady state of respiratory gas exchange had been achieved.

Figure 2 Individual values and means (SEM) of maximum heart rate and exercise time on treadmill exercise testing during VVIR and DDD pacing.

ATRIAL NATRIURETIC PEPTIDE (TABLE 2)

Before pacemaker implantation seven patients had resting values above the normal range. After one month of DDD pacing only two patients continued to have raised concentrations of atrial natriuretic peptide and there was a significant fall in the median concentration. No such fall occurred after VVIR pacing; five patients continued to have values above the normal range. Exercise produced significant rises in concentration of atrial natriuretic peptide in both pacing modes. Although the median concentration on exercise was higher in VVIR than DDD with 7/10 vs 4/10 subjects reaching concentrations above the normal range, the difference between the modes just failed to reach statistical significance (exact p value = 0.05). There was no difference between pacing modes in either the absolute or percentage increase in atrial natriuretic peptide on exercise. The patient with pacemaker syndrome during VVIR pacing had raised plasma atrial natriuretic peptide at rest with a substantial rise to 196 pg/ml on exercise. In DDD mode his atrial natriuretic peptide concentration was normal at rest and remained within the normal range on exercise.

CATECHOLAMINES (TABLE 2)

Before pacemaker implantation one patient had a slightly raised plasma concentration of noradrenaline at rest (5.3 nmol/l), but otherwise both adrenaline and noradrenaline concentrations were normal. Resting concentrations were all within normal limits in both pacing modes and there was no difference between modes in either the resting or exercise concentrations of adrenaline or noradrenaline. Though there was an overall increase in the concentration of both catecholamines on exercise in both modes, there was no difference between modes in either the absolute or percentage increases.
Discussion
The contribution to cardiac output of a properly timed atrial contraction diminishes with increasing heart rate\(^{10,11}\) and filling pressures.\(^6\) There were no significant differences in exercise capacity in earlier short term crossover studies of patients paced at a fixed ventricular rate similar to that achieved on exercise during atrioventricular synchronous pacing.\(^{15,16}\) In the present within patient comparative study the addition of atrioventricular synchrony produced no advantage over the provision of rate response alone. Physiologically the PR interval gradually shortens during exercise as heart rate rises, but studies attempting to show that such atrioventricular interval hysteresis improves exercise performance during DDD pacing have produced both positive\(^{17,18}\) and negative results.\(^{19,20}\) In view of this, we did not attempt to “optimise” the programmed atrioventricular interval. To maintain a 1:1 atrioventricular relation at high paced ventricular rates without atrioventricular interval hysteresis, it is necessary to shorten either the programmed atrioventricular interval or the post-ventricular atrial refractory period. But these manoeuvres reduce the time for atrial filling and predispose the patient to pacemaker mediated tachycardia respectively.

A limitation to the wider application of VVIR pacing is the problem of pacemaker syndrome, which was seen in one patient in this series. This prevalence of intact ventriculo-atrial conduction is identical to that found in a similar study by Lipkin et al.\(^4\) Temporal variability in the integrity of ventriculoatrial conduction weakens the relevance of any single pre-implantation assessment but it is known that the incidence of intact ventriculoatrial conduction is much higher in certain patient groups. Thus in sick sinus syndrome it is accepted that VVI pacing produces an unacceptably high incidence of pacemaker syndrome and that atrial or dual chamber pacing, which avoids this problem, is preferable.\(^21\)

However, in patients with complete anterograde and retrograde heart block DDD pacing seems to confer no benefit over VVIR in terms of symptoms or exercise performance.

Asynchronous atrial contraction, as occurs in complete heart block, raises intra-atrial pressure and stimulates the release of atrial natriuretic peptide.\(^22\) We found raised concentrations in most of our patients before pacemaker implantation. Dual chamber pacing in complete heart block restores atrial natriuretic peptide concentrations to normal in most patients and this has been offered as evidence of the physiological nature of this mode.\(^22\) By contrast, VVIR pacing did not

### Table 2 Neuroendocrine variables (median (interquartile range)) in study patients

<table>
<thead>
<tr>
<th></th>
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<th>DDD</th>
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<tr>
<td></td>
<td>Pre-implant Rest Exercise Change on exercise (%)</td>
<td>Rest Exercise Change on exercise (%)</td>
</tr>
<tr>
<td>Atrial natriuretic peptide (pg/ml)</td>
<td>66 (38-40) 52 (20-73) 114* (38-106)</td>
<td>61 (38-168) 20* (15-33) 40* (18-76) 76 (39-125)</td>
</tr>
<tr>
<td>Adrenaline (nmol/l)</td>
<td>0.20 (0.10-0.35) 0.10 (0.07-0.40) 0.40 (0.20-0.70)</td>
<td>0.09 (0.06-0.25) 0.75* (0.40-1.45) 0.99 (0.93-1.025)</td>
</tr>
<tr>
<td>Noradrenaline (nmol/l)</td>
<td>1.4 (0.8-2.6) 1.3 (0.3-3.0) 6.2 (0.5-7.0)</td>
<td>2.0 (1.8-2.4) 10* (4.7-12.2) 36* (12.3-453)</td>
</tr>
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*p < 0.05 v resting value; t p < 0.05 v pre-implant and VVIR values.
restored normal concentrations. It has previously been shown that atrial natriuretic peptide concentrations rise on exercise and during ventriculoatrial pacing. By providing higher ventricular rates on exercise, VVIR pacing increases the frequency of asynchronous atrial contraction, which may result in an augmented rise in atrial natriuretic peptide on exercise even in the absence of intact ventriculoatrial conduction. We did find a trend towards higher concentrations on exercise in the VVIR mode than in the DDD mode (exact p value = 0.05), but there was no difference between modes in either the absolute or percentage change on exercise. As in published reports, our only patient with pacemaker syndrome during VVIR pacing had very high plasma concentrations of atrial natriuretic peptide. However, the relevance of this finding to the vasomotor changes and symptoms of pacemaker syndrome remains unclear.

In patients with impaired ventricular function and cardiac release of noradrenaline on exercise is higher during VVI pacing than during atrial synchronous pacing. This accounts for the much greater increases in stroke volume on exercise seen in VVI mode and partly offsets the lack of a rate response. Though we only measured peripheral venous catecholamine concentrations, our results suggest that VVIR pacing is not associated with undue activation of the sympathetic nervous system either at rest or on exercise.

Single chamber ventricular pacemakers are easier and cheaper to implant than DDD systems and they avoid the problems of atrial lead displacement, atrial malensing, and cross-talk. They can continue to provide rate response if atrial fibrillation or chronotropic incompetence develop. A potential disadvantage of VVIR pacing is the possible increased incidence of the development of atrial fibrillation with its attendant risk of thromboembolism. However, this has been shown to be relevant in patients with sinus node disease, in theory it is less of a problem in patients with retrograde atrioventricular block. Our data indicate that it would be appropriate to consider VVIR activity sensing pacemakers or other single chamber rate-variable systems to provide rate response in patients with complete anterograde and retrograde heart block and preserved venricular function. Furthermore, it may not be necessary to have a policy of repeatedly exercising and reprogramming these patients in an attempt to obtain the maximum rate response out of the system. Indeed, perhaps the most interesting finding of this study is that despite a lower maximum heart rate in VVIR mode, comparable levels of symptoms and exercise performance to DDD pacing were achieved with only one or in some cases no adjustment to the nominal program settings. It may be that adaptive mechanisms permit the maintenance of tissue oxygen delivery during VVIR pacing 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. In the minority of patients with complete heart block and intact ventriculoatrial conduction it is probably better to avoid the risk of pacemaker syndrome by establishing atrial synchronous ventricular pacing. It remains to be determined whether other groups such as older patients and those with angina, significantly impaired ventricular function, and/or overt cardiac failure benefit from DDD pacing.

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PLANTS IN CARDIOLOGY

Aspirin
The success of quinine from 1630 onwards in treating malaria led to its use in other febrile conditions. So when the Reverend Edward Stone in 1763 noticed that powdered bark of the willow tree, *Salix* species (*Salicaceae*), had a bitter taste like quinine he used it as a substitute for the expensive imported cinchona bark. Its active principle—salicin, which is converted into salicylic acid in the body—was isolated in 1830 and introduced for the treatment of acute rheumatic fever by Dr Thomas Maclagan of Dundee in 1876. He used it in the erroneous belief, based on the Doctrine of Signatures, that because the disease was prevalent in cold damp localities *Salix*, a typical marsh plant, would be nature’s remedy. None the less, he got the right answer.

Salicylic acid was originally produced in 1835 from salicylaldehyde found in *Spiraea ulmaria* or *Filipendula ulmaria* (*Rosaceae*), the meadowsweet. It became freely available only with the development of a synthetic process in 1874. Its use as an "internal antiseptic" in typhoid fever revealed its antipyretic property. This, together with Maclagan’s work, led to its use in rheumatic fever and other rheumatic diseases.

After gastric irritation prevented his father from taking sodium salicylate to treat his chronic arthritis Felix Hoffman, a chemist with the Bayer Company, produced acetylsalicylic acid in 1899 (it had been synthesised elsewhere in 1853). He gave it the trade name Aspirin (a for acetyl; *spir* for spiraeas; and *in*, a common ending for drugs). This is now the generic name.

The family *Salicaceae* consists mainly of trees and shrubs from the northern temperate region and has only three genera. The *Rosaceae* are more numerous (over 100 genera and 3000 species) and more widely distributed. They vary from trees to herbs and include apples, plums, and strawberries. Some of the *Rosaceae* species yield vitamin C but otherwise neither the *Rosaceae* nor the *Salicaceae* contain other important medicines.

A HOLLMAN