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

K G Oldroyd, A P Rae, R Carter, C Wingate, S M Cobbe

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 Synergy St 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.

In most patients who need permanent pacemakers, symptoms and exercise performance are better with rate responsive pacing than with fixed rate ventricular pacing. This has been shown in comparisons with dual chamber (DDD) pacing and also with various sensor-driven single chamber ventricular rate responsive (VVIR) systems. However, it is not clear whether either of these rate responsive modes is better than the other. Because the Synergy 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 Synergy St I (Medtronic) pacemaker in 10 consecutive patients presenting with complete anterograde atioventricular 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

at the end of which they crossed over to the opposite mode for a further month. Peripheral venous blood samples were taken from indwelling cannulas at rest before implantation of the pacemaker, and at rest and after exercise after each one month period. Symptom questionnaires were also completed at each visit. All pacemaker programming and electrocardiographic monitoring during exercise testing was performed by one operator (CW). All of the exercise tests were supervised by a different observer (RC) who was not aware of the pacing mode and was screened from the electrocardiographic monitor during testing.

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.4 Three sets of eight questions related to dyspnoea, fatigue, and mood disturbance were answered by marking an ungraduated 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 to increases in treadmill speed rather than incline.5

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).](http://heart.bmj.com/content/189/11/189)
**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>
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<tr>
<td>Peak ventilation (l/min)</td>
<td>62.7 (5.5)</td>
<td>59.6 (4.9)</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>23.0 (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>
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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 atioventricular conduction. In six this upper tracking rate was 144 beats per minute. There was no significant difference between the modes in exercise heart rates (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 mmol/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 and filling pressures. 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. 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 and negative results. 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 VVI 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. 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. However, in patients with complete anterograde and retrograde heart block DDD pacing seems to confer no benefit over VVI 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. 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. By contrast, VVI pacing did not...

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

<table>
<thead>
<tr>
<th>VVI</th>
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<tr>
<td></td>
<td>Pre-implant</td>
<td>Rest</td>
<td>Exercise</td>
<td>Change on exercise (%)</td>
<td>Rest</td>
<td>Exercise</td>
<td>Change on exercise (%)</td>
<td></td>
</tr>
<tr>
<td>Atrial natriuretic peptide (pg/ml)</td>
<td>66 (38-80)</td>
<td>52 (20-73)</td>
<td>114* (38-196)</td>
<td>61 (38-168)</td>
<td>20 (15-33)</td>
<td>40* (18-76)</td>
<td>76 (39-125)</td>
<td></td>
</tr>
<tr>
<td>Adrenaline (nmol/l)</td>
<td>0.20 (0.10-0.35)</td>
<td>0.10 (0.07-0.40)</td>
<td>0.40 (0.20-0.70)</td>
<td>0.40 (0.00-0.40)</td>
<td>0.09 (0.06-0.25)</td>
<td>0.75* (0.40-1.45)</td>
<td>566 (193-1025)</td>
<td></td>
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<tr>
<td>Noradrenaline (nmol/l)</td>
<td>1.4 (0.8-2.6)</td>
<td>1.0 (0.3-3.0)</td>
<td>4.2 (0.5-7.0)</td>
<td>4.20 (0.20-0.40)</td>
<td>2.0 (1.8-2.4)</td>
<td>10.2* (4.7-12.2)</td>
<td>366 (123-453)</td>
<td></td>
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</table>

*p < 0.05 v resting value; †p < 0.05 v pre-implant and VVI values.
They pacemaker syndrome remains a stage of development with its attendant risk of stroke. Patients with high plasma concentrations of atrial natriuretic peptide may experience symptoms of atrial fibrillation, which can be exacerbated by exercise, exercise tests, or pacing. The role of atrial fibrillation in patients with pacemakers is complex, and the benefits and risks of atrial fibrillation pacing are variable. Further studies are needed to clarify the role of atrial fibrillation pacing in patients with pacemakers.

References:
raised plasma atrial natriuretic peptide concentrations in complete atrioventricular block. BMJ 1988;296:94.

**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*, now *Filipendula ulmaria* (Rosaceae), the meadowsweet. It became freely available only with the development of a synthetic process in 1874. Its use as an “internal anti-septic” 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 spiraea; and in, a common ending for drugs). This is now the generic name.

The family Rosaceae 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
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