Randomised controlled trial of physiological and ventricular pacing

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SUMMARY Thirteen patients have completed a randomised double blind cross over study to compare the effects of chronic ventricular and atrial synchronous pacing on exercise capacity and symptoms. Maximal symptom limited exercise was significantly increased after one month of atrial synchronous pacing compared with ventricular pacing. Symptomatic assessment (by diary card and monthly symptom scores) of "shortness of breath", "palpitation", and "general well-being" was significantly improved during the physiological pacing mode. Atrial synchronous pacing has been shown to be superior to ventricular pacing.

Cardiac pacing is a safe and established treatment for patients with symptomatic bradycardia caused by atrioventricular block. Until recently, however, this treatment has been restricted to ventricular demand pacing at a constant rate. Recent advances in lead design allow the reliable implantation of endocardial atrial leads,¹⁻³ and several pacemakers are now available which can restore the normal activation sequence of atrial contraction followed by ventricular systole and which, furthermore, can follow physiological increases in heart rate during exercise. The indications and applications of these pacemakers have recently been reviewed.⁴

There remains controversy as to whether these more complex and, at present, more expensive pacemakers confer any real advantages to the patient. Pacemakers are now available which are programmable to either ventricular inhibited (VVI) pacing or a physiological mode (atrial synchronous ventricular inhibited, VDD or universal, DDD).⁵ It has been possible therefore using these pacemakers to compare these two modes of pacing in terms of both exercise performance and patient symptoms in a double blind trial.

Patients and methods

PATIENT SELECTION

Patients in whom a mode programmable VDD pacemaker had been implanted for at least three months were considered suitable candidates for the

trial. At the time of the study the exclusion criteria for implantation of a VDD pacemaker were: severe physical disability (for example arthritis or stroke), the coincidence of another disease with a short prognosis, chronic atrial fibrillation, the presence of dominant sinus rhythm with rare episodes of bradycardia, carotid sinus syndrome, retrograde atrioventricular conduction, isolated sick sinus syndrome, and very thin patients. In the four years before the trial 350 patients had been paced, of whom 42 had received VDD or VAT (ventricular paced atrial sensed) implants. Of these, only 16 were mode programmable (VDDM). One patient refused and two patients had intermittent 2:1 block at the time of the study, leaving 13 patients. Their clinical details are shown in Table 1. All patients had symptomatic Mobitz II or complete atrioventricular block and normal (nine patients) or borderline (two patients) sinus node disease assessed by pre-pacing electrophysiological studies. Their mean age was 65 years (range 32 to 87). None of the patients had been found to conduct during exercise before entry. The patients had had their pacemaker implanted in VDD mode for a mean of 11 months (range three to 27) before entry into the trial to ensure that they were haemodynamically stable at entry.

TRIAL DESIGN

The trial was designed as a within patient double blind prospective study of symptoms and exercise tolerance between two pacing modalities, VVI and VDD. The design is shown in Fig. 1. There were three consecutive one month periods during which patients were asked to keep diary cards of their symptoms and a maximal stress test was performed at the

Table 1 Patient data

Case No.	Age, sex	Pacemaker	Months since implant	Pre-pacing symptoms	Pre-pacing electrocardiogram	Aetiology
1	64 M	VDDM	16	Syncope	Mobitz II 2:1	Fibrosis*
2	67 F	VDDM	16	Syncope	CHB	Fibrosis
3	51 M	VDDM	13	Syncope	Mobitz II 2:1	Fibrosis
4	63 M	VDDM	27	Syncope	Mobitz II 2:1	COCM
5	51 F	VDDM	12	Syncope, dyspnoea	CHB	After CABG
6	87 M	VDDM	27	Syncope, dyspnoea	CHB	Fibrosis
7	68 M	VDDM	14	Dyspnoea	Mobitz II 2:1	Fibrosis
8	66 F	VDDM	8	Syncope	Mobitz II 2:1	Fibrosis
9	84 M	VDDM	5	Syncope	CHB	Fibrosis
10	73 M	VDDM	3	Syncope	Mobitz II 2:1	Ischaemia
11	74 M	VDDM	6	Syncope, dyspnoea	CHB	Fibrosis
12	32 F	DDDM	3	Dyspnoea	CHB	Congenital
13	66 M	DDDM	3	Syncope	Mobitz II 2:1	Fibrosis

*Fibrosis indicates that the presumed aetiology was idiopathic fibrosis of the ventricular conduction system. CHB, congestive heart block; COCM obstructive cardiomyopathy; CABG, coronary artery bypass graft.

end of each study period. All patients had been in the VDD pacing mode for at least three months before the study.

The first month was a run-in period to familiarise the patients with the symptom cards and the stress tests. During this first month the pacemaker mode was randomly programmed to either VVI or VDD mode but data collected for this first period were not subsequently analysed. The sequence of modes for each patient is shown in Table 2. For the second and third months the choice of mode was random between VVI followed by VDD or VDD followed by VVI. The mode was programmed randomly in the run in

period to ensure that all possible combinations of change in pacing mode were possible (the sequence VVI-VVI-VDD and VVI-VDD-VVI would not have occurred otherwise).

At entry to the trial and at the end of each study month the patients underwent a symptom limited maximum exercise stress test (bicycle ergometer) and total exercise capacity and maximum atrial rate were recorded. These tests were performed at the same time of day for each patient. In the VVI mode ventricular rate was set at 70 bpm; in the physiological mode the back-up rate was 50 bpm, the atrioventricular delay 150 ms, and the upper synchronous rate 150 bpm. The programmed mode was blind to the patient and observer.

The patients kept a daily diary card of their symptoms and were asked to record the number of attacks of chest pain, dizziness, palpitation, and syncope experienced each day. At the end of each month the patients were asked in addition to give a subjective score to the following symptoms in comparison with the previous month: chest pain, dizziness, shortness of breath, palpitation, and general well-being. The scores were 1—much worse, 2—a little worse, 3—no change, 4—a little improved, 5—much improved.

Table 2 Sequence of pacing modes

Case No.	Period 1	Period 2	Period 3
1	VDD	VDD	VVI
2	VDD	VVI	VDD
3	VVI	VDD	VVI
4	VDD	VVI	VDD
5	VVI	VVI	VDD
6	VVI	VDD	VVI
7	VVI	VDD	VVI
8	VDD	VVI	VDD
9	VDD	VVI	VDD
10	VDD	VDD	VVI
11	VVI	VVI	VDD
12	VDD	VDD	VVI
13	VDD	VDD	VVI

Fig. 1 Trial design.

Fig. 2 Maximal effort tolerance after chronic ventricular (VVI) and physiological pacing (VDD).

Only symptoms experienced during the second and third months were subsequently compared and analysed.

Analysis of the record card data was blind to the

observer. The patients were blind to the pacing mode. In view of the necessity to monitor the electrocardiogram during the exercise test this part of the study could not be blind to the observer. All stress tests and pacemaker programming were therefore performed by one of us (SLC) who was not subsequently involved in the analysis. In view of the ease of determining which pacing mode the patients were in (by, for example, feeling the pulse) the patients were deliberately not interviewed or examined during the study period.

STATISTICAL METHODS

Comparisons of the maximal exercise tests were made by a paired Student's *t* test. The comparisons for symptoms were expressed as number of attacks a week for each month and compared by Wilcoxon's ranked pairs test. The latter test was also used to compare the symptom scores. A *p* value of <0.05 was regarded as significant.

Results

Exercise tolerance was significantly greater during the physiological pacing mode (Fig. 2 and Table 3). The mean effort tolerance was 3250 ± 1676 kpm during VDD pacing and 2542 ± 1269 kpm during VVI pacing, an improvement of 27% ($p < 0.01$). None of the patients developed retrograde atrioventricular conduction during VVI pacing. There were no significant differences between the maximal atrial rates achieved during the two pacing modes. Four patients had little change in maximum effort tolerance. Three of these were found to have developed intermittent antero-

Table 3 Monthly symptom scores for shortness of breath and general well-being: total workload achieved in VVI and VDD modes together with maximum atrial rates

Case No.	Effort tolerance (kpm)		Maximum atrial rate (bpm)		Symptom score "shortness of breath"		Symptom score "general well-being"	
	VVI	VDD	VVI	VDD	VVI	VDD	VVI	VDD
1	3150	3100	148	150	1	3	2	3
2	1450	1600	100	120	3	3	2	4
3	4500	7100	140	150	1	4	1	4
4	4100	5300	135	145	3	3	2	2
5	650	1500	130	140	1	5	1	5
6	2200	3700	145	145	2	5	2	4
7	4300	4100	120	130	1	3	2	4
8	700	1300	145	140	3	3	3	3
9	1700	2350	125	125	3	3	1	4
10	2250	1900	82	85	3	3	2	3
11	2150	2800	140	145	2	4	2	3
12	2800	3100	145	130	2	3	2	4
13	3100	4400	110	150	1	3	1	3
Mean	2542**	3250**	128.1†	135†	2.0**	3.45**	1.72**	3.54**
	± 1269	± 1676	± 20.2	± 18.0	± 0.91	± 0.80	± 0.60	± 0.80

** $p < 0.01$.

† $p = \text{NS}$.

Fig. 3 Symptom scores for "shortness of breath".

grade conduction during the VVI stress test and had achieved similar ventricular rates during both modes. The fourth patient developed angina soon after the start of the study and was given beta blockers and was unable to achieve an atrial rate during exercise of greater than 85 bpm in either mode. The statistical analysis was on an "intention to treat basis", that is these patients were not excluded. The subjective assessment of "shortness of breath" was also improved during the physiological mode, with a mean symptom score of 3.45 ± 0.8 during VDD and 2.0 ± 0.91 during VVI ($p < 0.01$, Table 3, Fig. 3). The comparisons of symptoms during VVI and physiological pacing are shown in Tables 4 and 5. It can be seen that no patient experienced syncope during the

Table 4 Weekly attack rates and monthly symptom scores of symptoms—dizziness, palpitation, and chest pain

Symptom	Attacks per week			Mean symptom score		
	VVI	VDD/DDD	P	VVI	VDD/DDD	P
Syncope	0	0	NS	3	3	NS
Dizziness	2.49	1.45	NS	2.3	3.5	<0.02
	± 4.7	± 2.67		± 0.91	± 0.70	
Palpitation	1.76	0.35	<0.05	2.6	3.3	<0.05
	± 2.86	± 1.22		± 0.69	± 0.67	
Chest pain	1.08	1.16	NS	2.9	3.1	NS
	± 1.30	± 2.01		± 0.31	± 1.1	

Table 5 Weekly attack rates for individual patients

Case No.	Palpitation (attacks/wk)		Dizziness (attacks/wk)		Chest pain (attacks/wk)	
	VVI	VDD	VVI	VDD	VVI	VDD
1	0	0	0	0	0	0
2	1.5	0	9	8	0.5	0
3	8.5	4	0	3.5	4	1
4	1.5	0.5	0	0	1.5	7
5	0	0	0	0	0	0
6	1	0	1	0	0	0
7	3.5	0	1.45	1.17	3	0.5
8	0	0	0	0	2.25	1.5
9	0	0	2.25	6	0.91	3.17
10	0	0	2.75	0	1.5	2
11	0	0	0	0	0	0
12	0	0	0	0	0	0
13	7	0	16	0.25	0.5	0
Mean	1.76*	0.35*	2.49†	1.45†	1.08†	1.16†
	± 2.86	± 1.22	± 4.7	± 2.67	± 1.30	± 2.01

* $p < 0.05$.
† $p = NS$.

study. Dizziness was experienced more often during VVI pacing, but this only reached statistical significance for the monthly symptom score. Feelings of palpitation were also more frequent during VVI pacing and this was significant ($p < 0.05$) for both the weekly attack rate and the monthly symptom score. There were no significant differences between the two pacing modes for chest pain.

Fig. 4 Symptom scores for "general well-being".

The patient's subjective sensation of well-being was much improved during physiological pacing (symptom scores 3.54 ± 0.08 VDD, 1.72 ± 0.06 VVI, $p < 0.01$) (Fig. 4.)

Discussion

There are currently few published data concerning the long term clinical effects of physiological pacing in man. There have been several haemodynamic studies comparing atrioventricular sequential (DVI) and VVI pacing acutely at rest and during exercise.⁶⁻⁸ These authors have shown improved left ventricular haemodynamics when atrioventricular synchrony is maintained. Very few long term data are available, however. Sutton *et al.*⁹ have reported sustained improvement in exercise capacity after physiological pacing and two recent papers have shown chronic improvement in haemodynamic variables during VDD compared with VVI pacing.^{10,11} Neither of these two studies, however, has looked at symptoms in detail nor were they randomised controlled trials. Though the theoretical symptomatic benefits of physiological pacing are often expounded, no controlled data exist.

This prospective controlled study has shown that physiological pacing increases the maximal effort tolerance of patients when compared with VVI pacing and that this improvement persists over a period of one month. This is in contrast to VVI pacing where a diminution in haemodynamic performance has been seen chronically.¹² Three of the four patients with no benefit were found to have conducted intermittently during the stress test in the VVI mode. If these patients are excluded from analysis of exercise data then the *p* value changes from <0.01 to <0.001 .

Many patients with pacemakers, however, do not normally exercise to their maximum capacity and it is important therefore that subjective symptoms are improved by physiological systems. Ventricular pacing is an extremely effective treatment for preventing syncope caused by bradycardia and patients in the pacemaker clinic generally have few complaints after VVI pacing. Recent work, however, has shown that minor symptoms of dizziness and palpitation are common in VVI paced patients because of atrioventricular dissociation or retrograde atrioventricular conduction, often termed the pacemaker syndrome. An extreme form of this is when syncope occurs usually at the onset of ventricular pacing.¹³ Some groups of patients are exceptionally susceptible to this phenomenon, particularly patients with the hypersensitive carotid sinus syndrome.¹⁴ Similarly, patients with predominantly normal sinus rhythm may be acutely aware of the onset of ventricular pacing. This was one rationale behind the negative rate hysteresis

pacemaker.¹⁵

It is of importance therefore that subjective symptoms of dizziness and palpitation were less during the physiological mode, as was the improvement in the patient's overall feelings of well-being and improved effort tolerance. This occurred despite the fact that all of the patients had predominantly paced rhythm in the VVI mode and had been shown at electrophysiological study and subsequently not to exhibit retrograde atrioventricular conduction. There was considerable individual variation in symptoms, with patients often expressing a preference for the physiological mode with respect to a particular symptom without recording any specific instances of that symptom in the daily diary.

This study was designed as a within patient double blind trial. Unfortunately it was impossible to maintain blindness to the observer during the stress test and this may have biased the results. The intelligent patient could of course determine which mode he was in by feeling his own pulse and it is impossible to know how much this influenced the results. It is interesting to note that several patients were acutely aware of the change from VVI to VDD mode. These problems could only be overcome by a large parallel group study.

This study has been carried out on a small selected group of patients and has shown clear symptomatic benefits of atrial synchronous pacing compared with ventricular inhibited pacing. Dual chambered pacing systems are, however, more complex and expensive and are not applicable to all patients. It does not seem justified to implant these systems in severely disabled patients or those with another terminal condition unless the patient has a clear symptomatic complication of VVI pacing, for example pacemaker syndrome. These patients may, however, be managed more simply by rate hysteresis VVI pacing¹⁶ or DVI pacing rather than VDD or DDD units. Permanent atrial fibrillation is a clear contraindication to any conventional atrial system; intermittent atrial fibrillation, however, may allow a DDD system to be implanted if the arrhythmia is suppressed with drugs such as amiodarone but it has not yet been our practice to do this. Retrograde atrioventricular conduction is a relative contraindication because of the possibility of pacemaker induced artificial circus movement tachycardias. This problem has recently been reviewed.^{17,18} Retrograde conduction may be expected in about 13% of patients with complete heart block, 46% with intermittent (Mobitz II) block, and 89% of other patients with symptomatic bradycardia.¹⁹ Though artificial circus movement tachycardias may be to some extent controlled by advances in technology (for example programmable atrial refractory period) in the newer multiprogrammable DDD

pacemakers and in some instances by drugs,²⁰ retrograde atrioventricular conduction must be carefully assessed before implantation of a dual chamber atrial sensing system is contemplated. The physical size of these units is still a problem in some patients. At this centre only 30 to 40% of patients presenting for pacing are found to be suitable for physiological pacing.

In conclusion this study has shown that physiological pacing offers improved effort tolerance and symptomatic improvement when compared with ventricular pacing. The increase in implant complexity and cost is clearly justified in selected patients, and atrial synchronous ventricular inhibited pacemakers should be at least considered in all patients with symptomatic bradycardia caused by atrioventricular block.

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Requests for reprints to Dr David L Stone, Regional Cardiac Unit, Papworth Hospital, Papworth Everard, Cambridge CB3 8RE.

Notice

British Cardiac Society

The Autumn Meeting will be held at Wembley on 21 and 22 November 1983, and the closing date for abstracts was 26 July 1983.

The Annual General Meeting for 1984 will take place in Leicester on 11 and 12 April 1984, and the closing date for receipt of abstracts will be 3 January 1984.

The Autumn Meeting in 1984 will be held on 3 and 4 December 1984, and the closing date for receipt of abstracts will be 15 August 1984.

Corrigendum

We regret the following errors in the paper in the August issue by Dr E J Perrins and others on randomised controlled trial of physiological and ventricular pacing (p 112). In the footnote to Table 1 CHB should read complete heart block and COCM should read congestive cardiomyopathy.