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CARDIAC PACING

A Randomized Double-Blind Crossover Comparison of Four Rate-Responsive Pacing Modes

NEIL SULKE, BSc, MRCP, JOHN CHAMBERS, MD, MRCP, ATHANASE DRITSAS, MB, EDGAR SOWTON, MD, FRCP, FACC

London, England

The aim of this study was to compare, both subjectively and objectively, four modern rate-responsive pacing modes in a double-blind crossover design. Twenty-two patients, aged 18 to 81 years, had an activity-sensing dual chamber universal rate-responsive (DDDR) pacemaker implanted for treatment of high grade atrioventricular block and chronotropic incompetence. They were randomly programmed to VVIR (ventricular demand rate-responsive), DDIR (dual chamber demand rate-responsive), DDD (dual chamber universal) or DDDR (dual chamber universal rate-responsive) mode and assessed after 4 weeks of out-of-hospital activity.

Five patients, all with VVIR pacing, requested early reprogramming. The DDDR mode was preferred by 59% of patients; the VVIR mode was the least acceptable mode in 73%. Perceived "general well-being," exercise capacity, functional status and symptoms were significantly worse in the VVIR than in dual rate-responsive modes. Exercise treadmill time was longer in DDDR mode ($p < 0.01$), but similar in all other modes. During standardized daily activities, heart rate in VVIR and DDIR modes underresponded to mental stress. All rate-augmented modes overresponded to staircase descent, whereas the DDD mode significantly underresponded to staircase ascent.

Echocardiography revealed no difference in chamber dimensions, left ventricular fractional shortening or pulmonary artery pressure in any mode. Cardiac output was greater at rest in the dual modes than in the VVIR mode ($p = 0.006$) but was similar at 120 beats/min. Beat to beat variability of cardiac output was greatest in VVIR mode ($p < 0.0001$), with DDIR showing greater variability than DDD or DDDR modes ($p < 0.05$). Mitral regurgitation estimated by Doppler color flow imaging was similar in all modes, but tricuspid regurgitation was significantly greater in VVIR than in dual modes ($p < 0.03$).

Subjects who preferred the DDDR mode and those who found the VVIR mode least acceptable had significantly greater increases in stroke volume when paced in the DDD mode than in the ventricular-inhibited (VVI) mode at rest (22%) when compared with subjects who preferred other modes (2%, $p = 0.03$). No other objective variable was predictive of subjective benefit from any rate-responsive pacing mode. Thus, dual sensor rate-responsive pacing (DDDR) is superior objectively and subjectively to single sensor (VVIR, DDIR and DDD) pacing and subjective benefit from dual chamber rate-augmented pacing is predictable echocardiographically.

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The hemodynamic advantages of atrioventricular (AV) synchrony are well documented (1–3) and result in substantial clinical benefit (4,5). Rate-responsive pacing has similar advantages over fixed rate pacing (6,7). However, not all patients derive benefit from rate-augmented dual chamber pacing. Clinical acceptability may be related to cardiac output or chamber size. Differences in the incidence or severity of mitral or tricuspid regurgitation may affect symptoms.

The aim of this study was to correlate clinical findings after long-term pacing in four rate-responsive modes with echocardiographic assessment of cardiac function. Advances in echocardiography, specifically in Doppler technology, have allowed serial, noninvasive and accurate assessment of cardiac output and chamber dimensions as well as the incidence and extent of valvular regurgitation. These techniques have not been applied to evaluation of long-term changes in either cardiac output or valvular regurgitation in modern rate-responsive pacing modes.

Increasing pacemaker sophistication and development of new rate-responsive pacing modes allow the study of subjective, functional and hemodynamic effects of four modern rate-responsive pacing modes: VVIR (ventricular demand rate-responsive), DDIR (dual chamber demand rate-responsive), DDD (dual chamber universal) and DDDR (dual chamber universal rate-responsive) in a within-patient, prospective, randomized, double-blind, crossover design.

With the availability of new pacing modes and rate-response sensors it is essential to try to identify, before pacemaker implantation, those patients who may benefit from a specific programmed mode.

From the Department of Cardiology, Guy's Hospital, London, England.
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Address for reprints: Neil Sulke, BSc, MRCP, Guy's Hospital, Department of Cardiology, St. Thomas' Street, London SE1 9RT, England.

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Table 1. Patient Data

Pt. No.	Age (yr)/ Gender	Indication for Implantation*	Other Associated Diseases†	Pacemaker Type‡	Peak Programmed Sensor Rate (beats/min)	Peak Heart Rate Achieved in DDD Mode (beats/min)	LV Fractional Shortening (%) in DDD Mode
1	39/F	SNI, AVII		S	150	100	40
2	63/F	SNI, AVIII	MI	S	130	90	37
3	66/M	AVII	CHF, DM	M	138	130	30
4	52/M	SSS, AVII, AVIII		S	150	110	26
5	64/F	SSS, AVII, AVIII	CHF	S	130	120	27
6	43/M	SSS, AVIII	Post AVR	M	150	105	31
7	64/M	SSS, AVII	MI	S	135	145	29
8	18/F	SNI, AVIII		S	150	75	36
9	71/F	SNI, AVII, AVIII	MI	S	120	78	25
10	56/F	SNI, AVII, AVIII	DVT	S	150	96	33
11	50/F	HBA, SVT	VSD	M	150	148	34
12	27/F	HBA, SVT	AVNRT	M	150	132	43
13	60/M	SNI, AVIII	MI	S	150	100	29
14	41/M	AVIII	Post AVR, MI, CHF	M	160	142	15
15	48/F	AVII, AVIII		S	150	138	29
16	54/M	SNI, AVIII		S	150	109	40
17	52/M	SNI, AVIII	MI	S	150	90	23
18	63/F	SSS, AVII		M	140	104	39
19	81/F	SSS, AVII		M	125	125	40
20	37/F	HBA, SSS		S	150	151	36
21	74/F	SSS, AVIII	MI	M	135	81	28
22	18/M	SNI, AVII, AVIII	ASD	S	150	108	27

*Indication for implantation: AVII = second degree atrioventricular (AV) block; AVIII = third-degree AV block; HBA = after His bundle ablation; SNI = sinus node incompetence; SSS = sick sinus syndrome; SVT = supraventricular tachycardia. †Other associated diseases: ASD = atrial septal defect; AVNRT = AV node reentrant tachycardia; AVR = aortic valve replacement; CHF = congestive heart failure; DM = diabetes mellitus; DVT = deep venous thrombosis; MI = myocardial infarction; VSD = ventricular septal defect. ‡Pacemaker type: M = Siemens P51T Multilog; S = Pacesetter 2020T Synchrony. Left ventricular (LV) fractional shortening (normal range: 28–44%). F = female; M = male.

Methods

Study subjects (Table 1). Twenty-two patients, aged 18 to 81 years (mean 51.9), 41% men, had an activity-sensing DDDR pacemaker implanted; 14 had a Pacesetter 2020T Synchrony and 8 a Siemens P51T Multilog. Indications for implantation are shown in Table 1. Seventeen patients had sinus node incompetence demonstrated by failure to increase the P wave rate to >110 beats/min or by ≥10% of the rate at rest during (1) supine handgrip stress, (2) supine straight leg raising and (3), where possible (in 12 cases), during treadmill exercise. Fifteen patients showed an abnormal sinus node recovery time during electrophysiologic testing before implantation and seven patients had evidence of retrograde ventriculoatrial (VA) conduction. All patients were ventricular pacing dependent at rest.

Thirteen patients were randomized immediately after pacemaker implantation and nine were randomized a mean of 9.6 months (range 3 to 12) after implantation. During this time these patients were programmed to dual modes (DDD in five, DDDR in two, DDI in one and DDIR in one).

Study design. This was a prospective, randomized, double-blind, crossover comparison of four rate-responsive pacing modes: VVIR, DDIR, DDD and DDDR with each patient acting as his or her own control. Criteria for comparison were both subjective (symptomatic, functional state, exercise tolerance and health perception) and objective (maximal exercise treadmill tolerance, electrocardiogram [ECG] monitored standardized daily activities and echocardiography).

Each patient gave written informed consent and was programmed in a randomized sequence (using random number tables) to each of the four study modes for 4 week periods of out-of-hospital activity by one of the investigators (N.S.). Assessment was undertaken after each 4 week period. Throughout the study all patients and the other investigators remained blinded to the programmed pacing mode.

Pacemaker programming. Before patients were inducted into the study, satisfactory dual chamber pacing function was confirmed and rate-response slopes in each patient were programmed according to the manufacturer's instructions. All patients were programmed to the "medium" recovery slope. The rate-response variables remained unchanged thereafter and for the duration of the study. If the programmed mode caused intolerable discomfort or distress, early crossover to the next mode was instituted after full subjective and objective assessment was carried out.

Subjective assessment. Three questionnaires were used for subjective assessment. *The first* utilized visual analog scales to assess patient-perceived "general well-being" and exercise capacity. Subjects were required to place a mark on a line 15 cm long from 0% (extremely unwell or inability to exercise) to 100% (extremely well and unlimited exercise capacity). The result was expressed as a percent of the distance from the discrete minimal point to the position of the mark divided by the length of the line.

The second questionnaire assessed the patient's perceived physical capability using the well validated Specific Activities Scale functional status questionnaire (8). This grades patients from class I (unlimited physical capacity) to class IV (grossly incapacitated).

The third questionnaire assessed the incidence and frequency of symptoms of mild cardiac failure or pacemaker-induced hemodynamic dysfunction (pacemaker syndrome) (9), using a quantitative score where 1 = all of the time, 2 = most of the time, 3 = some of the time, 4 = occasionally and 5 = never.

Objective assessment. Patient performance was compared with that of 20 control subjects, aged 23 to 76 years (60% male, mean age 55 years) with no apparent heart disease, who performed identical protocols. Patients were continuously monitored by a six lead ECG during the objective study period.

Heart rate was calculated from the mean RR interval of the five consecutive beats immediately after each protocol stage was achieved. The percent change in heart rate was calculated as:

$$\frac{(\text{Observed heart rate} - \text{Rest heart rate})}{(\text{Rest heart rate})} \times 100.$$

1. *Graded exercise treadmill testing.* Patients were assessed using the chronotropic assessment exercise protocol (CAEP) (10). Total exercise time and rest and peak heart rates were determined in each patient and percent change in heart rate was calculated.

2. *Postural change.* Patients rested supine on an examination couch with two pillows for 3 minutes. They then elevated to the sitting position and immediately to the standing position.

3. *Mental stress.* While seated, patients were asked to serially subtract 7 from 100 for 2 minutes clearly vocalizing each calculation while the supervising clinician vigorously encouraged them. Rest and peak heart rates were obtained and percent change in heart rate calculated as before.

4. *Suitcase lifting.* A standard suitcase that measured 45 × 35 × 12 cm and weighed 10 kg was used. Patients were randomly assigned to suitcase lifting with either the right or the left arm and were instructed to raise the case from the floor to above hip height four times without stopping. After a rest period, the procedure was repeated with the opposite arm. Rest and peak heart rates were noted before and immediately after each series of lifts.

5. *Staircase ascent and descent.* Patients were monitored by telemetered ECG recordings using a Hewlett-Packard 78571B recorder while ascending two flights of stairs as rapidly as possible (30 steps, each 15 cm tall, pitch 27 cm). After resting, the patients then descended the same flights as fast as they could. Heart rate was assessed at rest and then at 15 s intervals from the beginning of ascent or descent for a total of 75 s. All patients completed the descent and all but two patients completed the ascent within the 1st 15 s; thus, the remaining 60 s constitutes the recovery period.

Echocardiographic assessment. A Hewlett-Packard 77020A system with a 2.5 MHz duplex probe and a 1.9 MHz continuous wave transducer was used. One investigator (J.C.) undertook all echocardiographic examinations, eliminating interobserver variability. So that the operator remained unaware of the pacing mode, simultaneous ECG was not used. Therefore, M-mode recordings were taken at conventional levels and dimensions measured from leading edge to leading edge (11), with left ventricular diastolic diameter measured as the greatest dimension in diastole and the systolic diameter as the smallest diameter in systole.

Stroke volume was calculated as the product of the systolic velocity integral and the cross-sectional area available for flow. Subaortic cross-sectional area was measured from inner to inner echo at the level of the anulus in a parasternal long-axis frame frozen early in systole (12). The systolic velocity integral was calculated from the aortic envelope recorded from the apical position. Continuous wave Doppler recording was used to avoid differences in positioning of the sample volume in serial measurements. However, in one patient with a prosthetic aortic valve, pulsed Doppler recording was used. The systolic velocity integral (SVI) was averaged over five beats by the method of triangulation (SVI = ½ × EJT × Vmax), where EJT = ejection time and Vmax = maximal velocity. This has been shown to be equivalent to planimetry (13,14).

Pulmonary artery systolic pressure was estimated, where possible, from the tricuspid regurgitant jet recorded by continuous wave Doppler ultrasound. Pressure was calculated using the formula: $6/5 \times 4\ (Vmax^2)$ (15). Signals that lacked a clearly defined envelope were discarded. The Doppler color flow system was set to the same enhanced threshold map for every study with maximal packet size, minimal reject and spatial filtering. The gain was set to the level just below that at which color flooding occurred. Mitral and tricuspid regurgitant jets were determined by planimetry in the view that gave the largest jet area and the results were expressed as a percent of the total left or right atrial area (16,17).

Pacemakers were reprogrammed to 120 beats/min to partially simulate the effect of exercise. If the study mode was VVIR or DDIR, VVI mode was used; if the study mode was DDD or DDDR, DDD mode was used. Five minutes was allowed after reprogramming as an equilibration period.

Statistical analysis. Results are reported as mean values ± SD. Continuous variables were compared between modes using the paired Student's t test; discrete variables were compared using the Wilcoxon signed rank test. When patients were categorized according to mode preference and continuous variables compared, unpaired t tests were used.

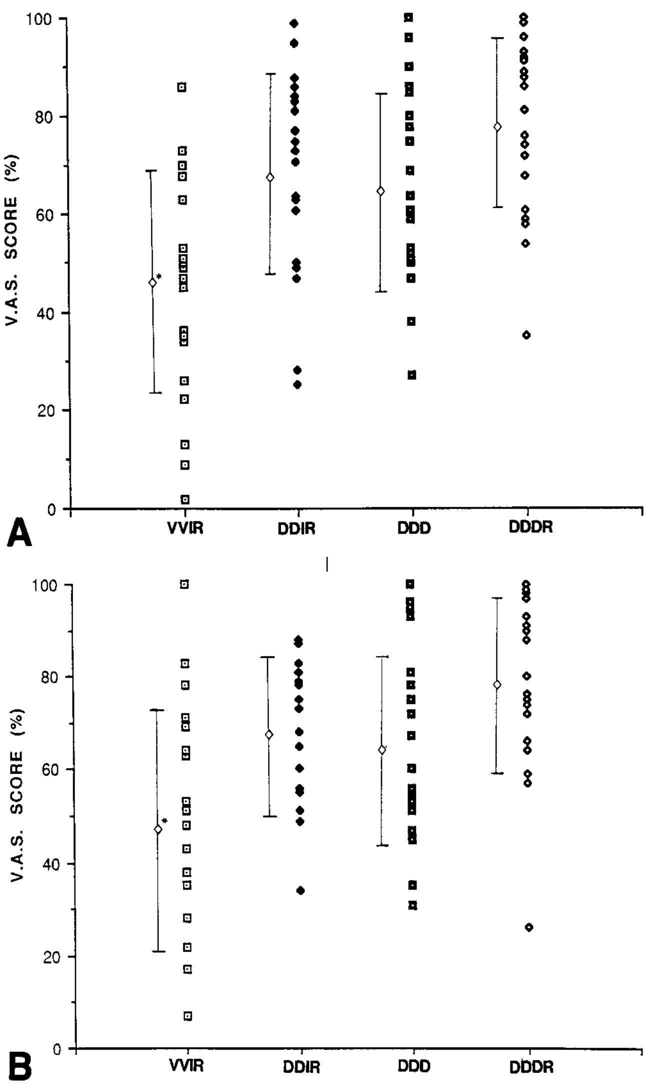

Figure 1. Patient perception of general well-being (**A**) and exercise capacity (**B**), both assessed by visual analogue scale (V.A.S.), with four modes of pacing. *$p < 0.001$.

When more than two comparisons were undertaken of a given variable, the Bonferroni correction was utilized. A p value <0.05 was considered significant.

Results

Subjective Assessment

Intolerable symptoms. Five patients, all with VVIR pacing, demanded early crossover, in three cases within 24 hours of programming to this mode. All had intolerable symptoms, such as effort dyspnea, palpitation, dizziness and tiredness, and in all cases symptoms were relieved by reprogramming to the next study mode.

Patient perception of general well-being and exercise capacity. Assessment was made by visual analogue scale (VAS) (Fig. 1). General well-being was significantly worse in VVIR mode than in any dual mode (VAS score 46.3 ± 23.1 in VVIR, 70.3 ± 14.7 in dual modes, $p < 0.001$). Perceived exercise capacity was also significantly lower in VVIR than in any dual mode (VAS score 47.9 ± 23.8 in VVIR, 70.1 ± 15.4 dual modes, $p < 0.001$).

Patient perception of cardiac functional status as assessed by the Specific Activities Scale. This revealed mean scores that were significantly higher (i.e., poorer functional class) in VVIR than in all dual modes (1.73 ± 0.63 in VVIR, 1.3 ± 0.54, all dual modes, $p < 0.05$).

Specific symptom scores. Specific symptom scores were also significantly higher (i.e., increased symptoms) in VVIR than in any dual mode (23.5 ± 11.5 in VVIR mode, 14.4 ± 8.1 in dual modes, $p < 0.01$). The most prevalent symptom in VVIR mode was "shortness of breath," in 11 patients (50%). In the other modes "tiredness" was the most prevalent symptom (DDIR, eight patients [36%]; DDD, 10 patients [45%]; and DDDR eight patients [36%]). The second most prevalent symptom was "tiredness" in VVIR, "shortness of breath" and "neck flutter" (equal) in DDIR, "shortness of breath" in DDDR and "light-headedness" in DDD.

Preferred and least acceptable modes (Fig. 2). The preferred mode was defined by the patient's selected period of preference after the study had been completed. This was not consistent with the results of the subjective questionnaires in six cases. In two cases the questionnaires unequivocally favored a mode different from that selected by the patient. In these cases the patient was asked to reassess. In both cases, modes consistent with those suggested by the questionnaire were then chosen. In two cases both questionnaires and patient selection were equivocal and "no preference" was chosen as the preferred mode. In two cases VVIR mode was clearly the least acceptable by both questionnaire and patient choice, but other modes were of equal preference and therefore "any dual" was chosen as the preferred mode.

Patients also selected the least acceptable mode after the study was completed. In all but two cases, in which "no preference" was selected, the least acceptable period during the study was consistent with the least acceptable mode suggested by the subjective questionnaires.

Objective Assessment

Graded exercise treadmill tests (Fig. 3). Exercise times did not significantly differ among VVIR, DDIR and DDD modes (10.2 ± 3.6, 10.15 ± 3.4 and 10.0 ± 3.2 min, respectively, p = ns). However, exercise time in the DDDR mode was significantly longer (11.3 ± 3.4 min, $p < 0.01$, although this value did not differ from that in control subjects). Peak heart rate was similar in all rate-augmented modes (VVIR, DDIR and DDDR), but that in DDD was significantly less during this protocol (DDDR 137 ± 21, DDD 113 ± 23 beats/min, $p < 0.01$).

Mental stress (Fig. 4). The maximal percent increase in heart rate during this protocol was similar to that of control subjects in DDD and DDDR modes, but was significantly less in DDIR and VVIR modes (14.8 ± 14.2% DDD, 12.9 ± 12.1% DDDR, 12.0 ± 7% controls, p = NS; 5.1 ± 6.5% VVIR and 5.6 ± 7.0% DDIR, $p < 0.01$).

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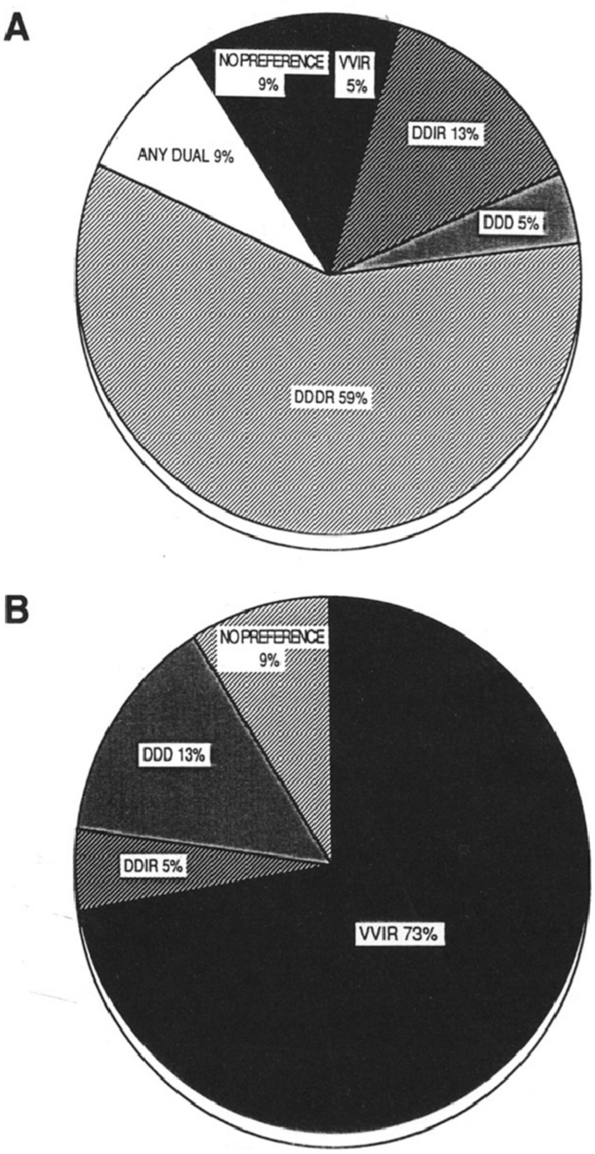

Figure 2. Preferred (**A**) and least acceptable (**B**) rate-responsive pacing modes.

Postural change. Change in heart rate from lying to sitting was lowest in the DDD mode and from sitting to standing it was least in VVIR mode (5.8 ± 5.8 and 4.8 ± 4.4%, respectively), but heart rate changes did not differ significantly in any mode or from control values during this protocol.

Suitcase lifting. The maximal increase in heart rate during suitcase lifting with the nonpacemaker arm was lower than that with the pacemaker arm in all modes except DDD; however, this was not statistically significant. Heart rate changes were similar in all modes and did not significantly differ from those in control subjects during this protocol (VVIR—9 ± 8% nonpacemaker arm, 19 ± 14% pacemaker arm; DDIR—10 ± 10% nonpacemaker arm, 16 ± 13% pacemaker arm; DDDR—13 ± 7% nonpacemaker arm, 18 ± 10% pacemaker arm; DDD—10 ± 9% nonpacemaker arm, 10 ± 9% pacemaker arm; control—11 ± 14% right arm, 12 ± 13% left arm).

Staircase ascent and descent (Fig. 5). The percent change in heart rate at 15 s was significantly less in DDD mode than in control subjects (22 ± 15 and 42 ± 18%, respectively, $p < 0.001$). However, heart rate changes were similar to control values in all modes at every other stage of the staircase ascent.

During staircase descent, percent change in heart rate at 15 s was significantly greater in VVIR, DDIR and DDDR modes ($p < 0.001$, $p < 0.001$, and $p < 0.01$, respectively) than in control subjects. By 30 s, however, only VVIR showed a significantly higher heart rate response compared with the control value (20 ± 7 and 13 ± 5%, $p < 0.01$).

Echocardiography

Hemodynamic measurements. Left atrial internal dimensions and left ventricular internal dimensions during systole and diastole did not differ in any mode at rest or during pacing at 120 beats/min. Left ventricular fractional shortening was similar in all modes (VVIR 33.7 ± 9.7%, DDIR 32.9 ± 7.3%, DDD 32.4 ± 9.3% and DDDR 30.7 ± 7.2%; p = NS).

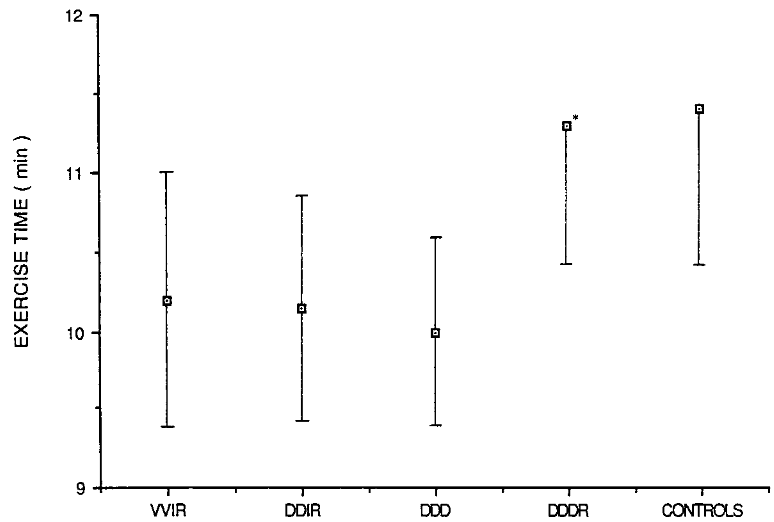

Figure 3. Peak exercise time during graded treadmill testing (chronotropic exercise assessment protocol) in four rate-responsive pacing modes and in 20 control subjects. *$p < 0.01$.

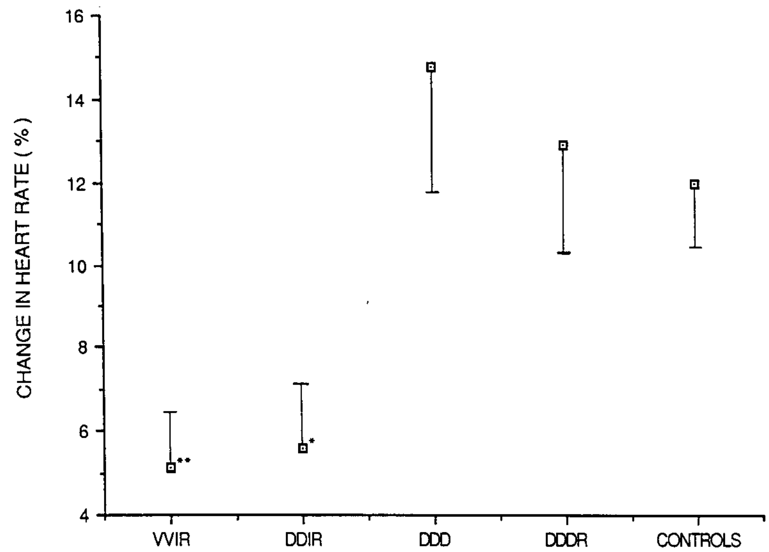

Figure 4. Heart rate response to mental stress in four rate-responsive pacing modes and in 20 control subjects. *p < 0.02; **p < 0.01.

Pulmonary artery pressure could be evaluated in all four modes in only 10 patients. In this subgroup, pulmonary artery pressure did not significantly differ in any mode.

Cardiac output at rest in the VVIR mode was significantly less than in dual modes (3.6 ± 0.7 liters/min in VVIR, 4.41 ± 1.02 liters/min in all dual modes, $p = 0.006$). However, when programmed to 120 beats/min there was no difference in cardiac output (VVI 4.7 ± 0.9 and DDD 4.95 ± 0.96 liters/min, p = NS).

Valvular regurgitation. Incidence of tricuspid and mitral regurgitation was greater in VVIR mode than in dual chamber modes. This was not statistically significant at rest or at 120 beats/min in any mode (incidence of tricuspid regurgitation at rest—VVI mode 73%, DDI 59%, DDD 57%; at 120 beats/min: VVI mode 75% and DDD 60%; incidence of mitral regurgitation at rest—VVI mode 45%, DDI 32%, DDD 34%; at 120 beats/min: VVI mode 41% and DDD mode 27%).

The extent of Doppler color flow imaging–estimated mitral regurgitation was also similar in all modes at rest and at 120 beats/min. However, the extent of tricuspid regurgitation was significantly greater in VVI mode than in dual modes at rest and at 120 beats/min (Fig. 6).

Beat to beat variability of cardiac output (Fig. 7). Beat to beat variability was measured as the percent change in stroke volume index over five consecutive beats. It was significantly greater at rest in the VVI (VVIR) mode than in DDI (DDIR) or DDD (DDD or DDDR) modes (VVI 32 ± 16%, DDI 22 ± 9%, $p < 0.05$; DDD 15 ± 6%, $p < 0.0001$). At 120 beats/min this difference was more marked between VVI (VVIR, DDIR) and DDD (DDD, DDDR) modes (VVI percent change 39 ± 20%, DDD 17 ± 7%, $p < 0.0001$).

Objective Predictors of Subjective Benefit

Role of ventricular performance and valvular regurgitation. Further data analysis based on each subject's preferred and least acceptable mode was undertaken to evaluate objective predictors of subjective benefit. There was no difference in left ventricular fractional shortening, mean left atrial internal diameter, or extent of tricuspid regurgitation assessed by Doppler color flow mapping between subjects finding the DDDR mode preferable or VVIR the least acceptable mode, and those preferring modes other than the DDDR mode or finding the dual chamber modes least acceptable.

There was no difference in exercise tolerance or less appropriate heart rate response to standardized daily activities in the least acceptable mode compared with the preferred mode.

Role of VA conduction. The incidence of retrograde VA conduction at implantation did not result in increased preference for dual chamber modes (56% of subjects with intact VA conduction preferred DDDR versus 62% without intact VA conduction). Fewer subjects with intact VA conduction (56%) found VVIR mode the least acceptable, although this difference was not statistically significant (85% without VA conduction found VVIR least acceptable).

There was no difference in beat to beat variability of cardiac output in patients preferring DDDR mode or finding VVIR least acceptable compared with those preferring single chamber rate-responsive pacing or finding dual chamber pacing least acceptable.

Role of stroke volume (Fig. 8). Subjects who preferred the DDDR mode had significantly greater increases in stroke volume when paced in the DDD mode than the VVI mode at rest compared with those preferring other modes (subjects preferring DDDR: percent increase in stroke volume from VVI to DDD pacing, 21.9 ± 23.1%; those preferring other modes: 1.75 ± 15.5%, $p = 0.03$). Similarly, subjects who found the VVIR mode least acceptable had significantly greater increases in stroke volume from VVI to DDD pacing than did subjects who found other modes least acceptable (subjects finding VVIR least acceptable: stroke volume increase VVI to DDD pacing 19.25 ± 21.1%; subjects finding

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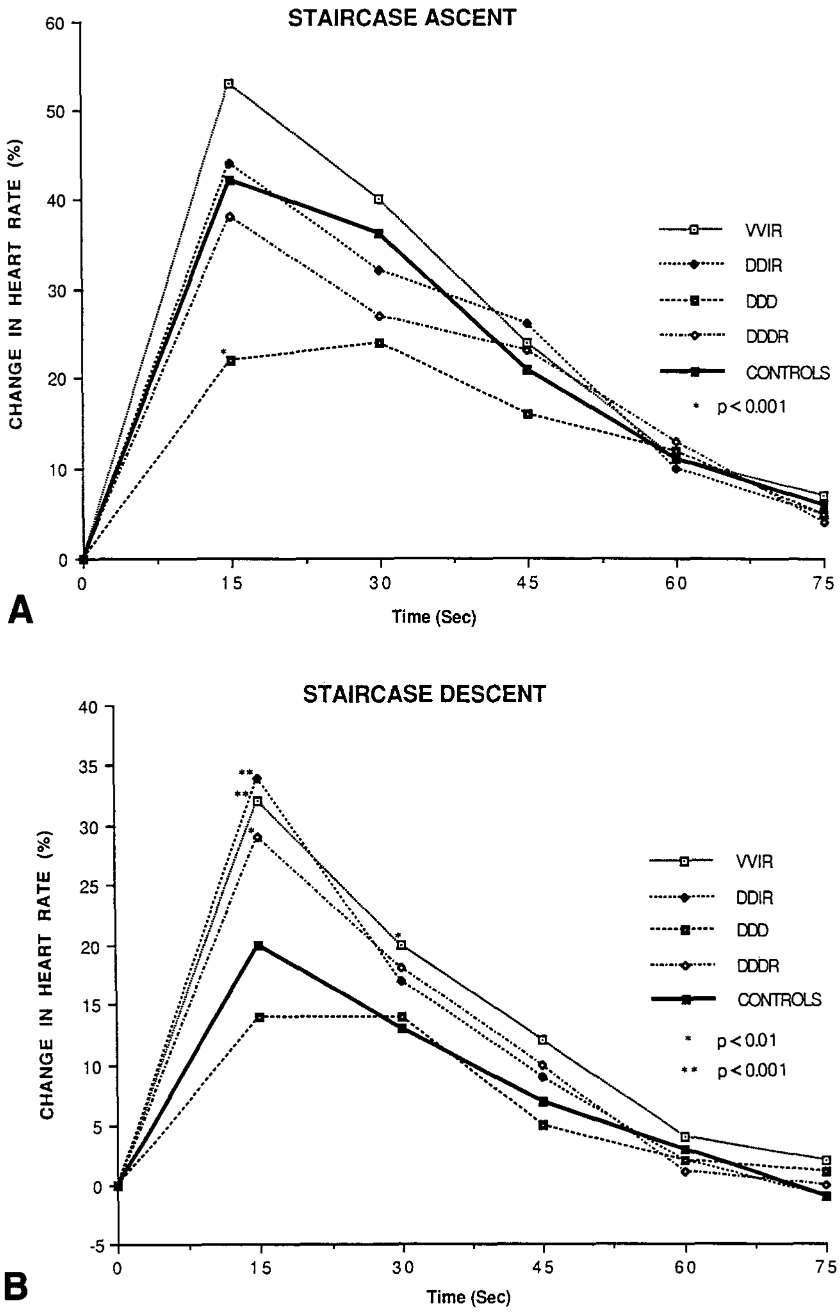

Figure 5. Change in heart rate during staircase ascent (**A**) and during descent (**B**).

other modes least acceptable: stroke volume decrease 4.2 ± 17.3%, $p < 0.03$). This effect was not seen during pacing at 120 beats/min (Fig. 8).

Discussion

Advances in atrial electrode design and in pacing electronic circuitry have resulted in widespread use of dual chamber pacing, with its known hemodynamic advantages over fixed rate ventricular pacing. More recently, with the advent of rate-responsive sensors, candidates for dual and single chamber pacing now include patients with chronotropic incompetence (18).

Patients who benefit from dual chamber pacing. The increased complexity of dual chamber and rate-responsive pacemakers, and the increased cost over simpler alternatives, demands better definition of the roles of these modern pacemakers. Subgroups of patients who benefit from DDD (dual chamber) pacing over fixed rate VVI (ventricular) pacing have been identified to include those who manifest the pacemaker syndrome (9) (hypotension, retrograde VA conduction or unacceptable symptoms during ventricular pacing), those with congestive heart failure, and young and active patients requiring rate adaptation (19,20). Elderly patients also derive significant benefit from rate-responsive pacing (21). However, cost comparison studies of VVI and DDD pacing suggest that generalized use of dual chamber pacing is unjustified and specific patients should be identified who will derive most benefit from more costly devices (22).

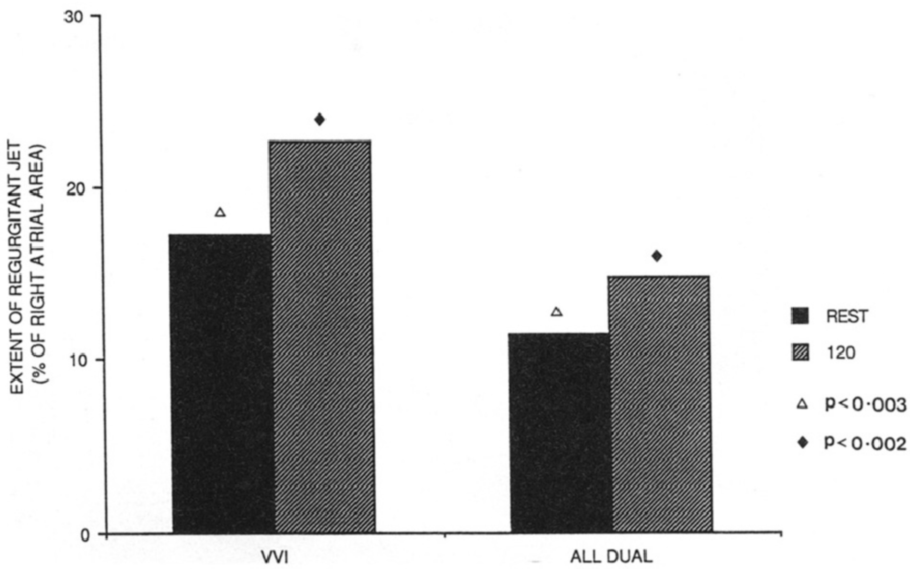

Figure 6. Extent of tricuspid regurgitation, assessed by Doppler color flow mapping, at rest and during pacing at 120 beats/min in VVI and dual chamber modes.

Previous randomized studies of different pacing modes. Perrins et al. (4), comparing VDD and VVI pacing, observed symptomatic benefit and a 27% increase in exercise tolerance in the dual chamber mode. Kristenssen et al. (23) observed a 14% increase in exercise tolerance in VDD over VVI pacing and symptomatic improvement. Rediker et al. (24) compared DDD and VVI pacing and found that most patients preferred the DDD mode and had improved exercise tolerance in this mode.

Present study: patient pacing mode preference. No study has compared modern rate-responsive pacing modes in this way or used modern Doppler technology to assess cardiac output and valvular regurgitation. The DDDR mode represents the only dual sensor (atrial rate plus activity sensing in this study) rate-responsive pacemaker available. It thus differs from the remaining study modes, which are all single-sensor-triggered (VVIR mode, single lead; DDIR mode, dual lead, both effectively nonatrial tracking, activity sensor-triggered; DDD mode, dual lead, atrial-triggered [18]).

Our study patients were deliberately selected on the basis of clinical criteria to benefit from rate-response augmentation because they had known chronotropic incompetence combined with high grade AV block before implantation. These preselection criteria could be the reason that most patients in our study selected DDDR as the preferred pacing mode.

Rate-responsive versus fixed rate pacing. However, 73% of patients found VVIR the least tolerable rate-responsive pacing mode. Nevertheless, only five patients (23%) demanded early crossover, in each case from the VVIR mode. This rate is markedly lower than that of a previous crossover study (24) in which up to 42% could not tolerate single chamber pacing. This difference may be due to the enhancing effect of rate-response augmentation over fixed rate

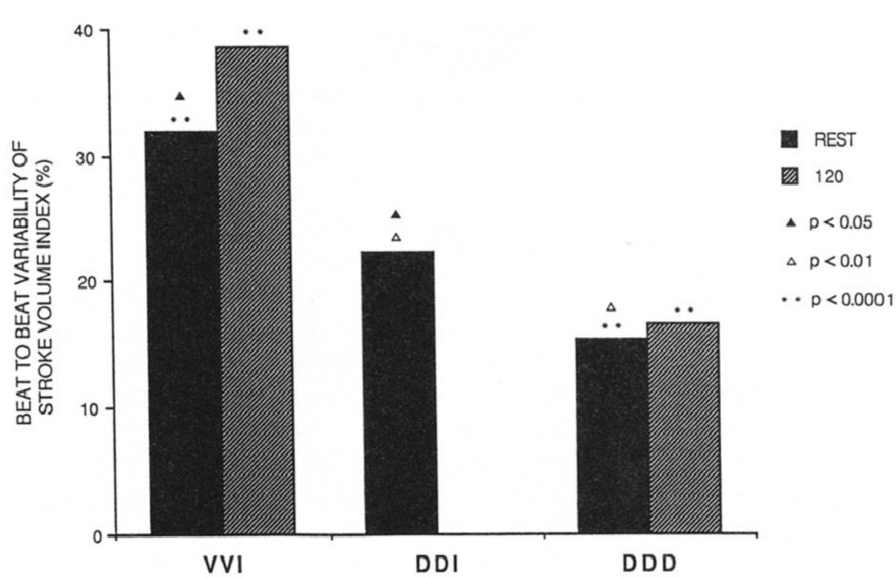

Figure 7. Beat to beat variability in stroke volume index in single and dual chamber rate-responsive modes at rest and during pacing at 120 beats/min.

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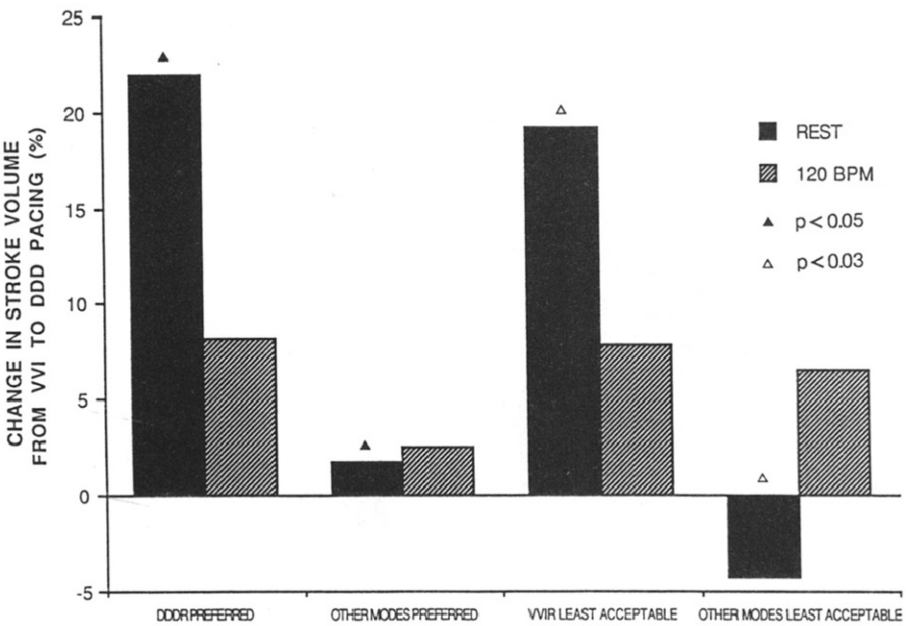

Figure 8. Stroke volume changes as a predictor of pacing mode preference. At rest, patients preferring DDDR mode or finding VVIR least acceptable have significantly greater increases in stroke volume when paced in DDD mode than in VVI mode.

pacing. We (25) have previously shown that 30% of patients demand early crossover to VVIR mode from fixed rate VVI pacing.

Role of dual chamber demand rate-responsive mode (DDIR). The DDIR mode has been advocated as a universal pacing mode with no absolute contraindications and therefore one that is suitable for use in the bradycardia-tachycardia syndrome or in patients undergoing His bundle ablation for supraventricular arrhythmias (26). During our study, four patients (18%) preferred DDIR pacing over the remaining modes. These patients all had paroxysmal supraventricular tachycardia, but none had undergone His bundle ablation. In contrast, three patients who had undergone His bundle ablation preferred either the DDDR mode (two patients) or had no preference for any mode (one patient).

Exercise testing and daily activity performance. We have shown, as have previous studies (27), that exercise tolerance does not differ between VVIR and DDD modes. In addition, exercise tolerance in DDIR mode was similar to that in both VVIR and DDD modes. However, treadmill exercise time in DDDR mode was significantly longer and similar to that found in the control subjects. This may be because most patients required rate augmentation. During the treadmill protocol, sustained AV synchrony supplied in the DDDR mode, culminating in an appropriately increased heart rate, was clearly superior to the alternative modes. Several patients had similar maximal heart rates in both DDD and DDDR modes, but in most cases this was not maintained in the DDD mode because of sinus node incompetence. This inadequate rate response adversely affected overall exercise tolerance. In the DDIR mode, three patients exhibited sustained high atrial rates during the protocol and thereby lost AV synchrony. Other patients had more rapid initial increases in atrial rate than the programmed sensor slope and therefore lost the benefit of AV synchrony in the early exercise phase. This suggests that the DDIR mode is most useful in a small minority of appropriately selected patients.

Heart rate response in rate-augmented modes during standardized daily activity protocols and graded exercise treadmill tests. These showed the benefits and deficiencies of activity-sensor-driven, rate-responsive pacing compared with absent sensor response (DDD mode) and control subjects. Smooth and appropriate chronotropic response was seen in all sensor-augmented rate-response modes during the chronotropic assessment exercise protocol, confirming appropriate rate-response programming. However, the DDD mode induced a lower maximal heart rate response as well as inappropriate rate fall-off during the exercise phase. During mental stress the atrial tracking modes, DDD and DDDR, yielded peak heart rate responses similar to those in control subjects, but the nontracking modes, DDIR and VVIR, relying on a sensor type that does not respond to such stress, significantly underresponded. Similarly, during activities requiring upper thorax movement on the side of the pacemaker implant (as in our suitcase elevation protocol), heart rate response was greater in all rate-augmented modes than in DDD mode. This was not seen with nonpacemaker arm activity. During staircase descent the sensor overresponded in VVIR, DDIR and DDDR modes compared with DDD and control heart rate responses, as has been reported with activity sensors (27,28).

Heart rate during the standardized daily activity protocol did not significantly differ in either preferred or least acceptable modes and therefore cannot be considered a predictive test of acceptability of single or dual chamber rate-responsive pacing.

Previous echocardiographic studies of pacemaker hemodynamics. Stewart et al. (29) first identified patients with "VA conduction or pacemaker syndrome" as having a greater increase in cardiac output at rest with DDD than with VVI pacing. Labowitz et al. (30) suggested that patients with "normal" left atrial dimensions were most "sensitive" to loss of AV synchrony. The crossover study of Rediker et al. (24) suggested that both percent fractional shortening and cardiac output were higher with DDD pacing, but these variables were not predictive of intolerance to VVI pacing. Lascault et al. (31) noted increased beat to beat variability in aortic and mitral flow in the VVI mode and suggested that this was predictive of benefit from dual over single chamber pacing. Pearson et al. (32) found that patients with a decreased cardiac output, VA conduction and lower stroke volume in the VVI mode than in DVI and VDD modes benefited most from dual chamber pacing.

Echocardiographic findings after long-term pacing in four rate-responsive modes. Echocardiographic assessment was performed at rest; therefore, in effect, we assessed pacing in only three modes: VVI, DDI and DDD. To partly simulate the effect of chronotropic response to exercise, each patient was assessed while paced at 120 beats/min. VVIR and DDIR modes were programmed to VVI at 120 beats/min and DDD and DDDR to DDD at 120 beats/min. Thus, each patient was studied twice in VVI and DDD modes at 120 beats/min. This procedure also allowed confirmation of the consistency and accuracy of the echocardiographic technique. Stroke volume and cardiac output variability after serial assessment in this way was <10% in all patients in both VVI and DDD modes.

Objective prediction of subjective benefit. Most previous studies of pacemaker hemodynamics have assumed that improved cardiac output can be equated with enhanced clinical benefit during everyday activity. Our data are based on a controlled, double-blind, within-patient comparison of subjective and objective variables and we have not assumed that optimal hemodynamic variables correlate with improved quality of life. We have not shown that left atrial size is a predictor of benefit from dual chamber rate-responsive pacing, in contrast to the findings of Labowitz et al. (30); however, fewer patients in our study had congestive heart failure or a significantly enlarged atrium.

Incidence of retrograde VA conduction at implantation. This variable did not predict either a lower cardiac output or a poorer functional performance in any rate-responsive pacing mode or preference for dual chamber rate-responsive pacing in contrast to the suggestion of others (29,32). Our findings may differ because we also studied long-term subjective changes and VA conduction is a highly variable measure, accurately assessed only by endocardial electrograms and not by the surface ECG (33).

Percent fractional shortening. No significant difference in percent fractional shortening occurred in any rate-responsive pacing mode. It was therefore not predictive of benefit from dual over single chamber rate-responsive pacing unlike the findings of Rediker et al. (24).

Beat to beat variability of cardiac output. This is greatest in the VVI mode after long-term VVIR pacing. The DDIR mode showed greater beat to beat variability than did the DDD or DDDR mode. Although this finding is consistent with that of Lascault et al. (31) with regard to VVI and DDD pacing, greater variability was not evident in VVI mode or decreased variability in DDD mode among patients who preferred dual chamber rate-responsive pacing. It is thus not a predictive variable of mode preference in rate-responsive pacing.

Extent of Doppler color flow imaging-estimated valvular regurgitation. This has not been assessed previously in different pacing modes. Tricuspid regurgitation is more extensive in VVIR mode than in dual rate-responsive modes, but neither the incidence nor extent of tricuspid regurgitation was predictive of benefit from dual chamber rate-responsive pacing. The incidence of valvular regurgitation in our patients is somewhat higher than might be expected in a normal population. This difference may be partly due to the presence of the ventricular electrode preventing normal tricuspid valve apposition, as well as to the abnormal left and right ventricular contraction that results from artificial pacing by way of an electrode placed at the right ventricular apex.

Cardiac output at rest. This was less in VVI than in dual modes, but a lower cardiac output in the former was not suggestive of symptomatic benefit from dual chamber over single chamber rate-responsive pacing. These hemodynamic findings are therefore in agreement with those of Stewart et al. (29), but argue against inferring symptomatic benefit solely from increased cardiac output at rest during rate-responsive pacing. An appropriate increase in cardiac output in response to metabolic demand, as occurs in VVIR pacing, may modify patient acceptability of single chamber pacing so that when single chamber pacing is compared with dual chamber pacing, cardiac output at rest is not a predictor of symptomatic benefit.

Stroke volume at rest: the only predictor of mode preference. Stroke volume at rest was the only echocardiographic variable that predicted improved patient acceptability of dual chamber over single chamber rate-responsive pacing. Patients who showed a mean percent increase in stroke volume of >15% from VVI to DDD pacing at rest preferred the DDDR mode and found the VVIR mode the least acceptable of the four rate-responsive pacing modes assessed. Conversely, patients with a small increase (<5%) or a decrease in stroke volume tended to derive little benefit from dual chamber rate-responsive pacing.

During fixed rate VVI pacing, patients with a compliant ventricle adapt to increased metabolic demand by increasing stroke volume (34). Our findings and those of Pearson et al. (32) confirm that stroke volume is an important variable for prediction of benefit from either single or dual chamber rate-responsive pacing.

Clinical implications. In patients who require implantation of a pacemaker, a method predicting benefit from a specific pacing mode would be helpful in management and conserve resources. This study shows that stroke volume is a predictor of rate-responsive mode preference. However, although echocardiographic examination itself is noninvasive and easy to perform, either temporary or permanent pacing electrodes must be inserted into the right atrium and right ventricle and appropriate cardiac stimulation undertaken in order to derive this information. We also cannot be sure that our echocardiographic assessment after long-term pacing in rate-responsive modes can be extrapolated to a single echocardiographic assessment of temporary cardiac pacing.

Study limitations. Several limitations to our study are evident. First, patients were preselected to derive benefit from rate-augmented pacing because most had sinus node incompetence. Second, although subjective assessment was reproducible using our validated questionnaires and was always undertaken in a double-blind setting, the accuracy is highly patient dependent. Third, assessment of mitral and tricuspid regurgitation by Doppler color flow mapping is semiquantitative and allows comment on changes only. Finally, reprogramming to 120 beats/min is a poor simulator of exercise and a further study is under way to assess the effects of different rate-responsive pacing modes on cardiac hemodynamics during exercise.

Conclusions. Assessment of four rate-responsive pacing modes in a prospective double-blind crossover study has revealed that most patients with chronotropic incompetence prefer DDDR (dual chamber) pacing and find VVIR (ventricular) pacing the least acceptable. Treadmill test performance improved with DDDR pacing. The other rate-responsive modes did not differ in this respect.

The only predictor of benefit from dual chamber over single chamber rate-responsive pacing was a larger percent increase in echocardiographically derived stroke volume during pacing in DDD mode compared with VVI mode at rest. Thus, "dual sensor" rate-responsive pacing (DDDR) appears to be superior objectively and subjectively to single sensor (VVIR, DDIR and DDD) rate-responsive pacing in patients with chronotropic incompetence and high grade AV block.

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