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CARDIAC PACING

The Feasibility of Utilizing the Systolic Pre-Ejection Interval as a Determinant of Pacing Rate

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Rate-modulated pacing modes adjust the stimulus rate by responding to sensed alterations in physiologic indexes of metabolic demand. This study was designed to determine whether right ventricular pre-ejection interval, measured in patients by a prototype pacemaker system capable of tracking intraventricular volume, changes predictably with exercise and, if so, whether it can be used in an algorithm to vary heart rate appropriately. This system utilizes intraventricular electrical impedance measurements of injected microampere currents to determine intracavitary volume changes.

Five pacemaker-dependent patients underwent temporary insertion of a tripolar electrode connected to an external device that sensed cardiac signals, generated an impedance wave form and produced stimuli at rates dependent on pre-ejection interval. Pre-ejection interval did not change as a result of variations in pacing rate itself (347 ± 41 ms at 70 beats/min versus 321 ± 19 ms at 130 beats/min), but consistently decreased during graded exercise (by 23% from baseline). During rate-modulated pacing based on pre-ejection interval, heart rate significantly increased during exercise compared with ventricular demand pacing (by 46 ± 6 versus 7 ± 6 beats/min, respectively), and increased appropriately during burst exercise.

Thus, the pre-ejection interval appears to be a specific, reliable physiologic determinant of pacing rate during exertion, which may be applicable in implantable rate-modulated pacemakers.

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Patients who exhibit inappropriate bradycardia during exercise may be limited in their activities because of inadequate cardiac output. When bradycardia is not due to abnormal sinus node function, pacemaker rate modulation can be restored by P-synchronous (DDD) pacing. Individuals whose sinus node function is not suitable as an indicator of physiologic heart rate modulation, however, include those with atrial fibrillation or other supraventricular tachyarrhythmias associated with a slow ventricular response, atrial standstill, chronotropic incompetence of the sinus node and those in whom satisfactory atrial sensing cannot be achieved. Pacemaker systems incorporating sensors of other physiologic variables that reflect the global metabolic demand of the patient and, thus, might be used as a determinant of pacing rate are currently in clinical use or under investigation.

One such variable is the systolic pre-ejection interval, which is the measurable duration of time reflecting isovolumic contraction of the ventricle. It has long been recognized that the pre-ejection interval decreases in response to increased stroke volume or end-diastolic volume (1,2) or to augmented contractility caused by adrenergic influences during exercise (3–5). Conversely, heart rate itself has little direct effect on the duration of the pre-ejection interval (6), particularly within the physiologic range of heart rate variation (1). This profile of the qualities of the pre-ejection interval potentially permits its application as a physiologic determinant of heart rate requirements in a rate-modulating pacing system.

The development of a pacing system that is capable of monitoring intraventricular volume by measuring changes in the electrical impedance of the ventricular chamber has allowed testing of the hypothesis that determination of the pre-ejection interval can form the basis of a pacing system that modulates heart rate in response to the metabolic

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Table 1. Clinical Features of Five Patients

Patient No.	Age (yr)/ Gender	Pacemaker Indication	Other Medical Diagnoses	Concurrent Medications
1	62/M	CHB	Hypertension	Maxzide, prazosin
2	60/M	CHB	HCM (nonobstructive)	Inderide
3	68/M	CHB	Gout, esophageal reflux	Cobenemid
4	28/F	Intermittent CHB	None	None
5	62/M	CHB	Crohn's disease	Gelusil, Metamucil

CHB = complete heart block; F = female; HCM = hypertrophic cardiomyopathy; M = male.

demand imposed by exertion. This study examined the effect of exercise on the measured pre-ejection interval and paced heart rate when such a pacing system was utilized in five pacemaker-dependent patients.

Methods

Patient selection. Patients were selected for participation from the group of pacemaker-dependent patients who had previously undergone permanent pacemaker implantation and who were being followed up by the pacemaker division of the Mayo Clinic. Criteria for selection included 1) consistent pacemaker dependency during serial telephone monitoring, 2) absence of previous pacemaker complications, 3) geographic proximity to Rochester, Minnesota, and 4) willingness to participate as evidenced by signing informed consent forms. Patients were excluded if there was 1) clinical or laboratory evidence of ischemic heart disease, 2) a history of significant exertion-related tachyarrhythmia or syncope, 3) inability to perform upright bicycle exercise because of orthopedic or other limitation, 4) clinically significant valvular disease, or 5) any contraindication to inserting a temporary pacing electrode into the right ventricle by means of subclavian or internal jugular venipuncture. Eight potential subjects who were willing to participate were identified. Two subjects, however, had normal sinus rhythm with appropriate pacemaker inhibition at the outset of the study. One subject was found to have previously unsuspected superior vena cava obstruction at the time of attempted right ventricular pacemaker wire insertion. The remaining five patients (Table 1) completed the entire procedure without complications.

Patient recruitment and study methods were reviewed and approved by the Institutional Review Boards of the Mayo Clinic and Cardiac Pacemakers, Inc.

Equipment. The investigational pacing apparatus consisted of a special tripolar pacing lead connected to an external pacing system. The lead is a 10F pacing lead, with a pacing tip and two ring electrodes positioned to be within the right ventricle. The external pacing system (Fig. 1) consists of 1) analog circuitry to sense R waves and pacing pulses, generate 2.6 KHz, 10 to 30 μA current signals (for impedance measurements) and measure induced intraventricular voltages (from which impedance measurements were calculated); 2) an analog to digital (A/D) converter to transform real time, analog circuitry measurements into digital signals; 3) an Intel computer (model 86/330) to provide smoothing and filtering of sensed direct current and low frequency signals, calculations of impedance and estimates of the pre-ejection interval, and 4) a pacing interface module

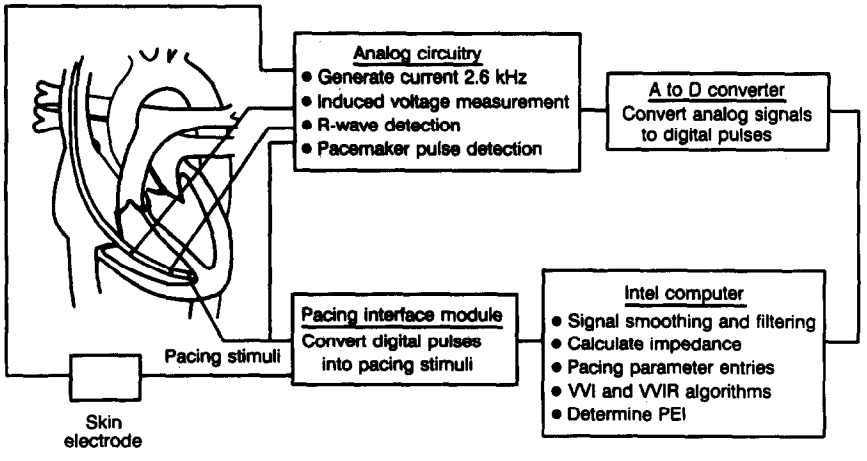

Figure 1. Components of investigational pacing system (see text). A to D = analog to digital; PEI = pre-ejection interval; VVI and VVIR = ventricular demand and ventricular rate-adaptive pacing, respectively.

to convert the output signals from the computer unit into pacing stimuli delivered to the temporary pacing electrodes. The pacing stimuli could be produced in a ventricular demand (VVI) mode or in a rate-modulated fashion determined by changes in measured pre-ejection interval.

Impedance measurement. The system just described is designed to measure the impedance of electrical currents injected into the right ventricle to derive information about right ventricular volume. The relation of intracavitary volume to impedance is based on the observation that for an insulated cylinder containing an electrically conductive medium with a constant homogeneous resistivity: volume = resistivity × length^2/impedance. As applied to this pacemaker system (Fig. 1), a subthreshold current of 10 to 30 μA is injected from the distal electrode at a frequency of 2.6 KHz. The voltage is measured across the two proximal electrodes that determine the length of the quasi-cylindrical right ventricular segment being assessed. Impedance is calculated (by Ohm's law) approximately every 10 ms, thereby providing a continuous index of intracavitary right ventricular volume. Because the right ventricle is not truly cylindrical nor perfectly insulated, volume determinations are only approximate, but provide useful information regarding mechanical ventricular function, including beat to beat changes in "stroke volume," the rate of volume change during contraction and the interval between electrical and mechanical systolic events.

Pre-ejection interval measurement. The pre-ejection interval is defined as the time from the onset of electrical systole until the reliable detection of ventricular ejection. The onset of electrical systole is determined from the initiation of a pacing pulse or the detection of a native QRS complex. Ventricular ejection is defined as the point after systole where the impedance waveform exceeds a previously determined percent of the total impedance variation, rather than as the precise onset of mechanical contraction. Although this method includes a portion of mechanical systole in the pre-ejection interval measurement, it was chosen because it greatly simplifies the detection process and improves consistency when implemented in a microprocessor environment. Because this interval includes the true left ventricular pre-ejection period plus the early portion of the left ventricular ejection time, pre-ejection interval values are longer than conventional left ventricular pre-ejection period determinations. Pre-ejection intervals and conventional pre-ejection periods probably change in parallel fashion during stress. It is possible, however, that exertional shortening of the pre-ejection interval may be somewhat exaggerated because of a concomitantly steeper increase in impedance, which causes the detection point signaling the end of the pre-ejection interval to be reached earlier.

The pre-ejection interval varies with changes in adrenergic input to the heart (1–5). By measuring beat to beat changes in the pre-ejection interval, this pacemaker system hypothetically can modulate pacing rate in response to the exercise-related change in sympathetic tone. This study was designed to test this hypothesis.

Procedure. Each patient was electrocardiographically monitored continuously using a modified chest lead I configuration. The investigational electrode was inserted into the right ventricle by standard subclavian venipuncture techniques using fluoroscopic guidance on the side contralateral to the permanent pacemaker. Once positioned, the electrode was attached to a pacing system analyzer to determine capture threshold and sensing amplitude. After satisfactory pacing variables were established, the electrode was connected to the external microcomputer pacing equipment. The patient's permanent pacemaker was programmed to the ventricular demand mode (VVI) at a rate of 50 beats/min for the duration of the procedure, during which effective pacing was maintained by the investigational system.

The following maneuvers were then performed. 1) With the patient sitting, the ventricle was paced for 1 min intervals at 70, 90, 110 and 130 beats/min, and the pre-ejection interval was measured at each rate.

Steps 2 and 3 were performed in a randomly determined sequence. A minimal 15 min recovery time was permitted between exercise sessions, during which blood pressure returned to baseline values. 2) During the VVI paced mode at a rate of 70 beats/min (75 beats/min for one patient), the patient performed upright graded bicycle ergometer (Bio-Dyne) exercise. One minute stages at levels of 150, 300, 600, 900 and 1,200 kiloponds were performed to completion of the exercise protocol or termination because of symptoms. 3) During rate-modulated ventricular-paced mode using pre-ejection interval sensing, the exercise protocol was repeated. An upper paced rate limit of 130 beats/min was programmed.

Step 4 was done to determine the response of the pacing system to sudden onset, high level exercise of short duration. This final exercise protocol was performed after a 15 min rest period. 4) During rate-modulated ventricular pacing, the patient exercised for 1 min at the highest level that had been achieved during graded exercise.

The electrocardiogram, blood pressure, heart rate and pre-ejection interval were monitored throughout each exercise period and during postexercise recovery. At the conclusion of the procedure, the temporary electrode was removed under fluoroscopic guidance. A chest X-ray film was obtained 2 h after completion of the procedure. Permanent pacemakers were reprogrammed to baseline status.

Statistics. The likelihood of results occurring by chance was assessed using Student's two-tailed t test for paired data. Statistically significant results were considered to be those with $p < 0.05$. Values for pre-ejection interval and heart rate at each level of exercise were derived from the last

Table 2. Pre-ejection Interval (in ms) Response to Exertion in Five Patients

Patient No.	Pacing Mode	Rest	Exercise Level			Δ Rest-Heavy	3 min Post-exercise
			Light	Medium	Heavy		
1	VVI	531	497	498	449	−82	483
	VVIR	525	497	346	329	−199	398
2	VVI	296	279	263	238	−58	295
	VVIR	381	371	347	324	−57	304
3	VVI	403	352	342	317	−86	422
	VVIR	417	347	317	314	−103	428
4	VVI	252	214	214	208	−44	267
	VVIR	321	293	271	254	−67	309
5	VVI	420	331	282	258	−162	382
	VVIR	423	347	350	324	−99	432
Mean	VVI	380 ± 49	335 ± 47	320 ± 49	294 ± 43	−86 ± 20*	369 ± 40
± SEM	VVIR	413 ± 33	371 ± 34	326 ± 15	308 ± 14	−105 ± 25*	374 ± 28

*Difference between pre-ejection interval at rest and during exercise significant at $p < 0.025$. Δ Rest-Heavy = change from rest to heavy exercise; VVI = ventricular demand; VVIR = rate-adaptive ventricular pacing determined by pre-ejection interval.

30 s of that stage, which was the point when these values were most stable.

Results

No adverse effects or complications were experienced by any subject during or after exercise or as a result of reprogramming.

Effect of incremental ventricular pacing rate on pre-ejection interval. A variable response of the measured pre-ejection interval occurred in response to ventricular pacing at progressively higher rates. In general, the pre-ejection interval decreased somewhat or remained unchanged. The average pre-ejection intervals were 347 ± 41, 371 ± 26, 364 ± 22 and 321 ± 19 ms at 70, 90, 110 and 130 beats/min, respectively (p = NS).

Effect of exertion on pre-ejection interval and heart rate during ventricular demand pacing. In all cases, pre-ejection interval decreased progressively to its shortest duration at peak exercise. Patient 4 developed intact atrioventricular conduction during exercise, but exhibited a shallow decrease in pre-ejection interval. Data from all patients are summarized in Table 2. Every patient except Patient 4 was pacemaker-dependent throughout exercise and remained at the fixed pacing rate (Table 3).

Effect of exertion on pre-ejection interval and heart rate during rate-adaptive pacing. With the pacing system programmed to permit rate increases in response to detected

Table 3. Heart Rate (in beats/min) Response to Exertion in Five Patients

Patient No.	Pacing Mode	Rest	Exercise Level			Δ Rest-Heavy	3 min Post-exercise
			Light	Moderate	Heavy		
1	VVI	70	70	70	70	0	70
	VVIR	71	78	130	130	+59	82
2	VVI	75	75	75	75	0	75
	VVIR	76	84	102	120	+44	81
3	VVI	70	71	70	70	0	70
	VVIR	70	111	129	129	+59	70
4	VVI	73	87	93	105	+32	72
	VVIR	70	81	89	104	+34	77
5	VVI	70	72	71	73	+3	71
	VVIR	72	96	103	106	+34	70
Mean	VVI	72 ± 1	75 ± 3	76 ± 4	79 ± 7	7 ± 6	72 ± 1
± SEM	VVIR	72 ± 1	90 ± 6	110 ± 8	118 ± 6	46 ± 6*	76 ± 3

*Difference between heart rate at rest and during exercise significant at $p < 0.005$. Abbreviations as in Table 2.

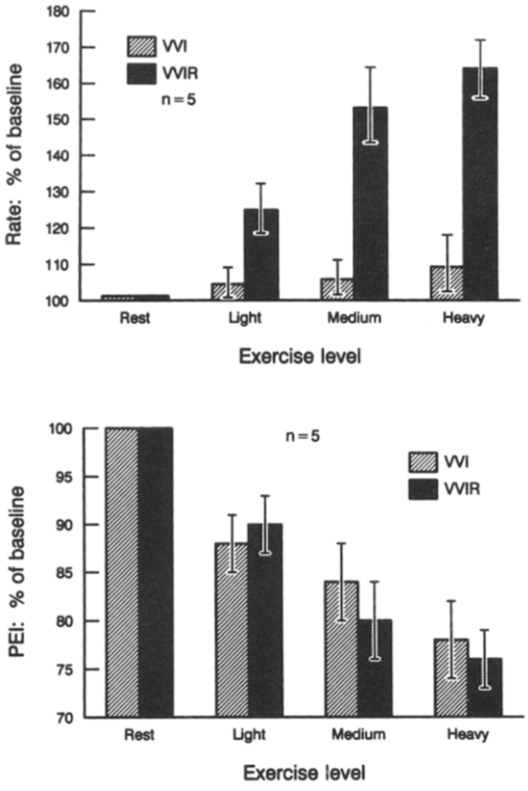

Figure 2. Effect of graded upright bicycle exercise on heart rate (**top**) and pre-ejection interval (PEI) (**bottom**) in the five study patients during ventricular demand (VVI) and ventricular rate-adaptive (VVIR) pacing.

decreases in the pre-ejection interval, an increase in heart rate with exercise was observed in each patient. The peak heart rate in this mode was 39 ± 11 beats/min or 54 ± 14.6% over that observed in the ventricular demand mode at comparable workloads ($p < 0.025$) (Table 3). However, changes in pre-ejection interval were similar to those observed during VVI pacing (Table 2). Figure 2 illustrates the obvious rate responsiveness of the pacing system, and shows that the pre-ejection interval is similar at similar work loads despite the differences in heart rate during the two pacing modes.

Sudden relatively strenuous exertion produced a very rapid decrease in the pre-ejection interval and a concomitant increase in pacing rate, usually to the upper rate level (Fig. 3). This was followed by a relatively rapid return to baseline values after cessation of exercise, similar to that observed after graded exercise (Tables 2 and 3).

Discussion

Pre-ejection interval as rate modulator. The purpose of this study was to determine whether the pre-ejection interval could serve as a reflection of global metabolic demand and, thus, as a determinant of pacing rate. Our results indicate

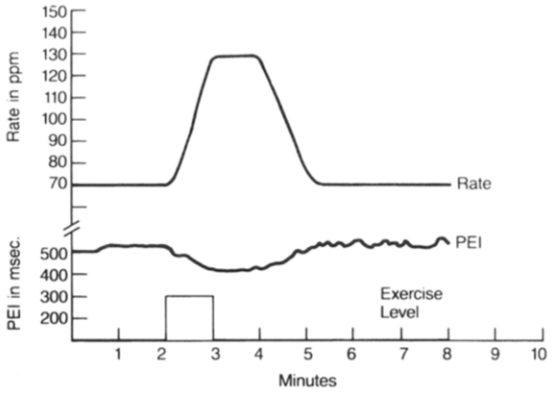

Figure 3. Effect of sudden onset, short duration (1 min), strenuous exertion in typical patient. PEI = pre-ejection interval.

that pre-ejection interval sensing meets the main prerequisites of a rate-modulating pacing system: the sensed variable (pre-ejection interval) 1) varies with degree of exertion, 2) responds rapidly after the onset of exertion, 3) can be used in an algorithm that increases pacing stimulus frequency with exertion and permits return to baseline rates appropriately after termination of exercise, and 4) is not significantly affected by heart rate changes (thereby avoiding a positive feedback phenomenon). By utilizing a pre-ejection interval sensing system, the pacing rate could be increased in a qualitatively physiologic manner in all pacemaker-dependent patients.

Whether the rate-modulating pacing mode is capable of improving exercise tolerance or reducing symptoms related to fixed rate pacing was not evaluated in the present study. Previous studies (7–8) of other rate-modulating pacing systems or models suggest that such benefit does occur. Also, no comparison was attempted between patients with and without appropriate sinus node function.

Advantages of pre-ejection interval sensing system. One potential specific advantage of a pre-ejection interval sensing system is that it responds to alterations in a variable that reflects the net neurohumoral regulatory input to the heart, regardless of specific cause. In effect, the pre-ejection interval represents a common denominator of adrenergic stimulation caused by any metabolic demand, whether it is elicited by isometric or dynamic activity, a febrile state, emotional stress or medication. Thus, not only should it respond to a broad number of stimuli that normally influence heart rate, but also it is perhaps less likely to be artifactually influenced by signals mimicking physiologic stimuli. A further advantage of a pre-ejection interval sensing system is its utilization of a volume-sensing electrode catheter that is capable of sensing other physiologic indexes such as relative stroke volume and rate of change of volume during ventricular contraction and relaxation. This may permit additional or alternative determinants of pacing rate, as well as useful

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information (by telemetry) regarding cardiac output and the contractile status of the myocardium.

Potential disadvantages. As with most rate-modulated pacing systems, potential disadvantages may occur. Physiologic rate responsiveness in chronically bradyarrhythmic patients may induce symptoms, particularly if underlying ischemic heart disease is present. Relatively higher paced heart rates have a small likelihood of enhancing tachyarrhythmias in some patients with reentrant arrhythmias. Potential disadvantages unique to this pacing system, if any, await clinical trials of an implantable device; no specific adverse outcomes were noted in this study. At present, the requirement for a tripolar electrode would not permit an implantable pacemaker of this type to be used with a previously inserted conventional electrode.

Implications. This study provides the impetus for the development and clinical testing of an implantable pacing system incorporating pre-ejection interval sensing as a determinant of physiologic pacing rates. It also suggests that such a system will be capable of providing patients with all the advantages of rate modulation, as well as additional theoretical benefits.

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