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CARDIAC PACING

Respiration-Dependent Ventricular Pacing Compared With Fixed Ventricular and Atrial-Ventricular Synchronous Pacing: Aerobic and Hemodynamic Variables

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A pacemaker that adapts heart rate in response to the patient's metabolic requirements has been developed. The pacemaker uses breathing frequency and tidal volume as the indicators of physiologic demand. Maximal physical work capacity, anaerobic threshold, oxygen uptake (16 patients) and hemodynamic variables (9 patients) were assessed with fixed rate (VVI), atrial synchronous (VDT/I) and respiration-dependent ventricular (VVI-RD) pacing.

All subjects attained their anaerobic threshold in stress tests with VVI pacing. The maximal physical capacity ($p < 0.001$), work time to attain the anaerobic threshold ($p < 0.01$) and oxygen uptake ($p < 0.001$) were significantly greater with VVI-RD than with VVI pacing. The transition from the supine to the standing position was characterized by a significant increase of cardiac index at rest with both VDT/I and VVI-RD pacing as compared with VVI pacing. Progressive increments in the cardiac index and average left ventricular stroke work index were significantly different at submaximal and maximal exercise when VVI and VVI-RD were compared. At maximal exercise, mean cardiac output was also significantly different: 10.21 ± 2.5 (SD) liters/min with VVI, 11.2 ± 0.8 liters/min with VDT/I ($p < 0.05$) and 12.65 ± 3.1 liters/min with VVI-RD ($p < 0.05$) pacing. Maximal oxygen extraction values were greater with VVI and VVI-RD pacing than with VDT/I pacing. Pulmonary artery end-diastolic pressures at maximal exercise were within the normal range with the three different modes of pacing.

In conclusion, there is a significant (25%) improvement in exercise performance with VVI-RD pacing as compared with VVI pacing. Aerobic and hemodynamic variables were not different when VVI-RD and VDT/I pacing were compared.

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For many patients with complete heart block and intact sinus node function, the most effective mode of pacing is atrial-ventricular (AV) synchronous stimulation. Beneficial hemodynamic effects from this type of pacing have been described (1,2). A comparison of fixed ventricular and AV synchronous pacing has shown a significant increase in maximal exercise capacity in both young and old patients (3) with the latter mode of pacing.

The improvement in cardiac output produced by AV synchronous pacing is mainly dependent on the heart rate increase at rates below 100 beats/min, while at higher rates, atrial contribution to ventricular filling seems to be more important (4–6). During work, however, the average cardiac output is only 8% greater with AV synchronous pacing, than with fixed ventricular pacing at the same rate (2).

The ideal form of physiologic pacing is one that responds to the body's needs for varying cardiac output. In patients with abnormal sinoatrial function and single chamber ventricular pacing, alternative methods of sensing physiologic demands must be used to produce a physiologic rate response to exercise. Recently, we described a rate-responsive, respiration-dependent pacemaker capable of being noninvasively programmed to either a fixed rate inhibited pacing mode or a rate-responsive mode dependent on the respiratory rate (7,8).

The aims of the present study were 1) to compare the maximal physical work capacity achieved with fixed ventricular or atrial pacing (VVI or AAI) with rate-responsive, respiration-dependent pacing (VVI-RD or AAI-RD); and 2) to evaluate hemodynamics at rest and during exercise with fixed rate ventricular pacing (VVI), respiration-dependent ventricular pacing (VVI-RD) and AV synchronous pacing (VDT/I).

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Methods

Cardiac pacemakers. Patients were randomized with respect to VDT/I, VVI or VVI-RD pacing. Pacemaker reprogramming to each mode was performed at least 3 hours before each exercise study. VDT/I was temporary pacing, VVI-RD was permanent pacing and VVI was either temporary or permanent pacing.

For VVI and VDT/I pacing, an external pacemaker (CPI model 22003) was used. This pacemaker provides a constant PR delay of 140 ms when in the AV synchronous mode. Since a maximal AV synchronous rate of 160/min was programmed, occasional blocking of conducted impulses occurred when the atrial rate of the patient reached the programmed upper rate limit of the pacemaker.

The respiration-dependent pacemaker (RD) consists of a demand cardiac pacemaker in which pacing rate is controlled by an algorithm based on sensing of respiration rate which, in turn, is monitored by impedance variations in respiration. Impedance variations are detected by an auxiliary lead tunneled subcutaneously from the pulse generator pocket to a site 8 to 10 cm away on the thorax. The respiration-dependent pacemaker (S.p.A., Biotec) is programmable in the following variables:

1) Respiration dependency: on-off.
2) Respiration sensitivity: assessed in relation to changes in tidal volume, thus avoiding interference and artifacts.
3) Respiration rate/paced rate ratio: individual rate response slope and end points can be selected for each patient; the end points are minimal (65 to 75 beats/min) and maximal (100 to 150 beats/min) pacing rate. The VVI-RD pacemaker increases ventricular pacing rate during exercise (Fig. 1).

Patients. The respiration-dependent pacemaker was implanted in 16 patients (mean age 66 years, range 22 to 88); 13 patients received a rate-responsive ventricular pacemaker (VVI-RD), and 3 patients received a rate-responsive atrial pacemaker (AAI-RD). Patients who had ventricular pacing (VVI-RD) exhibited chronic complete AV block both at rest and during exercise. Patients who had atrial pacing (AAI-RD) were diagnosed as having sick sinus syndrome.

Exercise tolerance was determined in the 16 patients on two separate occasions using treadmill exercise in accordance with the Bruce protocol (9). Both fixed and rate-responsive pacing were used with each patient. Hemodynamic variables were determined in nine patients at each stage of the exercise test, using three modes of pacing: VVI, VDT/I and VVI-RD. Selected data from these patients are presented in Table 1. Exercise tests were performed on a treadmill, according to a protocol using 6 minute work loads (Table 2) to achieve a steady state.

At the time of study, no patient exhibited clinical signs of myocardial dysfunction or was taking medication. Only one patient had a moderately enlarged heart noted on chest X-ray film. Patient 4 had a spontaneous rhythm in the later stages of the exercise test and was omitted from the statistical analysis. All other patients exhibited the rhythm of the selected pacing mode during exercise. A Student's *t* test for paired differences was used for statistical data comparisons using an alpha level of significance of 0.05.

Hemodynamic measurements. After patient consent was obtained, a Swan-Ganz flow-directed triple lumen catheter (CVI model 600-017, Edwards Laboratory model 93A 1317F) was advanced to the pulmonary artery through an antecubital vein and an AV catheter with a bipolar atrial sensor (CPI model 4000-4001) positioned in the apex of the right ventricle. All patients were then transported to the exercise

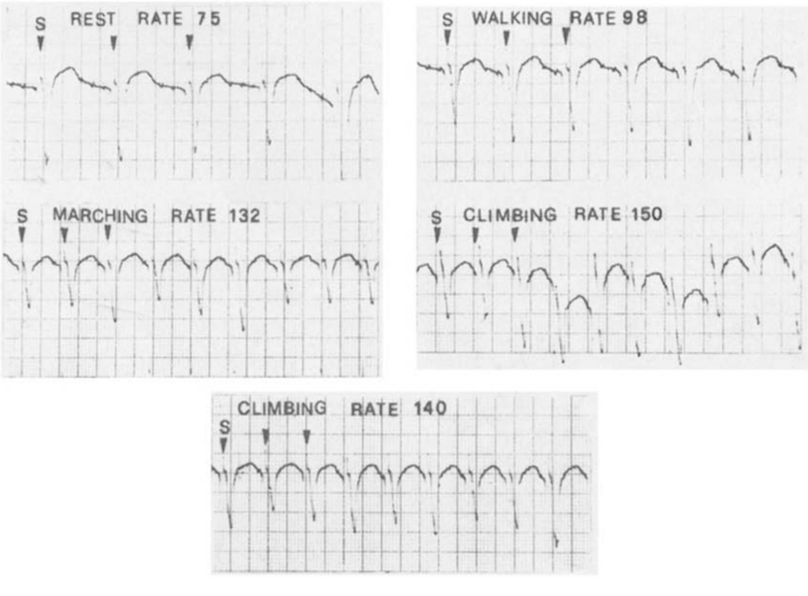


Figure 1. Ambulatory Holter electrocardiogram of a 73 year old patient who had an implanted rate-responsive, respiration-dependent ventricular pacemaker for 17 months. During exercise, the pacing rate increases. The small **notches** on the TR segments are produced by a rheographic system that measures impedance variations in respiration. S = pacing stimuli.

Table 1. Clinical Characteristics of Patients Performing 6 Minute Work Load Stress Testing

		Body					Complete AV Block	
Case	Age (yr) & Sex	Weight (kg)	Surface Area (m^2)	Heart Disease	Cardiac Volume (ml/m^2)	NYHA Functional Class	P Rate	QRS Rate
1	62F	62	1.6	CHD	570	II	85	38
2	73M	63	1.6	CHD	650	II	80	30
3	75M	56	1.55	CHD-MI	505	II	84	27
4	74M	81	1.8	CHD-AI	650	II	80	32
5	88M	84	1.8	CHD	540	II	84	28
6	49M	91	1.9	HHD	380	I	78	29
7	67M	69	1.6	CHD	520	I	80	25
8	56F	70	1.55	CHD	480	I	80	40
9	73M	54	1.5	CHD	750	II	72	52

AI = aortic insufficiency; AV = atrioventricular; CHD = coronary heart disease; F = female; HHD = hypertensive heart disease; M = male; MI = mitral insufficiency; NYHA = New York Heart Association.

facility. Each subject was well acquainted with the monitoring devices in order to minimize any levels of emotional interference.

An adjustable arm affixed to the support railing of the treadmill was clamped to a Statham P 23DB transducer and positioned at mid-heart level. The blood pressure transducer was then coupled to an Elema-Schonander (Mingograph) amplifier to monitor pulmonary artery pressure during upright exercise. Throughout exercise, the position of the transducer remained constant with respect to mid-heart level. The monitoring system was calibrated with an internal electronic signal before each set of measurements was obtained.

Cardiac output was determined in triplicate by thermodilution techniques (CVI model 600, Edwards Laboratory model 9250) with a variance of less than 10%. A 10 ml bolus of iced saline solution was used for the thermal indicator. Left ventricular stroke work index (g·m/beat per m^2) was calculated as: stroke index × (mean systolic pressure − pulmonary end-diastolic pressure) × 0.0136. Oxygen saturation was determined by use of an ABL3 radiometer. Exhaled respiratory gases were analyzed with a Biotec Oxitest system equipped with a fuel cell type oxygen analyzer and flow meter for determination of oxygen uptake (S.T.P.D. = standard, temperature, pressure, dry) and ventilation (B.T.P.S. = body, temperature, pressure, saturated with vapor).

The patient was connected to this system by means of a three-way, rubber mouthpiece with unidirectional valves of very low inertia and negligible resistance. The mouthpiece was made completely air tight by affixing it to the patient's face with two elastic straps and connected to the cardiopulmonary analyzer by a corrugated tube of sufficient diameter to minimize load losses.

Table 2. Protocol of Exercise Test on Treadmill

Step (of 6 min)	Slope (%)	Velocity (ml/h)
1	0	1.7
2	6	1.7
3	10	1.7
4	12	2.5
5	14	3.4
6	16	4.2

Pulmonary artery pressure, cardiac output, arterial and mixed venous oxygen saturation, brachial artery cuff pressure, ventilation, oxygen consumption and respiration rate were measured in the supine position. Thereafter, the patient was in the standing position during treadmill exercise and all measurements were repeated before exercise.

Exercise testing. After an electrocardiogram at rest was obtained, exercise was started. Work load was increased every 6 minutes until the patient could no longer exercise because of exhaustion. An electrocardiogram was obtained and respiration rate determined during the last 10 seconds of each minute during exercise. In addition, the electrocardiogram was continuously monitored on an oscilloscope during the procedure.

Ventricular and atrial rates were calculated from the electrocardiograms. Systolic brachial artery cuff pressure, ventilation and oxygen consumption were recorded during the 1st, 3rd and 6th minutes of each work load. Cardiac output and pulmonary artery pressure were recorded at the 5th or 6th minute of each work load. All measurements were repeated immediately after and 3 and 6 minutes after exercise with the patient in the sitting position.

All exercise tests were performed during strictly standardized conditions by the same investigators. To eliminate biased results in exercise time and total work performed, such an investigation should preferably be performed with the investigator unaware of the pacing mode; however, because this was not possible, all patients performed a maximal exercise test.

Although maximal exercise testing is considered to be one of the best objective methods for functional assessment of the cardiac patient (10,11), it includes a certain subjective bias, because the end point can be determined by the patient. Furthermore, the maximal exercise test may be impractical in elderly patients. We have chosen anaerobic threshold (12,13), and the work load and oxygen uptake associated with it, as an objective means to assess patient aerobic capacity during exercise (14,15).

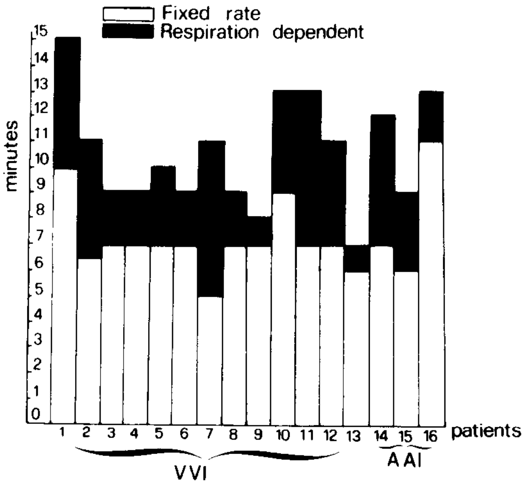
The anaerobic threshold was determined by visual inspection of the x-y plot of ventilation versus oxygen consumption. The point of departure from linearity of this graphic plot (that is, the first intersection point or marked change in slope) was selected as the patient's anaerobic threshold point. The corresponding value of oxygen consumption defined the anaerobic threshold of these patients.

Results

Exercise tolerance. During treadmill exercise testing with respiration-dependent pacing, a progressive adaptation of pacing rate to work load and oxygen uptake was observed. Maximal pacing rate, coincident with peak exercise work load, attained peak values as predicted by the selected regression line for each patient. The mean value of maximal ventricular pacing rate was 136 ± 16 beats/min (range 118 to 155) with respiration-dependent pacing (VVI-RD) and 137 ± 25 beats/min (range 120 to 155) with AV synchronous pacing (VDT/I). Figure 2 depicts the individual gain in work capacity or improvement in exercise tolerance with respiration-dependent (RD) pacing as compared with fixed pacing in 16 patients: 13 with ventricular pacing and 3 with atrial pacing. All subjects increased their work time with respiration-dependent pacing.

Oxygen utilization. During stress testing with respiration-dependent ventricular pacing, the mean work time to attain the anaerobic threshold was prolonged and the mean corresponding oxygen uptake was significantly greater (Fig. 3). Exercise tolerance expressed in metabolic equivalents and total work time were significantly greater with VVI-RD pacing than with VVI pacing (Fig. 4). In contrast, the oxygen pulse was significantly greater with VVI pacing than with VVI-RD pacing (Fig. 4). Figure 5 demonstrates that maximal minute ventilation and respiration rate were not significantly different for the three modes of pacing.

Figure 2. Total work time attained in 16 patients with the Bruce protocol with fixed rate pacing (VVI or AAI) and rate-responsive, respiration-dependent pacing (VVI-RD or AAI-RD).



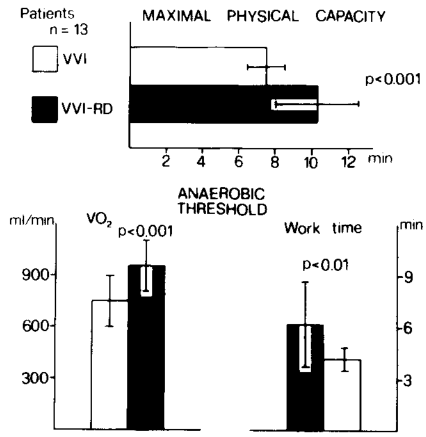
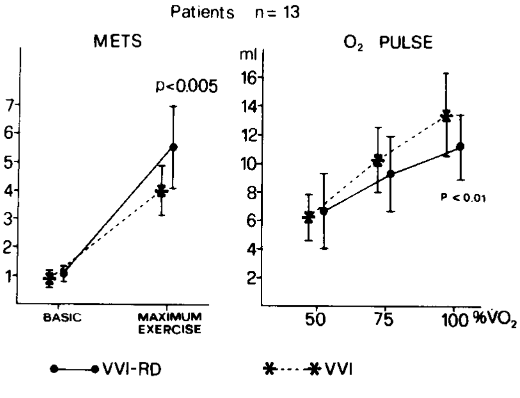


Figure 3. Mean (± SD) of work time (maximal physical capacity) and oxygen uptake ($\dot{V}O_2$) to attain the anaerobic threshold in the Bruce protocol with fixed-rate (VVI) and rate-responsive, respiration-dependent (VVI-RD) ventricular pacing.

Hemodynamic responses to exercise. *Cardiac index (Fig. 6 and 7).* The average (± SD) cardiac indexes measured in the supine position for VVI, VDT/I and VVI-RD pacing were 2.91 ± 0.5, 3.10 ± 0.7 and 3.48 ± 0.5 liters/min per m^2, respectively. The mean cardiac index at rest of patients in the standing position and cardiac output at maximal exercise were significantly greater with VDT/I and VVI-RD pacing than with VVI pacing (Fig. 6 and 7).

Figure 4. Mean (± SD) of metabolic equivalents (METS) and oxygen (O_2) pulse achieved in stress testing with fixed rate (VVI) and rate-responsive, respiration-dependent (VVI-RD) ventricular pacing.



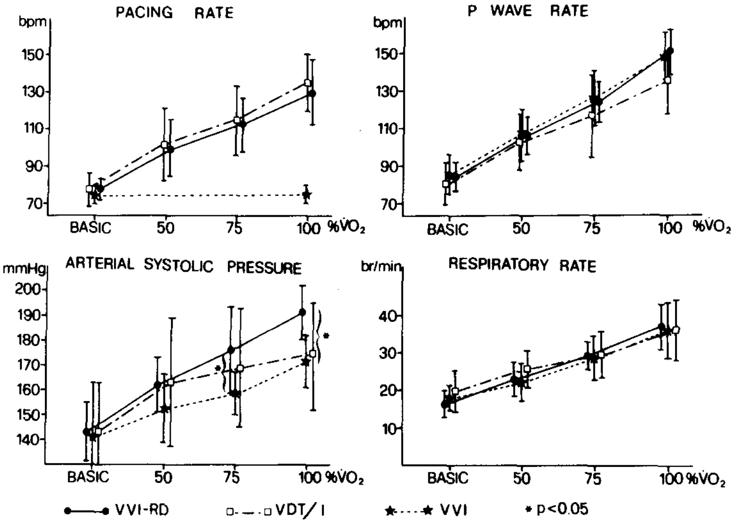


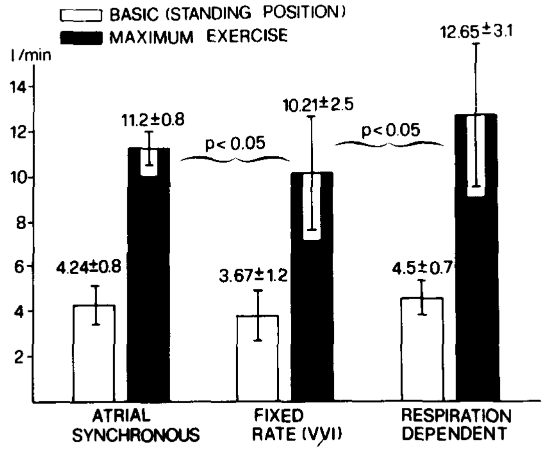
Figure 5. Ventricular pacing rate, P wave rate, arterial systolic pressure and respiratory rate attained with progressive increments in muscular work. VDT-I = atrial synchronous pacemaker; see Figure 4 for other abbreviations.

Figure 7 demonstrates that with progressive increments in muscular work, expressed as a percent of maximal oxygen uptake, changes in cardiac index were significantly different with submaximal and maximal exercise, comparing VVI with VDT/I ($p < 0.05$) and VVI-RD ($p < 0.01$) pacing.

The increased cardiac index observed during exercise with VDT/I and VVI-RD pacing (Fig. 7) was obtained by a significant ($p < 0.05$) increase in pacing rate (Fig. 5). In contrast, an increased cardiac index with VVI pacing was attributed to a significant increase in oxygen pulse and stroke volume as shown in Figures 4 and 6, respectively. The average left ventricular stroke work index was significantly greater with VVI pacing than with VDT/I and VVI-RD pacing.

Atrial rate (Fig. 5). Atrial rates during all work levels of maximal exercise were higher with VVI and VVI-RD pacing than with VDT/I pacing. Atrial rates were 147 ± 15 beats/min with VVI pacing, 137 ± 13 beats/min with VDT/I pacing and 150 ± 10 beats/min with VVI-RD pacing. However, these differences were not statistically significant.

Figure 6. Mean (± SD) maximal cardiac output attained at 6 minute work loads with the three modes of pacing. See Figure 4 for other abbreviations.



Pulmonary pressure (Fig. 7). During exercise, pulmonary artery end-diastolic pressure increased at similar rates with all three modes of pacing. Peak filling pressures at maximal exercise were 20 ± 7.1 mm Hg with VVI pacing, 18.2 ± 7.1 mm Hg with VDT/I pacing and 22.5 ± 3.7 mm Hg with VVI-RD pacing. These differences were not statistically significant.

Systemic pressure (Fig. 5). Comparing the three modes of pacing, there was no statistically significant difference between systolic and diastolic pressure at rest. Systolic pressure during submaximal and maximal work differed significantly ($p < 0.05$), being greater with VVI-RD pacing (193 ± 14 mm Hg) than with VVI (173 ± 14 mm Hg) and VDT/I (176 ± 35 mm Hg) pacing.

Oxygen extraction. A difference in oxygen extraction with progressive increments in exercise was demonstrated with VVI pacing. The maximal values were greater with VVI (8.51 ± 4 vol %) and VVI-RD (9.28 ± 4 vol %) pacing than with VDT/I (5.74 ± 3 vol %) pacing.

Discussion

The restoration of a normal temporal relation between atrial and ventricular contraction and the capacity to increase heart rate during exercise improve the hemodynamic response to physical work in patients with complete heart block (2,6). There is evidence that the volume contribution of atrial systole to cardiac output is less important during exercise (2) and with high ventricular filling pressures (17). The latter observation is not surprising because AV synchrony may increase cardiac output by as much as 20 to 30% in patients with normal ventricular function (5). The increase that occurs with atrial systole becomes insignificant

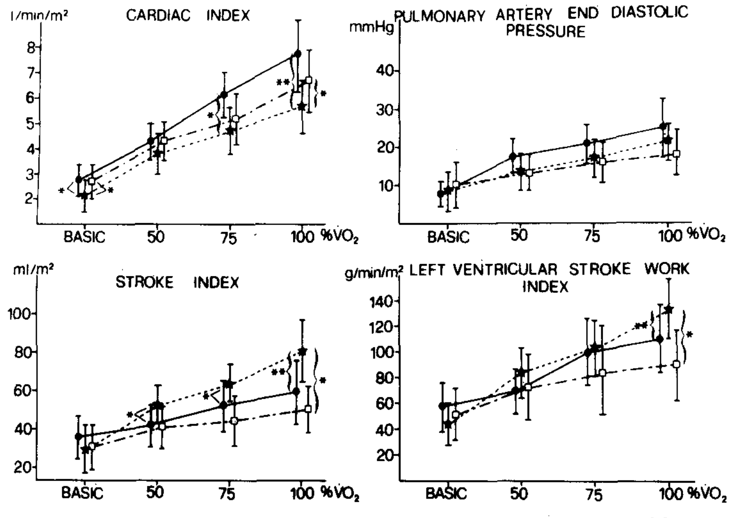


Figure 7. Hemodynamic values with progressive increments in muscular work expressed as a percent of maximal oxygen (O_2) uptake. See Figure 4 for other abbreviations.

when a 200 to 300% increase is required by the demands of exercise.

Work capacity in sick sinus syndrome. Our data show that physical work capacity is improved with either AAI-RD or VVI-RD pacing, as compared with VVI or AAI pacing. In sick sinus syndrome, the chronotropic response of the heart to exercise may be lower than normal, either at submaximal or maximal work loads. The three patients with sick sinus syndrome in our study exhibited a progressive increase in pacing rate during exercise with AAI-RD pacing, because spontaneous sinus rate was lower than the respiratory-dependent atrial pacing rate.

Exercise cardiac output. In our patients the transition from the supine to the standing position was characterized by an increase in cardiac index at rest with VDT/I and VVI-RD pacing as compared with VVI pacing. This reflex effect can be of importance to avoid the pacemaker syndrome of patients with VVI pacing. During exercise, an increase in cardiac output was achieved by increases in both heart rate and stroke volume.

Normally, the increase in stroke volume is most important during the transition from upright rest to submaximal levels of upright work; maximal stroke volume is reached at approximately 40 to 50% of oxygen uptake (18). Heart rate contributes to increases in the cardiac output during all stages of exercise (19). With severe impairment in cardiac function, stroke volume either fails to increase during exercise or increases slightly relative to the cardiac reserve (20,21). In our patients with normal cardiac function, increased cardiac output with exercise could be obtained during VVI pacing by a significant increase in stroke volume and during VDT/I and VVI-RD pacing by a significant increase in heart rate.

With progressive increases in muscular work, the response in cardiac output was greater with VDT/I and VVI-RD–dependent pacing than with VVI pacing. These differences could be observed 3 hours after changing the pacing mode. These results are in agreement with previous studies (3) employing short- or long-term periods of pacing.

Pulmonary artery end-diastolic pressure at maximal exercise with the three modes of pacing was within normal limits for healthy men (22). These findings are consistent with pacemaker-dependent patients who have normal left ventricular performance. The greater arterial-mixed venous oxygen differences with VVI and VVI-RD pacing can be regarded as a compensatory mechanism to achieve maximal physical effort. The higher P wave rates observed during exercise with VVI and VVI-RD pacing can be regarded as an indirect proof of sympathetic overdrive.

Anaerobic threshold. The noninvasive determination of maximal oxygen uptake and anaerobic threshold provides an objective, quantitative description of functional capacity and cardiac reserve (12,13). These variables precluded biased results that may occur as a result of nonphysiologic factors such as patient attitude or motivation. To avoid the influence of training induced by repeated exercise testing, patients were randomly tested with VVI, VDT/I and VVI-RD pacing. Because all patients exercised with VVI pacing until they reached their anaerobic threshold and extended their work time with VVI-RD, we can exclude the influence of any psychologic and emotional factors. Work time was extended with VVI-RD pacing and the recovery period was less than that observed in stress tests with VVI pacing.

Advantages of the respiration-dependent pacemaker. Our study results verify that both VDT/I and VVI-RD pacing are superior to VVI pacing. These results were supported not only by measured improvements in physical work capacity but also by the subjective judgment of the patients.

The advantages of using respiratory rate as a control variable for rate-responsive pacing are as follows (23): 1) the sensor is stable, with very low energy consumption and therefore has a limited effect on pacemaker longevity; 2) open loop regulation employs the human body as a computer to attain and maintain effective paced rates in response to metabolic demand rates with a quick response time; 3) the respiration/pacing rate relation can be adapted easily to the individual patient; 4) the respiration-dependent pacing is tightly related to work load and oxygen uptake; and 5) the reflex increase in cardiac index at rest that occurs with VVI-RD pacing in patients in the standing position can protect them from VVI pacemaker syndrome.

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