Maintenance of exercise stroke volume during ventricular versus atrial synchronous pacing: role of contractility

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ABSTRACT Although atrial synchronous and rate-responsive ventricular pacing have been compared, the importance of maintaining synchronized atrial systole in addition to rate responsiveness has been incompletely defined. That is, the effects of these two pacing modes on cardiac volumes and contractility have not been studied. Accordingly, 16 patients with normal ventricular function were studied while in the upright position and at rest with gated radionuclide ventriculography during both atrial synchronous and ventricular pacing. Twelve of these patients were also studied during low-level upright exercise (300 kilopond-meters). Rest and exercise ventricular pacing heart rates were matched to those recorded with synchronous pacing. Ventricular volumes were determined with a counts-based method. The ejection fraction and peak systolic pressure/end-systolic volume ratio were used as measures of contractility. At rest there were no significant differences in either volumes or contractility between the two pacing modes. However, during exercise to identical heart rates, blood pressures, and workloads, although stroke volume was the same during exercise with atrial synchronous and ventricular pacing (78 ± 13 vs 75 ± 12 ml), end-diastolic and end-systolic volumes were lower with ventricular pacing than with atrial synchronous pacing (end-diastolic volume 101 ± 13 vs 113 ± 16 ml, p < .001; end-systolic volume 26 ± 4 vs 35 ± 7 ml, p < .001). Stroke volume during ventricular paced exercise was maintained at atrial synchronous pacing levels by means of increased contractility (ejection fraction of 74 ± 4% during ventricular pacing vs 69 ± 5% during atrial synchronous pacing, p = .002; peak systolic pressure/end-systolic volume ratio of 6.51 ± 1 during ventricular pacing vs 4.85 ± 1 during atrial synchronous pacing, p < .001). Thus, during upright bicycle exercise to workloads corresponding to those of usual daily activities, rate-responsive atrial synchronous pacing results in enhanced ventricular filling and spares contractile reserve when compared with rate-responsive ventricular pacing.

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DUAL-CHAMBER (DDD) pacemakers allow atrio-ventricular synchronization and a chronotropic response to exercise or stress. By comparison, rate-responsive pacemakers that respond to various physiologic sensors, i.e., evoked QT, respiratory rate, etc., afford an increase in ventricular rate alone. Work done to date has shown similar cardiac outputs and exercise capacities with the two pacing modes.1 How cardiac output is maintained with rate-responsive ven-

tricular pacing and whether hemodynamic differences exist between the two pacing modes is of importance in assessing the need for maintenance of atrioventricular synchrony in patients with pacemakers.2 Accordingly, we used previously validated radionuclide ventriculographic techniques in patients with normal ventricular function to examine cardiac volumes and contractility at upright rest and with low-level exercise during both atrial synchronous pacing and rate-adjusted ventricular pacing. In addition to the ejection fraction, the peak systolic pressure/end-systolic volume ratio was used as an index of contractility, since it has been shown to be more sensitive in detecting subtle changes in myocardial function.3, 4

Methods

Patient population. Patients with implanted DDD pacemakers and normal ventricular function who were not receiving

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cardiac medications were prospectively screened from the Montefiore Medical Center Pacemaker Clinic. Sixteen patients (11 men and five women; mean age 60 ± 15 years) gave informed written consent for the study. All were asymptomatic after pacemaker implantation programmed to the DDD pacing mode, and none had a history of hypertension, diabetes, chest pain, or previous myocardial infarction. Results of physical examinations and chest x-rays were normal. None of the patients had electrocardiographic evidence of a prior myocardial infarction. All patients had normal ventricular function at rest, prospectively defined as an ejection fraction of 55% or greater without any regional wall motion abnormalities. Seven patients had received pacemakers for symptomatic sinus node dysfunction, three for complete heart block, four for incomplete or intermittent heart block, and two for carotid sinus hypersensitivity. The time from implantation was less than 11 days in seven of the patients, and ranged from 1.5 to 16 months in the other nine. None of the subjects were trained athletes and none were receiving cardiac medications.

Four patients studied at rest could not be studied completely during exercise. Two patients developed severe discomfort (shortness of breath, chest pulsations, and weakness) during exercise in the ventricular mode — symptoms consistent with intolerance of ventricular pacing, or the pacemaker syndrome. One was too tired to exercise, and one developed a higher sinus rate with ventricular paced exercise and could not be studied at a rate comparable to that produced by atrial synchronous pacing. These four patients were studied in the two pacing modes at rest only.

**Pacing protocol.** On the day before the radionuclide study, subjects underwent a 5 min period of bicycling in the DDD pacing mode with electrocardiographic monitoring to determine their heart rate at the end of the exercise period. During the actual exercise study, this heart rate was programmed in the ventricular pacing mode at the onset of exercise. During exercise in the atrial synchronous mode, the ventricular pacing rate was dictated by the patient’s atrial rate. This procedure allowed us to randomly alternate the initial pacing mode used in consecutive patients and resulted in similar exercise heart rates with ventricular pacing (VVI) and atrial synchronous pacing (atrial tracking with synchronous ventricular pacing in the DDD mode), with an atrioventricular interval of 150 msec. Continuous electrocardiographic monitoring demonstrated that the patients were paced in the programmed mode at all times. During all parts of the protocol, ventricular contraction was precipitated by a pacemaker stimulus (i.e., atrioventricular conduction through the normal pathway did not occur during synchronous pacing) to eliminate pacemaker-induced vs normal ventricular depolarization and contraction as a potential confounding variable.

**Exercise protocol.** The patients were studied while in the 90 degree upright position and in the postabsorptive state. Ten minutes after each patient was in the starting position in the first pacing mode, scanning was done while he or she was at rest with a heart rate as close to 70 beats/min as possible. After the resting scans were obtained, the patients exercised in the same pacing mode on a bicycle ergometer-imaging table combination (Nuclear Associates, Carle Place, NY) that allowed the subject to exercise vigorously in the 90 degree upright posture while maintaining a stable position under the gamma camera. Continuous bicycle exercise was done at a constant workload of 300 kilopond-meters (kpm) at a pedal speed of 60 to 70 rpm. After 3 min of exercise, a scan was acquired spanning the subsequent 2.5 min of exercise. Blood pressure measurements were taken at rest and at each minute of exercise and recovery by a single observer who was unaware of the pacing mode. After a 30 min rest period, scanning was repeated in the same pacing mode at upright rest to ensure return to baseline. Pacemakers were then programmed to the alternate pacing mode and, again, to maintain a heart rate as close to 70 beats/min as possible, and the

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**Table 1**

<table>
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<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Diagnosis</th>
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<th>SBP</th>
<th>EDV</th>
<th>ESV</th>
<th>SV</th>
<th>EF</th>
<th>CO</th>
<th>P/V</th>
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HR = heart rate (beats/min); SBP = systolic blood pressure (mm Hg); EDV = end-diastolic volume (ml); ESV = end-systolic volume (ml); SV = stroke volume (ml); EF = ejection fraction (%); CO = cardiac output (l/min); P/V = peak systolic pressure/end-systolic volume ratio; CHB = complete heart block; CSS = carotid sinus sensitivity; IHB = incomplete heart block; SND = sinus node dysfunction.

* Studied at rest only.

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patient was allowed to rest for an additional 10 min. The rest and exercise protocol was then repeated with the patient in the second pacing mode.

**Radionuclide methods.** Upright gated blood pool cardiac imaging was used to assess changes in global and regional left ventricular function and volume. The details of the acquisition and imaging procedures have been published elsewhere and are briefly summarized here. The subjects red blood cells were incubated in vivo with stannous pyrophosphate and labeled with 25 mCi of \( ^{99m} \text{Tc} \) pertechnetate. A mobile, standard-field-of-view camera with a high-sensitivity collimator (Picker Corp., North Ford, CT) interfaced with a computer (Digital Equipment Corp., Marlborough, MA) dedicated to the acquisition and processing of nuclear medicine data was used. The camera was positioned in the left anterior oblique projection that best separated the left and right ventricles and the left atrium from the left ventricle. Triplicate resting acquisitions were obtained, and radionuclide data were averaged from these acquisitions. The exercise scan was acquired for 2.5 min as described above. Each acquisition consisted of 28 frames per RR interval in zoomed 64 × 64 matrices and a minimum of 4 × 10^6 counts.

Scans were processed by a single experienced operator with a semiautomated variable-region-of-interest method. Background-corrected end-diastolic and end-systolic count data were calculated from mathematically smoothed time-activity curves, corrected for frame duration, and normalized to 20 msec. Stroke counts were then determined as the difference between end-diastolic and end-systolic counts. All count data were corrected for the 4.5 hr effective half-life of the \( ^{99m} \text{Tc} \)-labeled red blood cell complex. For multiple determination of end-diastolic, end-systolic, and stroke counts, the percent standard deviations in this laboratory are 6.48, 8.31, and 12.49, respectively. The correlation between changes in stroke counts and in thermodilution stroke volume during intervention is \( r = .90, p < .001 \). Absolute volumes were determined by a modification of the method of Slutsky, in which counts in 5 ml samples of labeled blood, drawn at the time of the rest and exercise scans, are used to convert scintigraphic count data into volume data. In this laboratory, volume (scintigraphic) = volume (angiographic) – 17.3 (n = 25, SEE 5.83, \( r = .953, p < .001 \)).

Cardiac output was calculated according to the formula: cardiac output = heart rate × stroke volume, and left ventricular ejection fraction from: stroke volume/end-diastolic volume. Correlation between left ventricular ejection fraction determined by this method and that obtained with contrast cineangiography in this laboratory has been demonstrated to be \( r = .90, p < .001 \). The peak systolic pressure/end-systolic volume ratio was calculated as the sphygmomanometrically determined systolic blood pressure divided by end-systolic volume.

**Statistical analysis.** Left ventricular end-diastolic, end-systolic, and stroke volumes, cardiac output, ejection fraction, and peak systolic pressure/end-systolic volume ratio were measured at rest and during exercise with both ventricular and atrial synchronous pacing at similar heart rates. Results at rest and during exercise as well as with the two pacing modes were compared. All data were mean ± 1 SD. Statistical analysis was performed with the paired t test, and a p value (after Bonferroni adjustment) of <.0125 was considered indicative of statistical significance.

**Results**

Resting heart rate (71 ± 4 vs 72 ± 3 beats/min, atrial vs ventricular), systolic blood pressure (124 ± 12 vs 128 ± 15 mm Hg), and diastolic blood pressure (77 ± 7 vs 79 ± 9 mm Hg) were similar in the atrial synchronous and ventricular pacing modes. Left ventricular volumes were also comparable in the two pacing modes: end-diastolic volume was 95 ± 12 ml during atrial synchronous pacing vs 93 ± 11 ml during ventricular pacing and end-systolic volume was 32 ± 6 ml during atrial synchronous pacing vs 30 ± 5 ml during ventricular pacing with identical stroke volumes (63 ± 9 ml). The ejection fraction (66 ± 4% atrial synchronous pacing vs 67 ± 5% ventricular pacing) and peak systolic pressure/end-systolic volume ratio (3.98 ± 7 atrial synchronous pacing vs 4.30 ± 8 ventricular pacing) were also not significantly different. Individual results are given in table 1. In the four patients who were studied only at rest, two of whom were symptomatic with ventricular pacing, clinical and hemodynamic findings were similar to those in the other 12. Retrograde ventriculoatrial conduction was not observed on the surface electrocardiogram of any patient at rest or with exercise.

No patient developed chest pain or shortness of breath with exercise. Individual exercise results are in table 2. During exercise at a workload of 300 kpm for 5.5 min in each pacing mode, heart rate (101 ± 9 beats/min during atrial synchronous pacing vs 102 ± 9 beats/min during ventricular pacing), systolic blood pressure (165 ± 18 mm Hg during atrial synchronous pacing vs 168 ± 15 mm Hg during ventricular pacing), and diastolic blood pressure (81 ± 9 mm Hg during atrial synchronous pacing vs 83 ± 10 mm Hg during ventricular pacing) were not different.
TABLE 2
Upright exercise: comparison of atrial synchronous pacing and rate-matched ventricular pacing

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<th>SBP (mm Hg)</th>
<th>EDV (ml)</th>
<th>ESV (ml)</th>
<th>SV (ml)</th>
<th>EF (%)</th>
<th>CO (l/min)</th>
<th>P/V</th>
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HR = heart rate (beats/min); SBP = systolic blood pressure (mm Hg); EDV = end-diastolic volume (ml); ESV = end-systolic volume (ml); SV = stroke volume (ml); EF = ejection fraction (%); CO = cardiac output (l/min); P/V = peak systolic pressure/end-systolic volume ratio; VP = ventricular pacing; SP = synchronous pacing.

p value, ventricular pacing vs atrial synchronous pacing: *p < .001; **p = .002.

diastolic volume rose from rest to exercise during both pacing modes, but it increased more with atrial synchronous pacing (increase with ventricular pacing of from 93 ± 11 to 101 ± 13 ml or 9%, p < .001, and increase with atrial synchronous pacing of from 95 ± 12 to 113 ± 16 ml or 19%, p < .001), resulting in a larger end-diastolic volume during exercise with atrial synchronous pacing compared with ventricular pacing (113 ± 16 vs 101 ± 13 ml, p < .001). End-systolic volume did not change from rest to exercise with atrial synchronous pacing (32 ± 6 vs 35 ± 7 ml), but decreased 13% with ventricular pacing (30 ± 5 to 26 ± 4 ml, p < .001). These differences in end-systolic volume between the two pacing modes during exercise were also highly significant (p < .001).

Stroke volume rose during ventricular paced exercise to a level similar to that during atrial synchronous paced exercise (75 ± 12 vs 78 ± 13 ml, p = NS). Ejection fraction and peak systolic pressure/end-systolic volume ratio, which are measures of ventricular contractility, rose from rest to exercise during both atrial synchronous pacing (ejection fraction 66 ± 4% vs 75 ± 4%, p = .004; peak systolic pressure/end-systolic volume ratio 3.98 ± 0.7 to 4.85 ± 1, p = .005) and ventricular pacing (ejection fraction 67 ± 5 to 74 ± 4%, p < .001; peak systolic pressure/end-systolic volume ratio 4.30 ± 0.7 to 6.51 ± 1, p < .001), but increased more with ventricular pacing so that levels during exercise with ventricular pacing were greater (for ejection fraction, ventricular pacing vs atrial synchronous pacing = 74 ± 4% vs 69 ± 5%, p = .002; for peak systolic pressure/end-systolic volume ratio, ventricular pacing vs atrial synchronous pacing = 6.51 ± 1 vs 4.85 ± 1, p < .001) (figure 1).

Discussion

The purpose of this study was to compare ventricular performance at rest and with upright exercise during atrioventricular sequential and ventricular pacing to the same heart rate. Three new findings were that (1) end-diastolic volume at upright rest is similar in both pacing modes, (2) end-diastolic volume during exercise is greater with synchronous than with ventricular pacing, and (3) stroke volume is maintained at atrial synchronous pacing levels during ventricular paced exercise through increased contractility.

Previous studies have examined the contribution of atrial systole to ventricular function, but in patients with abnormal ventricles who were at supine rest. Under these conditions, well-timed atrial systole variably improves cardiac output.15-23 Fewer data are available on normal subjects, particularly in the upright posture,24-26 and cardiovascular hemodynamics and volumes differ in supine and upright subjects.7, 27, 28

At upright rest, in contrast to findings of previous studies in supine subjects, we found that end-diastolic, end-systolic, and thus stroke volume were similar in the two pacing modes. Furthermore, the volumes and measures of contractile function were equal to those of normal subjects at upright rest in sinus rhythm.7, 28 A
possible explanation for these observations is that with the assumption of the upright posture, diminished venous return “underfills” the central circulation, making the contribution of atrial systole (which varies with filling) relatively insignificant.29,30 Alternatively, changes in ventricular relaxation, which is load-dependent and responsive to metabolic and neurohumoral controls31 or venous tone,32 might maintain end-diastolic volume during ventricular pacing at synchronous paced levels in subjects at upright rest. Further work will be needed to clarify which mechanisms underlie our observations.

Many studies have demonstrated superior exercise capacity and cardiac output with rate-responsive than with fixed low-rate ventricular pacing.33-39 With the development of rate-responsive ventricular pacemakers,40 the important question is whether cardiac performance differs at matched heart rates. This question has been addressed, in part, previously. In a group of patients with heterogenous cardiac disease, cardiac output was only 8% higher and stroke volume only slightly greater with synchronous than with rate-matched ventricular pacing during supine exercise.33 These data are similar to our results in upright subjects and suggest that the ventricular rate response to exercise rather than atrioventricular synchrony accounts for most of the observed improvement in cardiac output in patients with synchronous pacing systems.1

Cardiac volumes and contractility during exercise with atrial synchronous and rate-matched ventricular pacing have not previously been compared. With upright low-level exercise in unpaced individuals, end-diastolic volume rises and end-systolic volume remains the same, with a resultant increase in stroke volume and hence cardiac output, and no change or a mild increase in contractility.28 These directional changes in end-diastolic volume were seen with both pacing modes, but with ventricular pacing end-diastolic volume did not increase as much as with atrial synchronous pacing (9% increase as compared with 20%). Thus, atrial synchrony apparently becomes important only during upright exercise, perhaps due to better filling of the central circulation through increased venous return.32 Responses of end-systolic volume were also different during exercise in the two pacing modes. End-systolic volume did not change with atrial synchronous pacing, while it fell 13% with rate-matched ventricular pacing. Given that systolic blood pressure rose to similar levels in both pacing modes, contractility increased more with ventricular than atrial synchronous pacing. Thus, during ventricular paced exercise, with the loss of consistent atrioventricular synchrony, stroke volume and cardiac output are maintained by means of lowered end-systolic volume, the result of increased ventricular contractility (figure 2). Although a single point of peak systolic pressure/end-systolic volume ratio does not necessarily reflect the slope of the end-systolic pressure/volume relationship as originally described,41 several clinical studies have empirically demonstrated the utility of this index of contractility.3,4 Our conclusions are supported by the directional changes in ejection fraction, which also indicate a greater increase in contractility with ventricular paced than with synchronous paced exercise.32

Certain limitations of the study design warrant discussion. Conclusions are limited to a fixed workload of 300 kpm, chosen to allow steady-state measurements that would reflect the physiology of daily activities (i.e., walking).42 It is possible that biases introduced by the experimental protocol may have influenced the

FIGURE 1. Changes in volumes and contractility from rest to exercise with ventricular and atrial synchronous pacing. Thin lines represent individual patient responses and heavy lines represent mean changes ± SD. EDV = end-diastolic volume (ml); ESV = end-systolic volume (ml); EF = ejection fraction (%); P/V = peak systolic pressure/end-systolic volume ratio (arbitrary units).
comparisons between ventricular and atrial synchronous paced exercise. We did avoid the confounding variable of differing ventricular contraction patterns by pacing the ventricle during all parts of the study. However, with synchronous pacing, ventricular rate rose during the first 30 sec of exercise as a function of atrial rate, whereas the exercise rate was programmed immediately at the onset of exercise with ventricular pacing. All measurements, however, were made after the patient had been exercising for 3 min, minimizing the influence of this variable. Also, all measurements in this study were made immediately after changes in pacing mode, but these have been shown to reflect hemodynamic changes that occur with long-term pacing in a given mode. Finally, we have no explanation for the symptomatic intolerance of two patients to ventricular pacing. Our results are therefore applicable only to patients with symptomatic tolerance to ventricular pacing.

In summary, ventricular volumes and contractility are similar with the two pacing modes in subjects at upright rest. During low-level exercise with atrial synchronous and rate-matched ventricular pacing cardiac output was similar, but ventricular volumes and contractility differed in the two pacing modes. During atrial synchronous pacing, as in normal subjects in sinus rhythm, stroke volume increased primarily as a function of the Frank-Starling effect. With ventricular pacing, a situation in which constant atrioventricular synchrony is absent, stroke volume was increased both by an increase in end-diastolic volume and a decrease in end-systolic volume, the latter reflecting a greater increase in myocardial contractility.

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