Clinical research

Walk test at increased levels of heart rate in patients with dual-chamber pacemaker and with normal or depressed left ventricular function

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Background This study focuses the role of heart rate on cardiac output (CO) at rest and during walk test in patients with dual-chamber pacemaker and depressed or normal left ventricular (LV) function.

Methods and results In nine patients with ejection fraction (EF) <50\% (group A) and in seven with EF 50\% (group B) haemodynamics were assessed at rest and during three randomized 6-min walk tests at fixed rate of 70, 90, and 110 beats·min\(^{-1}\). All patients had dual-chamber pacemaker implanted for complete heart block. Left ventricular function was monitored by a radionuclide system. In group A, with increasing pacing-rate from 70 to 110 beats·min\(^{-1}\), CO did not change both at rest and during walk, whereas end-systolic volume (ESV) increased (\(P<0.05\)) and stroke volume (SV) decreased from 68±6 to 47±9 ml at rest (\(P<0.0001\)) and from 112±21 to 76±17 ml during walk (\(P<0.005\)). In group B, with increasing pacing-rate, CO rose from 6.4±0.7 to 9.1±1.6 l·min\(^{-1}\) at rest (\(P<0.001\)) and from 10±1.5 to 14.1±2.2 l·min\(^{-1}\) during walk (\(P<0.0001\)), with no change in ESV and SV.

Conclusions Increasing heart rate in presence of ventricular asynchrony induced by dual-chamber pacing has negative effect on cardiac contractility and does not improve CO at rest or during physical activity in patients with depressed LV function as occurs in those with normal function.

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KEYWORDS
Heart rate;
Walk test;
Dual-chamber pacing

Introduction

It is well known that the ability to increase cardiac output determines exercise capacity and heart rate is one of the determinants of the enhancement in cardiac output through an increase of number of beats and myocardial contractility.\textsuperscript{1} The latter, known as Bowditch effect or force-frequency relation,\textsuperscript{2} in non-failing heart is enhanced by \(\beta\) adrenergic stimulation as occurs during exercise.\textsuperscript{3,4} In failing heart, the force-frequency relation may be attenuated, absent or even inverted\textsuperscript{5–9} and the enhancement by \(\beta\) adrenergic stimulation on the force-frequency relation is reduced or absent.\textsuperscript{1} It has been also demonstrated that right ventricular pacing induces left ventricular (LV) asynchrony\textsuperscript{10} and that increasing heart rate at rest by such pacing mode decreases cardiac performance in patients with heart failure.\textsuperscript{5} In exercising dogs the increase in heart rate by ventricular pacing resulted in a depressed contractile response as compared

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to spontaneous rhythm or atrial pacing. Despite the clinical relevance of these findings, the effects of increasing heart rate alone on cardiac output during exercise in the presence of LV asynchrony have not been investigated in humans. Accordingly, the present study was designed to assess the influence of heart rate changes on hemodynamics at rest and during moderate physical activity in patients with normal or depressed LV function and with dual-chamber pacemakers implanted for complete atrio-ventricular block. To monitor LV function during the study an ambulatory radionuclide system has been utilized, such as Vest, which provides a reliable, continuous, and non-invasive assessment of LV function during different activities and after drug administration.

Methods

Study population

We studied 16 patients (age 65±5 years) referred for evaluation of chest pain syndromes, but found to have no coronary artery disease. All patients had a dual-chamber rate responsive pacemaker implanted for complete atrio-ventricular block and none of them had spontaneous atrio-ventricular conduction defect or ventriculo-atrial conduction during dynamic electrocardiography and exercise test performed before the study. In each patient, Doppler mitral flow and cardiac output evaluated the optimal atrio-ventricular delay at the time of the pacemaker implantation, which ranged from 2 up to 5 years before the study. Exclusion criteria were coronary artery disease at coronary angiography, valvular heart disease or significant atrio-ventricular valve regurgitation, history of arterial hypertension and recent acute heart failure, severe ventricular arrhythmia or ventriculo atrial conduction during the study. The individual characteristics of the patients are reported in Table 1. Ventricular volumes and stroke volume were assessed by contrast cineangiography, performed within one week before the study. According to normal and depressed LV ejection fraction detected by radionuclide angiography, patients were divided into two groups: nine patients with LV ejection fraction <50% (group A) and seven with LV ejection fraction 50% (group B). In group A, one patient was in New York Heart Association class III, while the remaining eight were in class II. All patients of group A received angiotensin converting enzyme antagonists and diuretics; digoxin was discontinued at least one week before the study. The Ethical Committee of our University approved the protocol and all patients gave informed consent before the study.

Study protocol

All patients underwent equilibrium radionuclide angiography at 9 a.m. following in vivo labelling of red blood cells with 555 MBq of technetium-99m. Radionuclide angiography was performed at rest in the 45° left anterior projection with a 15° cranio-caudal tilt with the patient in supine position. A small field of view gamma camera (Elscint SP4HR, Haifa, Israel) equipped with a low-energy, all-purpose collimator was used. Data were recorded at a frame rate of 30 frames/cardiac cycle on a dedicated computer system. At least 200 000 counts/frame were acquired. At the conclusion of radionuclide angiography, all subjects wore the Vest, and the radionuclide detector (Capintec, Inc., Ramsey, New Jersey, USA) was positioned over the left ventricle. The position of the detector was confirmed by acquiring 2-min static image with the gamma camera. Baseline measurements were made with patients in seated position over a period of 5–10 min; thereafter they performed three walk tests. Each walk test (6 min at the optimal speed) was performed at 70, 90 and 110 beats-min⁻¹. The 6-min walk test was conducted as described previously.17 Pacemakers were programmed in dual-chamber mode at fixed rate of 70, 90 and 110 beats-min⁻¹. Patients were studied according to a randomized crossover design (i.e. the order of the pacing-rate was randomized). Changes in heart rate were performed within 10 min recovery after each walk test, when systemic arterial blood pressure, symptoms and cardiac volumes recovered. Each fixed level of pacing heart rate was maintained for at least 5 min under the three resting conditions before the respective walk test (Fig. 1). The atrio-ventricular delay was not modified during the study. Systemic arterial blood pressure was measured by cuff sphygmomanometer at the peak of the three walk tests.

<table>
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<tr>
<th>Patient (n)</th>
<th>Age/sex</th>
<th>NYHA class</th>
<th>Time of pacemaker implantation</th>
<th>LVEF (%)</th>
<th>LVEDVI (ml·m⁻²)</th>
<th>SVI (ml·m⁻²)</th>
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<td>1996</td>
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*NYHA=New York Heart Association; LVEF=left ventricular ejection fraction assessed by radionuclide angiography; LVEDVI=left ventricular end-diastolic volume index assessed by contrast cineangiography; SVI=stroke volume index assessed by contrast cineangiography.
2 min before starting each walk test and every 2 min during recovery period. At the conclusion of the Vest study, a second 2-min static image was obtained to confirm that the detector did not move during recording.

Data analysis

Radionuclide angiography was analysed with standard commercial software. LV ejection fraction was computed on the raw time-activity curve, while peak filling rate (PFR) was calculated after a Fourier expansion with four harmonics. Vest studies were analysed as previously described. Vest studies were analysed as previously described. At the end of monitoring, data were reviewed for technical adequacy. Briefly, the average count rate (decay-corrected) of the entire study was displayed: if the curve had <10% deviation from a straight line, the Vest study was considered adequate. Radionuclide and dynamic electrocardiographic data were analysed beat by beat and summed for 60-s intervals. Excellent agreement between Vest and radionuclide angiography in measuring ejection fraction (r=0.98, P<0.01) and PFR (r=0.84, P<0.01) has been found for 60-s time averaging. Relative end-diastolic volume (EDV) was considered to be 100% at the beginning of the Vest study and was subsequently expressed relative to this initial value. End-systolic volume (ESV) at any given time was expressed relative to EDV at that time. LV ejection fraction was computed as the stroke counts divided by the background-corrected end-diastolic counts. Background was determined by matching the initial resting Vest ejection fraction value to that obtained by the gamma camera. This background value was then used throughout the remainder of each individual’s Vest data analysis. PFR was obtained from the Fourier curve and computed as the inflection point after end systole at which the second derivative shifts from positive to negative. The accuracy and reproducibility of this technique has been previously validated in our laboratory. The correlation coefficients between the measurements of the LV ejection fraction and PFR obtained with radionuclide angiography and with Vest were 0.9 and 0.88, respectively (both P<0.01), and were maintained at the end of the monitoring period. Vest assessment of the LV ejection fraction and PFR within the same patients under steady-state conditions on different days of observation also showed significant correlation (r=0.97 and r=0.95, respectively, both P<0.05). Absolute volumes were obtained by using LV angiographic EDV to calibrate the baseline radionuclide Vest volume. Cardiac output was measured as stroke volume multiplied by heart rate. Good reproducibility of Vest-assessed stroke

Fig. 1 Cardiac response to walk test at increased levels of heart rate in a patient with depressed left ventricular function during continuous vest monitoring. Vertical dashed lines represent the start and the end of 6-min three walk tests performed in this patient at fixed pacing-rate of 70, 110 and 90 beats-min⁻¹. CO=relative cardiac output; EDV=relative end-diastolic volume; EF=ejection fraction; HR=heart rate.
volume and cardiac output responses to different stimuli (nitroglycerin: stroke volume \( r=0.94, P=0.0001 \) and cardiac output \( r=0.80, P<0.01 \); tilt test: stroke volume \( r=0.84, P=0.001 \) and cardiac output \( r=0.94, P=0.0001 \); handgrip: stroke volume \( r=0.89, P=0.0001 \) and cardiac output \( r=0.93, P=0.0001 \)) has been reported.\(^3\) For analysis and graphical presentation of the data, the mean values of the last minute of pacing tachycardia at rest and that of walk tests were used.

### Statistical analysis

The sample size was estimated to have an 90% chance of detecting a difference of 0.6 l·min\(^{-1}\) (standard deviation, 0.4) between 70 and 110 beats·min\(^{-1}\) in the two primary variables (i.e. cardiac output at rest and during walk test) with an overall significance level of 5% and a two-tail test. A sample of seven patients for each group was deemed to be necessary. Statistical analysis was performed by using the SYSTAT, version 7.0. To test the null hypothesis, analysis of variance for cross-over design was carried out for primary variable, with patients, period effects, levels of pacing and carry-over as factors in the model. The mean differences were estimated on the basis of the above model together with their 95% confidence intervals. Same model was applied to the other variables. Paired t test was used to compare basal values with those at peak in the same group.

### Results

All patients were able to complete the three walk tests without breaks in continuity. Patients of group A complained of mild dyspnoea and fatigue at the end of each walk test and no difference in symptoms among the tests was observed. Patients of group B did not develop any symptoms during the three tests. In the overall study population LV ejection fraction assessed by radionuclide angiography was closely related with that at contrast cineangiography (\( r=0.98, P<0.001 \)) and that at beginning of Vest study (\( r=0.99, P<0.001 \)).

### Effects of increased pacing-rate on haemodynamics at rest

In both groups of patients, pacing-tachycardia at rest did not induce any change in systolic and diastolic blood pressure (Table 2). In group A, increasing stimulation rate from 70 to 90 and to 110 beats·min\(^{-1}\) did not induce significant change in EDV, whereas a progressive increase in ESV was observed (\( F=16.3, P<0.001 \), Fig. 2). As a consequence, stroke volume and LV ejection fraction decreased (\( F=64.4, P<0.0001 \) and \( F=52.2, P<0.0001 \), respectively, Fig. 2). No change occurred in cardiac output and PFR (Fig. 3). In group B, increasing pacing-rate did not induce significant change in cardiac volumes, stroke volume and LV ejection fraction (Fig. 4), while cardiac output (\( F=15.87, P<0.001 \)) and PFR (\( F=20.44, P<0.001 \)) increased (Fig. 5).

### Effects of increased pacing-rate on hemodynamics during walk test

In both groups, increasing pacing-rate during walk did not induce any change in systolic and diastolic blood pressure (Table 2). In group A, increasing pacing-rate induced a decline of EDV (\( F=8.5, P<0.05 \)) and an increase of ESV (\( F=7.81, P<0.05 \)) (Fig. 2). As a consequence, stroke volume and LV ejection fraction decreased (\( F=12.46, P<0.005 \) and \( F=11, P<0.005 \), respectively) (Fig. 2). No significant change occurred in cardiac output and PFR (Fig. 3). In contrast, in group B, increasing pacing-rate determined a rise in cardiac output (\( F=30, P<0.0001 \)) and PFR (\( F=24, P<0.0001 \)) (Fig. 5). No significant changes in cardiac volumes, stroke volume and LV ejection fraction were observed (Fig. 4).

When haemodynamic data at peak of the three walk tests were compared to respective resting values in each group, systolic blood pressure increased whereas diastolic blood pressure did not change (Table 2). In addition, EDV, stroke volume, LV ejection fraction, cardiac output and PFR significantly increased in both groups at peak of walk tests as compared to those at rest; on the contrary, ESV did not change in group A, but showed a marked decrease in group B (Table 3).

### Discussion

The major findings of this study are that in patients with depressed LV function and asynchrony induced by dual-chamber pacemaker, increasing heart rate within a clinically relevant frequency range of moderate physical

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**Table 2** Systolic and diastolic blood pressure at fixed pacing rate at rest and at peak of walk tests in patients with depressed and normal left ventricular function

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Walk</th>
<th>Rest</th>
<th>Walk</th>
<th>Rest</th>
<th>Walk</th>
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<tr>
<td><strong>Heart rate (beats·min(^{-1}))</strong></td>
<td>70±0.8</td>
<td>70±0.6</td>
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<td>90±0.7</td>
<td>110±0.9</td>
<td>110±0.8</td>
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<td><strong>SBP (mmHg)</strong></td>
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<tr>
<td>Group A</td>
<td>120±10</td>
<td>141±9(^b)</td>
<td>116±6</td>
<td>140±8(^b)</td>
<td>18±13</td>
<td>143±10(^b)</td>
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<tr>
<td>Group B</td>
<td>125±14</td>
<td>142±23(^b)</td>
<td>124±17</td>
<td>142±24(^b)</td>
<td>128±13</td>
<td>146±20(^a)</td>
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<tr>
<td><strong>DBP (mmHg)</strong></td>
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<td></td>
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<tr>
<td>Group A</td>
<td>78±5</td>
<td>83±5</td>
<td>79±7</td>
<td>81±5</td>
<td>77±8</td>
<td>82±5</td>
</tr>
<tr>
<td>Group B</td>
<td>78±12</td>
<td>79±14</td>
<td>77±12</td>
<td>81±17</td>
<td>80±16</td>
<td>81±18</td>
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</table>

SBP=systolic blood pressure; DBP=diastolic blood pressure. Group A=depressed left ventricular function; Group B=normal left ventricular function.

\(^a\)P<0.05.

\(^b\)P<0.005 vs respective resting values.
Fig. 2  End-diastolic volume, end-systolic volume, stroke volume and left ventricular ejection fraction in patients with depressed left ventricular function at fixed pacing-rate of 70, 90 and 110 beats·min⁻¹ at rest and at peak of each walk test. *P<0.05, †P<0.005, ‡P<0.0005 vs 70 beats·min⁻¹ and **P<0.05 vs 90 beats·min⁻¹ by post-hoc analysis.
activity does not allow to improve cardiac output both at rest or during walk test. In contrast, pacing tachycardia produces a significant improvement of cardiac output in patients with normal cardiac function.

It has been reported that right ventricular pacing impairs LV function. Interestingly, with increasing heart rate by such pacing mode, cardiac index improved in patients with normal LV function and decreased in those with dilated cardiomyopathy. Our results demonstrate that increasing pacing-rate at rest has a different effect on cardiac output in the two groups of patients mainly depending on different response of ESV to tachycardia. In fact, in patients with depressed LV function, higher pacing-rates at rest did not change loading conditions (i.e. blood pressure and EDV), but significantly increased ESV. This result strongly accounts for a negative effect of increasing heart rate on cardiac contractility, as reversed Bowditch phenomenon. Accordingly, previous studies reported that in failing hearts contractile force is highest at low stimulation rates and decreases at higher frequencies. In our patients with LV dysfunction the reduction of stroke volume and LV ejection fraction at higher frequencies was determined by the deleterious effect of higher pacing-rates on myocardial contractile state. Cardiac output was unchanged throughout the whole frequency range because tachycardia balanced the reduction of stroke volume. Furthermore, the lack of change in PFR with increasing heart rate suggests that tachycardia affected not only cardiac contractility but also myocardial relaxation in patients with impaired LV function. In contrast, in patients with normal LV function, despite the asynchrony induced by atrio-ventricular pacing, higher pacing-rates at rest did not affect myocardial contractility, stroke volume and LV ejection fraction, but improved cardiac output and myocardial relaxation. Our results confirm the clinical relevance of experimental studies in isolated failing and non-failing human myocardium and in patients with normal and depressed LV function during pacing tachycardia.

Interestingly, our findings demonstrate that the effects of pacing tachycardia on cardiac output during physical activity were similar to those observed at rest in both groups. In fact, higher pacing-rates during walk increased cardiac output in patients with normal LV function. On the contrary, cardiac output remained unchanged at different pacing-rates in patients with LV dysfunction. This latter result might explain the similar exercise tolerance observed during the three walk tests in patients with depressed LV function. The different behaviour of cardiac output during exercise in the two groups of patients mainly depended on the contractile response to pacing tachycardia, Frank–Starling mechanism and β adrenergic stimulus. In fact, in patients with depressed LV function increasing pacing-rate during walk induced a significant increase of ESV, suggesting a

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**Fig. 3** Cardiac output and peak filling rate in patients with depressed left ventricular function at fixed pacing-rate of 70, 90 and 110 beats·min⁻¹ at rest and at peak of walk tests. All P=ns.
Fig. 4  End-diastolic volume, end-systolic volume, stroke volume, left ventricular ejection fraction in patients with normal left ventricular function at fixed pacing-rate of 70, 90 and 110 beats·min⁻¹ at rest and at peak of each walk test. All $P$=ns.
reversed Bowditch phenomenon as it was observed at rest. In contrast, in patients with normal LV function increasing pacing-rate did not modify ESV during walk. This strongly accounts for an attenuated Bowditch phenomenon in these patients. A previous study in exercising dogs demonstrated that increasing heart rate...
by right ventricular pacing resulted in a depressed contractile response as compared to spontaneous rhythm or atrial pacing. Moreover, our results demonstrate that, despite the increase in EDV due to augmented venous return, ESV did not change at the peak of the three walk tests as compared to resting value in patients with depressed LV function, but significantly decreased in those with normal function. These findings indicate that the myocardial contractile response to Frank–Starling mechanism and β adrenergic stimulus is impaired in patients with depressed LV function and preserved in those with normal LV function. It has been reported that in patients with congestive heart failure exercise was accompanied by a smaller-than normal decrease in ESV. However, the use of ambulatory radionuclide system overcome the difficulty to monitor the influence of heart rate changes on hemodynamics not only at rest but also during repeated walk tests.

Clinical implications

Tachycardia is thought to be compensatory if it allows achieving an adequate cardiac output in situations where organs perfusion is reduced as in heart failure and acute blood loss. The present study demonstrates that in patients with depressed LV function tachycardia may no longer be compensatory because does not improve cardiac output both at rest and during walk test as occurs in patients with normal LV function. These results suggest that the use of programming pacemakers in the rate responsive mode may be contra-indicated in patients with heart block and LV dysfunction. In this connection, it has been recently observed that, in patients with an implanted cardioverter defibrillator and with LV ejection fraction of 40% or less, dual-chamber rate responsive pacing increases the combined end-point of death or heart failure hospitalization when compared with ventricular backup pacing at 40 beats-min⁻¹. Moreover, there are also considerable evidences that the reduction of heart rate by amiodarone or β blockers improves exercise capacity in patients with heart failure while the increase in heart rate is an important risk factor for cardiovascular mortality independently of any other well-established risk factor.

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References


