Cardiovascular Responses During Static Exercise

Studies in Patients With Complete Heart Block and Dual Chamber Pacemakers

Thomas Alexander, MD; Daniel B. Friedman, MD; Benjamin D. Levine, MD; James A. Pawelczyk, PhD; Jere H. Mitchell, MD

**Background** During static exercise in normal subjects, the mean arterial pressure increases as a result of an increase in heart rate and thereby cardiac output with no significant change in stroke volume or systemic vascular resistance. We hypothesized that if one component of the blood pressure response to static exercise, ie, heart rate, were fixed, plasticity of the neural control mechanisms during exercise would allow for preservation of the blood pressure response by alternative mechanisms.

**Methods and Results** Thirteen patients 20 to 68 years old with structurally normal hearts, complete heart block, and dual chamber pacemakers performed static exercise during three conditions: (1) normal dual chamber sensing and pacing mode, (2) heart rate fixed at the resting value obtained in the DDD mode of 78±4 beats per minute, and (3) heart rate fixed at the peak value obtained during exercise in the DDD mode of 94±4 beats per minute. Heart rate, blood pressure, and cardiac output were measured and stroke volume and systemic vascular resistance were calculated at rest and at 1 and 5 minutes during static one-leg extension at 20% of maximal voluntary contraction. The mean arterial pressures at rest and at 5 minutes were higher when the heart rate was fixed at the faster peak exercise heart rate. In the DDD mode, heart rate increased by 16 beats per minute and cardiac output by 1.1 L/min, with a resultant 25 mm Hg increase in mean arterial pressure at 5 minutes with no change in the stroke volume or systemic vascular resistance. In both fixed heart rate pacing modes, mean arterial pressure increased by 24 mm Hg when the heart rate was fixed at the resting heart rate and by 25 mm Hg when the heart rate was fixed at the faster peak exercise heart rate pacing modes associated with an increase in stroke volume, with similar increases in cardiac output. During static exercise there was no change in systemic vascular resistance from the resting value in any pacing mode.

**Conclusions** When heart rate is fixed in the presence of normal left ventricular function, the mean arterial pressure increases normally during static exercise because of an increase in stroke volume with no change in the systemic vascular resistance. (Circulation. 1994;89:1643-1647.)

**Key Words** • cardiac output • heart block • pacing • exercise

Sustained static exercise causes an increase in blood pressure because of an increase in cardiac output secondary to an increase in the heart rate, whereas stroke volume and systemic vascular resistance do not change.1-5 Parasympathetic withdrawal is the eff erent mechanism for the early heart rate response noted during static exercise.6-9 As static exercise is continued, the sympathetic nervous system plays an increasing role in maintaining the blood pressure response. Sympathetic nerve activity to resting muscle, assessed by microneurography, shows an increase only after the first minute of static handgrip exercise,9-11 although sympathetic activation of the cardiac response may occur as early as 30 seconds.6 A number of experimental models have been used to investigate the role of heart rate in the blood pressure response to static exercise. Studies using autonomic blockade to prevent an increase in heart rate during static exercise did not inhibit the increase in blood pressure.2,6,8,12 The blood pressure responses in these studies were caused by an increase in the systemic vascular resistance, with no change in heart rate or stroke volume. Patients with Chagas' heart disease13 and evidence of cardiac parasympathetic denervation, as demonstrated by the lack of a heart rate response to atropine, also have an appropriate blood pressure response during static exercise because of an increase in the systemic vascular resistance. Their blood pressure response is similar to Chagas' heart disease patients with a normal parasympathetic nervous system, the latter increasing their heart rate and thereby cardiac output appropriately. The constancy of the blood pressure response to isometric exercise is similar to that of patients with orthotopic heart transplants.14 However, in subjects with autonomic blockade and in patients with Chagas' disease, cardiac function, in addition to heart rate, is affected.

Patients with complete heart block and otherwise functionally normal hearts who have dual chamber pacing and sensing pacemakers are uniquely suitable for examining the role of heart rate in the cardiovascular responses during static exercise in the absence of the confounding effects of drugs or of abnormal cardiac function. A preliminary report of these findings has been presented.15
Methods

Subjects

The subjects used in this study were 13 patients (2 men and 11 women) with programmable dual chamber pacing and sensing (DDD) pacemakers placed for complete atrioventricular conduction block. The mean age was 34 years (range, 22 to 68 years), mean height was 161 cm (range, 152 to 168 cm), and mean weight was 64 kg (range, 44 to 101 kg). The pathogenesis of the complete atrioventricular conduction block was congenital in 8 patients, secondary to successful atrioventricular nodal ablation for atrial tachycardia in 4, and idiopathic conduction disease in 1. None of the patients had evidence for coronary artery disease, and none were taking cardiovascular medications.

The research protocol was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center. All subjects gave written informed consent. A normal cardiovascular and neurological status was ascertained by evaluating past medical records and after a careful history and physical examination. None of the patients had active medical problems at the time of the study. Two patients were excluded from participating in the study because they failed to meet the entry criteria; one had ventricular preexcitation resulting from a bypass tract, and the other had intact atrioventricular conduction. A total of 13 subjects participated and completed all three phases of the exercise protocol.

Procedures

DDD pacemakers have leads in both the atria and ventricles with the capability to sense and to track intrinsic cardiac electrical activity. In patients with normal sinus node function and complete heart block, the intrinsic sinus rhythm is sensed and the ventricle is sequentially paced, thus simulating the normal physiological heart rate responses to static exercise. The heart rate can be fixed by programming the DDD pacemakers to the DDD mode, in which the pacemaker does not sense any intrinsic electrical activity and paces the atria and, after an appropriate delay, the ventricle. In the presence of a faster competing intrinsic sinus activity, successful atrial pacing may not occur because of failure to capture. Ventricular pacing would still occur at the programmed heart rate, since the presence of complete heart block would prevent conduction of any atrial activity. The effects of fixed heart rate pacing during static exercise in the absence of confounding drug effects or cardiac disease were examined in patients with DDD pacemakers. Heart rate was fixed either at the slower resting heart rate or at the peak exercise heart rate for the same exercise protocol to determine whether the cardiovascular responses would differ at either end of this spectrum.

All patients abstained from smoking and drinking caffeine-containing beverages on the day of the study and were told to avoid strenuous exercise in the preceding 24 hours. They were seated on a straight-back chair and asked to perform static knee extension using their dominant leg with the knee flexed at 90°. The generated force was measured with a strain gauge. Maximal voluntary contraction was determined as the maximal force generated during three separate attempts sustained for a period of 2 seconds. The 20% maximal voluntary contraction was calculated and displayed on an oscilloscope for visual feedback to the patient so that force could be maintained constant throughout the 5-minute exercise period. Heart rate was monitored continuously with limb leads from the ECG (Siemens, Mignograph 7). Mean arterial pressure was measured by photoplethysmography (Finapres, Ohmeda). Cardiac output was measured by a modified acetylene rebreathing system that has been described in detail previously. For this method the patients breathed a mixture of 0.60% acetylene, 45.00% oxygen, 9.50% helium, and the rest nitrogen from a rebreathing bag for a period of 20 seconds. Gas concentrations during rebreathing were analyzed by a mass spectrometer (model MGA 1100, Perkin-Elmer, Pomona, Calif), and the analog output was sampled at 50 Hz with a minicomputer (PDP 11-23, Digital Equipment, Maynard, Mass). During rebreathing there is an exponential decline in the exhaled acetylene concentration because of its uptake by the pulmonary capillary blood. The slope of this line was used to calculate cardiac output as described by Triebwasser et al. The stroke volume (SV=CO/HR, where CO is cardiac output and HR is heart rate) and systemic vascular resistance (SVR=MAP/CO×80, where MAP is mean arterial pressure) were then calculated and reported in milliliters and dynes·cm⁻¹·s⁻¹, respectively.

Initially, baseline resting measurements (Rest) of cardiac output, heart rate, and blood pressure were obtained in all subjects before exercise. Measurements of the cardiac output, heart rate, and mean arterial pressure were repeated at 1 minute and 5 minutes during static leg extension. All patients exercised first in the rate-responsive dual chamber sensing and pacing mode (DDD), which tracked the intrinsic atrial rate and after an appropriate atrioventricular delay paced the ventricle. The subjects then repeated the exercise in random order, either with heart rate fixed at the resting rate (DOO-Rest) or with the heart rate fixed at the peak exercise rate (DOO-Ex). During the latter two exercises, the sensing feature of the dual chamber pacemakers was turned off (DOO mode). No other pacemaker parameters were altered throughout the study. A 20-minute rest period was allowed between the different static exercise conditions.

Data Analysis

Two-factor repeated-measures ANOVA (mode×time) was used to analyze and compare changes in the hemodynamic variables (cardiac output, mean arterial pressure, stroke volume, systemic vascular resistance, heart rate) during sustained static one-leg extension among the three pacing modes (DDD, DOO-Rest, and DOO-Ex). However, because the cardiac output data were not normally distributed, these data were transformed logarithmically for statistical analysis. Statistical significance was established at P<.05. Probabilities were adjusted by use of the Huynh-Feldt method to account for departures from the assumption of sphericity. When significant differences were found among pacemaker modes or with time, contrasts were formed to test the difference between each set of measurements. Statistical significance was established with a Bonferroni-adjusted value of P=.017. An additional repeated-measures ANOVA was used to compare the mean response across exercise in the different pacemaker modes to ascertain whether the order of exercise (ie, whether the DOO-Rest or DOO-Ex were done second or third after the DDD mode) affected comparisons among pacemaker modes.

Results

Hemodynamic Data During Rest

During rest, heart rate and mean arterial pressure were higher in the DOO-Ex pacing mode (Table; Fig 1). The cardiac output was decreased in the DOO-Rest mode secondary to intermittent loss of atrioventricular synchrony (Table; Fig 2). This decrease was secondary to a decrease in the stroke volume, since heart rate was not different between DDD and DOO-Rest pacing modes. Mean arterial pressure was maintained in the DOO-Rest mode despite a drop in cardiac output by an associated increase in the systemic vascular resistance compared with the DDD pacing mode (Table; Fig 2).

The cardiac output in the DOO-Ex mode was not different from the DDD mode at rest (Table; Fig 2). With the elevated heart rate in DOO-Ex mode, stroke
Hemodynamic Values in the Different Pacing Modes at Rest and During Exercise

<table>
<thead>
<tr>
<th></th>
<th>DDD</th>
<th>DOO-Rest</th>
<th>DOO-Ex</th>
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<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Ex-1</td>
<td>Ex-5</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>79±4</td>
<td>86±4*</td>
<td>94±5*</td>
</tr>
<tr>
<td>Mean arterial</td>
<td>92±4</td>
<td>101±4*</td>
<td>115±5*</td>
</tr>
<tr>
<td>pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cardiac output,</td>
<td>4.50±0.27</td>
<td>5.13±0.41*</td>
<td>5.58±0.50*</td>
</tr>
<tr>
<td>L·min⁻¹</td>
<td></td>
<td></td>
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<tr>
<td>Stroke volume, mL</td>
<td>59±5</td>
<td>62±6</td>
<td>62±7</td>
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<tr>
<td>Systemic vascular</td>
<td>1702±114</td>
<td>1652±103</td>
<td>1777±136</td>
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<tr>
<td>resistance, dyne·s⁻¹·cm⁻⁵</td>
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DDD indicates dual chamber sensing and pacing mode; DOO-Rest, heart rate fixed at resting rate; DOO-Ex, heart rate fixed at peak exercise rate; Ex-1, exercise after 1 minute; Ex-5, exercise after 5 minutes; and bpm, beats per minute. Significance P<.017. *Compared with rest in same pacing mode. †Compared with DDD pacing mode.

volume was reduced, resulting in no change in the cardiac output at rest (Table; Fig 2).

**Hemodynamic Data During Static Exercise**

In the dual chamber DDD pacing mode the mean arterial pressure increased from rest at 1 and at 5 minutes of sustained static one-leg extension (Table; Fig 1). This was a result of an increase in cardiac output secondary to an increase in the heart rate. The stroke volume and systemic vascular resistance did not change during the exercise protocol (Table; Fig 2).

When heart rate was fixed at the resting level (DOO-Rest), the mean arterial pressure increased from rest at 1 minute and at 5 minutes during static exercise (Table; Fig 1). The mean arterial pressures at 1 and 5 minutes were not different from those obtained during exercise in the DDD pacing modes. Cardiac output increased by an increase in the stroke volume (Table; Fig 2) at 1 minute and at 5 minutes. The stroke volume, which was lower than that in the DDD pacing mode at rest, did not change during exercise.

**Fig 1.** Graphs showing mean arterial pressure (mm Hg) and heart rate (beats per minute) at rest and during 5 minutes of static leg extension at 20% maximal voluntary contraction. ● indicates DDD (dual chamber sensing and pacing); ▲, DOO-Rest (heart rate fixed at the resting value); and ○, DOO-Ex (heart rate fixed at peak exercise value). *Significant group difference; see Table for specific comparisons.

**Fig 2.** Graphs showing cardiac output (liters per minute), stroke volume (milliliters), and systemic vascular resistance (dyne·s⁻¹·cm⁻⁵) at rest and during 5 minutes of static leg extension at 20% maximal voluntary contraction. ● indicates DDD (dual chamber sensing and pacing); ▲, DOO-Rest (heart rate fixed at the resting value); and ○, DOO-Ex (heart rate fixed at peak exercise value). *Significant group difference; see Table for specific comparisons.
differ at 1 minute, and at 5 minutes it was higher than in the DDD mode. The stroke volume in the DOO-Rest pacing mode was also greater than that seen in the DOO-Ex pacing mode at 5 minutes (Table; Fig 2). In the DOO-Rest mode the systemic vascular resistance (Table; Fig 2) did not change from the control resting values during the exercise protocol, although the values obtained were greater at 1 and 5 minutes than those in the DDD pacing mode.

When heart rate was fixed at the peak exercise level (DOO-Ex), the mean arterial pressure increased from rest at 1 minute and at 5 minutes during static exercise (Table; Fig 1). At 5 minutes the mean arterial pressure was greater than that obtained in the DDD mode. At 1 minute, however, the mean arterial pressure in the DOO-Ex pacing mode was not different from those obtained in either the DDD or the DOO-Rest pacing mode. The mean arterial pressure response was due to an increase in cardiac output brought about by an increase in the stroke volume, since heart rate was fixed by pacing. The stroke volume (Table; Fig 2) increased from rest after 1 and 5 minutes of exercise. As during rest, the stroke volume at 1 minute was lower compared with the DDD mode and the DOO-Rest mode. At 5 minutes the stroke volume (Table; Fig 2) was not different from that in the DDD pacing mode but remained lower than in the DOO-Rest mode. The systemic vascular resistance did not change from rest during exercise in the DOO-Ex mode, as was seen with the other two pacing modes. However, the systemic vascular resistance was higher in the DOO-Ex mode than in the DDD mode at 1 and 5 minutes of static exercise.

Discussion

The important finding of this study is that mean arterial pressure increases normally during static exercise despite a fixed heart rate and, further, that this increase occurs by an increase in the stroke volume (hence cardiac output) without significant changes in systemic vascular resistance. The present study shows that stroke volume can compensate for a fixed heart rate to elicit a normal blood pressure response to static exercise. This observation is different from studies in which heart rate was not allowed to increase by use of autonomic blockade and the increase in blood pressure was due to an increase in systemic vascular resistance. However, autonomic blockade, in addition to preventing an increase in the heart rate, may have decreased cardiac contractility and prevented an increase in contractility from occurring during exercise. Similarly, studies in patients with Chagas’ disease, who have cardiac parasympathetic denervation, found that an increase in the systemic vascular resistance accounted for the blood pressure response when the heart rate did not change. Also, ventricular function may have been abnormal in these patients, and evaluation of the sympathetic nervous system was not performed. Thus, in previous studies stroke volume was unlikely to change because the heart itself was affected.

In the dual chamber atrial and ventricular sensing and pacing mode (DDD mode), the pacemaker tracks the intrinsic sinus rate and paces the ventricle after an appropriate atrioventricular delay. During sustained static one-leg exercise with the pacemaker in the DDD mode, the heart rate increases in a normal fashion and accounts for the increase in cardiac output and mean arterial pressure with no change in stroke volume and systemic vascular resistance from the resting values. This cardiovascular response was identical to that obtained with normal subjects. When heart rate was fixed at either the slower resting rate (DOO-Rest) or at the faster peak exercise rate (DOO-Ex), the increase in mean arterial pressure during exercise was the same. In both pacing modes, an increase in cardiac output accounted for the increase in mean arterial pressure during static exercise without a change in systemic vascular resistance. With heart rate held constant, an increase in stroke volume accounted for the increase in cardiac output and, thereby, an increase in mean arterial pressure.

The constancy of stroke volume observed during static exercise in the DDD mode is consistent with the general consensus that cardiac output, but not stroke volume, increases during static exercise. However, the observation that stroke volume changes account solely for the blood pressure response when heart rate is fixed has not been reported previously. From a similar investigation, Bergenswal et al found that systemic vascular resistance increased slightly during static handgrip exercise but increased dramatically from baseline with sustained atrial pacing at 109 beats per minute. The difference between that investigation and the present one may be explained by the fact that the pacing rate was beyond the heart rate measured during exercise without pacing, resulting in a 32% increase in cardiac output but only an 18% reduction in baseline stroke volume. Systemic vascular resistance decreased 20% at rest, perhaps as an arterial baroreflex-mediated compensatory response to the large increase in flow and blood pressure associated with relatively high-rate pacing. Thus, an increase in systemic vascular resistance with high-rate pacing was unmasked by the relatively low initial value of systemic vascular resistance. The present study reveals that when heart rate is matched closely with physiological states, the compensatory hemodynamic change occurs exclusively with stroke volume.

The increase in stroke volume that occurs with static exercise when the heart rate is fixed at the resting or peak exercise level can be explained by an increase in the end-diastolic volume (Frank-Starling mechanism), by an increase in contractility (caused by decreased parasympathetic and increased sympathetic nerve activity) or by both mechanisms. Such autonomic changes would result in a decreased end-systolic volume. Since no measurement of left ventricular volumes was made in this study, one can only speculate about which mechanism was important in increasing the stroke volume in the present study.

In the present study, systemic vascular resistance increased when fixed-rate pacing in the DOO-Rest or DOO-Ex pacing mode was initiated (Table; Fig 2). In the DOO-Rest pacing mode, the decrease in cardiac output caused by loss of atrioventricular synchrony may have triggered a baroreflex-mediated increase in systemic vascular resistance to maintain mean arterial pressure. Also, the blood pressure response to static exercise was accelerated during pacing at the faster peak exercise heart rate (DOO-Ex) compared with the
DDD pacing mode. At 5 minutes the mean arterial pressures were no different in either mode after a steady state was achieved.

In summary, the blood pressure response is maintained during static one-leg exercise patients with normal left ventricular function and dual chamber pacemakers when the heart rate is fixed at the resting or peak exercise rate. Further, this response is caused by an increase in stroke volume and not by an increase in systemic vascular resistance. Additional studies are needed to determine the mechanisms for this increase in stroke volume. It could be caused by an increase in end-diastolic volume (Frank-Starling mechanism), by an increase in the contractile state of the left ventricle with a decrease in end-systolic volume, or by both mechanisms.

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