Varying the heart rate response to dynamic exercise in pacemaker-dependent subjects: effects on cardiac output and cerebral blood velocity

Lysander W.J. BOGERT∗†1, Ayten EROL-YILMAZ†1, Raymond TUKKIE† and Johannes J. VAN LIESHOUT∗

∗Department of Internal Medicine, Academic Medical Centre, University of Amsterdam, 1100 DE Amsterdam, The Netherlands, and †Department of Clinical and Experimental Cardiology, Academic Medical Centre, University of Amsterdam, 1100 DE Amsterdam, The Netherlands

ABSTRACT

Cerebral blood flow increases upon the transition from rest to moderate exercise, but becomes affected when the ability to raise CO (cardiac output) is limited. HR (heart rate) is considered to contribute significantly to the increase in CO in the early stages of dynamic exercise. The aim of the present study was to test whether manipulation of the HR response in patients dependent on permanent rate-responsive ventricular pacing contributes to the increase in CO, MCA Vmean [mean MCA (middle cerebral artery) velocity] and work capacity during exercise. The effect of setting the pacemaker to DSS ('default' sensor setting) compared with OSS ('optimized' sensor setting) on blood pressure, CO, SV (stroke volume) and MCA Vmean was evaluated during ergometry cycling. From rest to exercise at 75 W, the rise in HR in OSS [from 73 (65–87) to 116 (73–152) beats/min; \(P < 0.05\)] compared with DSS [70 (60–76) to 97 (67–117) beats/min; \(P < 0.05\)] was larger. There was an increase in SV during exercise with DSS, but not with OSS, such that, at all workloads, SVs were greater during DSS than OSS. The slope of the HR–CO relationship was larger with DSS than OSS (\(P < 0.05\)). From rest to exercise, MCA Vsys (systolic MCA velocity) increased in OSS and DSS, and MCA Vdias (diastolic MCA velocity) was reduced with DSS. No changes were observed in MCA Vmean. Manipulation of the pacemaker setting had no effect on the maximal workload [133 (100–225) W in OSS compared with 129 (75–200) W in DSS]. The results indicate that, in pacemaker-dependent subjects with complete heart block and preserved myocardial function, enhancing the HR response to exercise neither augments CO by a proportional offset of the exercise-induced increase in SV nor improves cerebral perfusion.

INTRODUCTION

CBF (cerebral blood flow) [1] and MCA Vmean [mean MCA (middle cerebral artery) velocity] [2] increase upon the transition from rest to moderate exercise [3,4]. The exercise-related increase in cerebral perfusion is attenuated when the ability to raise CO (cardiac output) is limited [4,5]. Normally, both chronotropic and inotropic

Key words: cardiac output, cerebrovascular circulation, cycle ergometry, pacemaker sensor, stroke volume.

Abbreviations: BP, blood pressure; CBF, cerebral blood flow; CO, cardiac output; DAP, diastolic arterial pressure; DSS, default sensor setting; HR, heart rate; LVEF, left ventricular ejection time; MAP, mean arterial pressure; MCA, middle cerebral artery; MCA Vdias, diastolic MCA velocity; MCA Vmean, mean MCA velocity; MCA Vsys, systolic MCA velocity; OSS, optimized sensor setting; PetCO₂, end-tidal partial pressure of CO₂; PP, pulse pressure; SAP, systolic arterial pressure; SV, stroke volume; TPR, total peripheral resistance.

†These authors contributed equally to the study.

Correspondence: Dr Johannes J. Van Lieshout (email j.j.vanlieshout@amc.uva.nl).
cardiac adaptive mechanisms drive CO in the early stages of circulatory adaptation to exercise, the contribution of HR (heart rate) being as much as approx. 75 % [6].

With such a large contribution of HR to the increase in CO at the onset of exercise, the setting of pacemakers may be critical for the patient’s ability to maintain daily activities. Manipulation of HR is possible with rate-responsive pacing and the ability to increase CO may be improved [7]. Rate-responsive pacemakers are used in patients with atrioventricular nodal block, and rate-modulated pacing is considered preferable for patients with chronotropic incompetence [8]. Patients with complete heart block following atrioventricular ablation for atrial fibrillation are provided with a rate-modulated pacemaker, i.e. the pacing rate is modulated based on one or more internal sensors that detect exercise and metabolic need [8]. In these subjects there are several ways to programme the pacemaker and evaluate the effects on HR and CO.

During exercise, CO is tightly and linearly related to oxygen uptake [9,10]. Indeed, the increase in CO and BP (blood pressure) during dynamic exercise is also preserved when there is little change in HR, such as in patients with a heart transplant or in healthy subjects following autonomic blockade [11–13]. These observations raise the possibility that HR may not be an important determinant of the haemodynamic response to exercise in pacemaker-dependent subjects.

The aim of the present study was therefore to test whether manipulation of the HR response in patients dependent on permanent rate-responsive ventricular pacing contributes to the increase in CO, MCA $V_{\text{mean}}$ and/or to the increase in work capacity during exercise.

**METHODS**

**Study population**

Six ventricular paced untrained patients [66 (49–76) years] with permanent programmable ventricular rate-responsive pacemakers (Vitatron or Guidant) participated in the study (Table 1). Pacemakers were used because of drug-resistant atrial fibrillation with His bundle ablation ($n = 5$) and sick sinus syndrome ($n = 1$). On the basis of history, and medical and echocardiographic examination, myocardial function in all but one patient was considered normal without any evidence of inotropic dysfunction. One patient with a history of myocardial infarction and left ventricular ejection fraction of 25 % used amiodarone for recurrent non-sustained ventricular tachycardia. Separate examination of the study data of this patient revealed that the cardio- and cerebro-vascular response to exercise was not different from the group data, and this subject was included in the analysis.

All patients received a verbal and written explanation of the objectives, measurement techniques and risks and benefits associated with the study, and each provided written informed consent in accordance with the Helsinki Declaration. This study was approved by the Medical Ethical Committee of the Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.

**HR**

During consecutive runs of symptom-limited exercise, using a chronotropic assessment exercise protocol [14], the pacemaker sensor setting was adjusted in accordance with a database to produce a physiological HR response to exercise derived from electrodes mounted on a belt (Polar advantage system; Polar Electro). Pacemakers were provided with an activity sensor that uses a piezoelectric crystal for detection of body movement and a QT sensor with rate-independent shortening of the QT interval during increased sympathetic activity as input. In pacemakers with a QT sensor during a learning procedure lasting several weeks, software incorporated in the pacemaker correlated the longest QT interval and zero activity counts to an individual at rest, and the shortest QT interval and the maximum number of activity counts to the maximum level of exercise. Ultimately, the rate moves between the lower rate and the maximum sensor rate.

**Table 1  Patient characteristics and pacemaker settings**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Default setting</th>
<th>Optimized setting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sensor</td>
<td>URL</td>
</tr>
<tr>
<td>1</td>
<td>69</td>
<td>Male</td>
<td>AF</td>
<td>QT = ACT</td>
<td>120</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>Female</td>
<td>AF</td>
<td>QT = ACT</td>
<td>120</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>Male</td>
<td>AF</td>
<td>QT = ACT</td>
<td>120</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>Female</td>
<td>AF</td>
<td>ACT only</td>
<td>120</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>Male</td>
<td>SSS</td>
<td>QT = ACT</td>
<td>120</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>Female</td>
<td>AF</td>
<td>ACT only</td>
<td>130</td>
</tr>
</tbody>
</table>

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With pacemaker settings to the manufacturer’s DSS (‘default’ sensor setting), there is an equal contribution of the activity sensor and QT sensor to the pacing rate with the firing threshold set at medium level and with a limit set to the maximally attainable HR (Table 1). The HR response to exercise was used to vary the level of input between the activity sensor and the QT sensor, and the threshold of the activity sensor was adjusted to the minimal level of vibration required for producing a rate response. With succeeding series of exercise, the pacemaker sensors were adjusted in a stepwise manner until the derived HR curves [OSS (‘optimized’ sensor setting)] approached reference curves. OSS was established further by increasing the upper rate limit from 122 ± 4 to 157 ± 10 beats/min (Table 1) with the upper rate limit set as (220 – age) beats/min.

Study protocol
Experiments were performed after completion of the sensor-learning period. Following this period and at least 2 months following sensor ‘optimization’, patients were admitted to the laboratory for exercise testing. After a resting period of 15 min in seated position, resting data were collected and the patients performed graded ergometry cycle exercise twice with the pacemaker in the DSS and OSS.

Upright exercise was performed on an electrically braked stationary cycle ergometer from rest to maximal exertion with a constant pedalling speed of 60 rounds/min. Exercise started at 25 W for 3 min. From then on, each stage increased by 25 W from the previous stage and lasted 2 min in duration. The exercise was stopped when the subjects were no longer able to maintain 60 rounds/min. Subsequently, they rested in the supine position for at least 45 min to allow cardiovascular variables to return to resting levels. Thereafter, the pacemaker settings were switched from OSS to DSS or vice versa, followed by another resting period of 15 min in the seated position. The order of the pacemaker settings was fixed in four of the six patients, accounting for the requested QT sensor-learning time, and these subjects started exercise with the pacemaker in OSS. Both the subjects and observer were blinded to the settings of the pacemaker.

Central and cerebral haemodynamic measurements
BP was measured non-invasively by photoelectric plethysmography with a Finapres (Model 5; Netherlands Organization for Applied Scientific Research, Biomedical Instrumentation) with the finger cuff on the mid-phalanx of the middle finger of the dominant hand. To avoid hydrostatic level differences, the cuffed hand was held at the right atrial level in the mid-axillary line supported by a sling and with the non-dominant hand holding the handle bars. A built-in expert system (Physiocal) was in operation in the Finapres device to establish and adjust a proper volume clamp set point. During progressive exercise to fatigue, there was no significant difference in the intercept value from zero for systolic, mean and diastolic arterial pressure (SAP, MAP and DAP respectively) between the radial and finger arterial pressure with validity correlations ranging from 0.93–0.99 [15].

Beat-to-beat data of cardiovascular variables were collected on a personal computer with customized software. The HR, SV (stroke volume) and thus CO were determined from the non-invasive BP waveform using the Modelflow software program, incorporating age, gender, height and weight (BeatScope version 1.1 software; Biomedical Instrumentation). The pressure pulsation was entered into a three-element non-linear model of arterial input impedance and aortic inflow was computed by simulating that model [16]. The method detects the arterial pressure upstroke and the dicrotic notch at the end of left ventricular ejection. This flow pulsation is integrated over the period between the beginning of the upstroke and the notch to yield SV. This methodology has been shown to track fast and brisk changes in SV during various experimental protocols [17–19], including dynamic exercise [20,21]. If accurate absolute values are required, the methodology needs calibration against a standard method [18,22]; otherwise, CO is expressed as changes from control with the same precision in CO [23,24]. CO was calculated as SV × HR. TPR (total peripheral resistance) is the ratio of MAP and CO expressed as changes from its starting value in the seated resting position prior to exercise. Heart period was measured as the time between two consecutive arterial pressure upstrokes. LVET (left ventricular ejection time) was expressed as the time lapse between the beginning of the arterial pressure upstroke and the notch. LVET was measured from the foot of the pressure upstroke to the trough of the incisura [25].

Changes in cerebral perfusion were evaluated by following the blood flow velocity in the MCA. The MCA was investigated by insonating its proximal segment using a 2 MHz pulsed-wave Doppler instrument (Multidop X; DWL) with online spectrum analysis. The hand-held probe was held over the temporal bone window to insonate the MCA through the posterior temporal ‘window’. The artery was found at a depth of 45–55 mm, and velocity was shown as upwardly deflected pulse waves. When the optimal signal-to-noise ratio was obtained, the probe was secured with a headband (Mark 600; Spencer Technologies) [18,19,23]. MCA Vmean (time-averaged maximum velocity over the cardiac cycle) was expressed in cm/s.

PetCO2 (end-tidal partial pressure of CO2), as an estimate of arterial CO2 tension and breathing frequency, was obtained from a capnogram by means of a nose tubing connected to a sampling infrared CO2 analyser (Datex Normocap 200).
Table 2  Cerebral and central haemodynamics at two settings of pacemaker-determined HR

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
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<tbody>
<tr>
<td></td>
<td>DSS</td>
<td>OSS</td>
</tr>
<tr>
<td></td>
<td>25 W</td>
<td>75 W</td>
</tr>
<tr>
<td></td>
<td>25 W</td>
<td>75 W</td>
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<tr>
<td></td>
<td>25 W</td>
<td>75 W</td>
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<tr>
<td></td>
<td>25 W</td>
<td>75 W</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>89 (73–105)</td>
<td>93 (75–108)</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>58 (34–73)</td>
<td>59 (37–72)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>70 (40–74)</td>
<td>73 (65–87)</td>
</tr>
<tr>
<td>LVET (s)</td>
<td>0.27 (0.24–0.32)</td>
<td>0.27 (0.24–0.31)</td>
</tr>
<tr>
<td>SV (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>CO (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>TPR (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>MCA Vmean (cm/s)</td>
<td>46 (37–62)</td>
<td>46 (35–56)</td>
</tr>
<tr>
<td>PETCO2 (mmHg)</td>
<td>33 (29–37)</td>
<td>33 (29–37)</td>
</tr>
<tr>
<td>F (min⁻¹)</td>
<td>16 (12–20)</td>
<td>16 (12–19)</td>
</tr>
</tbody>
</table>

Analysis

For offline analysis, signals of arterial pressure, MCA velocity and capnogram were analogue-to-digital converted at a sampling rate of 100 Hz and stored. MCA $V_{mean}$, MCA $V_{sys}$ (systolic MCA velocity) and MCA $V_{dias}$ (diastolic MCA velocity) were measured. MCA $V_{mean}$ and MAP were obtained respectively, as the integral of velocity and pressure divided by the corresponding beat interval. PP (pulse pressure) was the SAP–DAP difference, and HR was obtained from the PP interval. The HR responses produced with DSS and OSS were evaluated according to the maximal HR attained.

To allow averaging of data obtained within subjects, data were transformed to equidistantly re-sampled data at 2 Hz by polynomial interpolation and expressed as 10 s averages. Baseline measurements were averaged values over a 1 min resting period seated on the bicycle prior to exercise. If data fitted a normal distribution, as determined by Kolmogorov–Smirnov test with Lilliefors’ correction, they were examined by paired Student’s test, otherwise they were examined by Wilcoxon signed-rank test. Effects of pacemaker mode on the increase in HR and CO were evaluated by linear regression analysis; the slopes of the HR–CO relationship with DSS compared with OSS were evaluated by analysis of covariance. Data are expressed as either means (range) or means ± S.E.M. A $P$ value < 0.05 was taken to indicate a statistically significant difference.

RESULTS

In the resting seated condition prior to exercise, HR, MAP and PP were comparable for DSS and OSS. Also, resting MCA $V_{mean}$, PETCO2 and breathing frequency were not affected by the pacemaker setting (Table 2). The increase in HR was larger with OSS than DSS during the first 3 min of exercise at 25 W (26 compared with 13 beats/min respectively), and this difference remained at 75 W (43 compared with 27 beats/min respectively; Figure 1 and Table 2). There was an increase in SV during exercise with DSS, but not with OSS, so that at all workloads SV was greater during DSS than OSS. The
Exercise with pacemaker-determined heart rate

Figure 2 Individual difference (OSS – DSS) curves for haemodynamic variables during exercise
The steeper increase in HR is compensated for by a less steep increase in SV in OSS. QO, CO optimized; QD, cardiac output default; SVO, SV optimized; SVD, SV default; HRO, HR optimized; HRD, HR default. S1–S6, subjects 1–6.

A 2-fold increase in CO was comparable for OSS and DSS (Table 2). The individual difference curves (OSS – DSS) for CO and SV at two levels of pacemaker-determined HR are shown in Figure 2. The slope of the HR–CO relationship was significantly greater ($P = 0.028$) with DSS ($CO = 3.3 \times HR - 115; R^2 = 0.96$) compared with OSS ($CO = 1.8 \times HR - 17; R^2 = 0.92$). At rest, LVET was comparable for OSS and DSS but, during exercise, LVET fell with OSS and was well maintained with DSS (Table 2).

The progressive reduction in TPR with increasing level of exercise was of comparable magnitude (44 % at 75 W) in OSS and DSS (Table 2). For OSS and DSS, the increase in SAP (37 and 33 % at 75 W; Figure 3) and PP (73 and 79 % at 75 W; Table 2) was comparable, and MAP increased. From rest to exercise, MCA $V_{sys}$ increased in OSS and DSS with a reduction in MCA $V_{dias}$ with DSS and without changes in MCA $V_{mean}$. The rise in breathing frequency was comparable, whereas $P_{ETCO_2}$ increased with OSS but not DSS (Table 2). The HR response did not
DISCUSSION

In the present study, we tested in patients dependent on permanent rate-responsive ventricular pacing whether manipulation of the HR response to exercise contributes to the increase in CO. The main new findings of the present study are that manipulating pacemaker sensor input enhanced the HR response to exercise, with a larger HR response balanced by a proportional attenuation in the increase in SV. As a consequence, optimizing pacemaker settings did not modify the exercise-induced increase in CO, MCA $V_{mean}$ or work capacity.

Methodological considerations

During dynamic exercise with a large muscle mass, diastolic cardiac volume is secured by venous return [26], and we considered that manipulation of the HR response in pacemaker-dependent subjects with normal cardiac function allows us to study the contribution of HR to the CO response to exercise. Our present study has, however, several potential limitations.

Right ventricular apical pacing results in an asynchronous ventricular contraction [8], and CO may possibly have been lower due to asynchronous activation or the absence of atrial contraction. However, each patient was his/her own reference and this possible restriction...
arterial CO2. The exercise-related change in MCA Vn significantly during variations in MAP [36], and changes in MCA Vmean during cranio-tomy reveal that the vessel diameter does not change significantly, rather than resistance, vessels and changes in MAP within the physiological range appear to have negligible effects on the diameter of the insonated artery [34,35]. Direct observations made during cranial arteriography reveal that the vessel diameter does not change. The large cerebral arteries in CBF, which is true only in so far as the diameter of the large cerebral arteries in CBF apply to both conditions. During exercise, CO is tightly controlled by and linearly related to oxygen uptake [27] and, in the present study, workload, duration of exercise and attained CO were comparable for the two levels of pacemaker-determined HR. By design, the two exercise protocols were performed in a fixed order to allow for the required QT sensor-learning period. Although both subjects and observer were blinded for the actual pacemaker setting, we cannot exclude an influence on the outcome.

BP values differed during exercise, but the changes evoked in MAP expressed as percentage change from baseline were comparable in OSS and DSS (Figure 3). The pressure decay related to flow in arteries is greatest for a high PP at a low MAP [28]. Accordingly, both pulse wave transmission and pressure gradient distort the peripheral arterial pressure waveform [29] with a reduction in PP amplification with age [30], but an enhancement with increasing HR [31,32]. Central DAP, but not SAP, increases significantly with pacing [31]. With an increase in HR there is a significant increase in the ratio of peripheral brachial PP/central PP due to the inverse relationship between aortic pressure augmentation and HR [31]. Although the reported finger-to-aortic pressure difference during exercise is not significant [33], we cannot exclude that the observed increase in PP during exercise may have overestimated central PP.

We assumed that changes in MCA Vmean reflect changes in CBF, which is true only in so far as the diameter of the vessel does not change. The large cerebral arteries are conductance, rather than resistance, vessels and changes in MAP within the physiological range appear to have negligible effects on the diameter of the insonated artery [34,35]. Direct observations made during cranio-tomy reveal that the vessel diameter does not change significantly during variations in MAP [36], and changes in MCA Vmean seem to follow cerebral 133Xe clearance [37]. Also, in healthy adults who performed at 60% of their maximum exercise capacity, cerebral noradrenaline (norepinephrine) spillover was not increased, making constriction of the MCA by an increase in brain sympathetic activity unlikely [2].

Arterial CO2 is an important determinant of CBF velocity. First, a postural reduction in CO2, together with gravity-induced ventilation/CO mismatch, both affect PetCO2 [38]. Also, from rest to peak exercise the arterial to end-tidal gradient for CO2 increases with exercise intensity [39], questioning PetCO2 as an estimate of arterial CO2. The exercise-related change in PetCO2 in the present study was, however, limited, rendering a significant contribution of this gradient to the MCA Vmean response less likely.

**Exercise and MCA velocity**

Normally, in healthy subjects during exercise, an increase in CO provides for the increased tissue oxygen demand, with a graded increase in local and regional cerebral perfusion [1,18]. In reverse, pharmacological reduction of the exercise-related increase in CO by cardioselective β1-adrenergic blockade reduces the increase in MCA Vmean without affecting MAP or PetCO2 [4].

Rapid changes in systemic BP that occur during exercise present a considerable challenge to cerebral autoregulatory mechanisms [40]. This situation is important especially in regards to the large increase in SAP that must be countered by cerebral autoregulation. MCA velocity varies in response to fluctuations in arterial pressure [41]. During exercise, the change in MCA velocity between MCA Vsys and MCA Vdias increases as CO and PP increase [42]. The observation that exercise increased MCA Vsys but tended to decrease MCA Vdias in DSS (Figure 3) conforms to what is found in exercising subjects in sinus rhythm [42,43]. A decrease in MCA Vdias with exercise has been ascribed to a reduced effectiveness of dynamic cerebral autoregulation to counter the rapid decreases in pressure during diastole [42]. With both OSS and DSS, MCA Vmean as the balance of the diverging responses of systolic and diastolic velocities did not change significantly during exercise; in addition, the level of exercise attained may also have contributed [42].

**HR and CO**

In response to exercise intensities of approx. 40–60% of maximal oxygen uptake, the increase in CO results from both chronotropic and inotropic cardiac responses, i.e. an instantaneous increase in HR and a more gradual rise in SV [9,10]. At higher workloads, the increase in SV reaches a limit or SV may even fall; this is especially so in older endurance-trained subjects who have an impaired ability to maintain SV at high levels of exercise [10,44]. The effect of an increase in HR on such a decline in SV is observed by inhibiting the rise in HR using β-adrenergic blockade [45]. Under those conditions, the decline in SV is smaller, indicating that, during exercise at higher HR, SV may no longer be maintained [45].

In the present study in pacemaker-dependent subjects with complete heart block and preserved myocardial function, enhancing the HR response to exercise did not affect the increase in CO and workload achieved. The proportional attenuation of the exercise-induced increase in SV during pacing in OSS compared with DSS mode illustrates the intrinsic relationship between HR and SV during exercise, supporting the findings that HR is not an important determinant of the haemodynamic response to exercise in pacemaker-dependent subjects [11–13]. During exercise, LVET fell with OSS but was well maintained with DSS, and we attribute the larger increase in SV in DSS mode to maintained LVET.

**Conclusion**

In summary, in pacemaker-dependent subjects with complete heart block and preserved myocardial function,
enhancing the HR response to exercise neither augmented CO by a proportional offset of the exercise-induced increase in SV nor improved cerebral perfusion.

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