Right ventricular pacing impairs endothelial function in man

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Received 23 November 2010; accepted after revision 14 January 2011; online publish-ahead-of-print 22 February 2011

Aims
Clinical trial data show that right ventricular pacing worsens cardiovascular outcomes. The underlying pathophysiology of this is undetermined. We studied the effects of right ventricular pacing on cardiac measures of vascular health (endothelial function), ventricular wall stress (B-type natriuretic peptide), and cardiac reserve (cardiac output response to exercise) in subjects with pacemakers.

Methods and results
Twenty-two subjects [mean age 68.4 ± 8.8 (SD) years] with dual-chamber pacemakers implanted for sino-atrial disease were studied in a randomized crossover study comparing minimal right ventricular pacing [RVP-min; pacing with long atrioventricular delay (AVD)] to maximal right ventricular pacing (RVP-max; pacing with short AVD). Endothelial function was measured with reactive hyperaemia peripheral arterial tonometry. Cardiac output at rest and during exercise was determined using an inert gas rebreathing method. Right ventricular pacing was significantly higher in RVP-max when compared with RVP-min (90 ± 16 vs. 15 ± 20%, P < 0.001). Reactive hyperaemia peripheral arterial tonometry index was significantly lower after RVP-max vs. RVP-min (1.73 ± 0.33 vs. 1.96 ± 0.37, P < 0.05). B-type natriuretic peptide was not significantly different between pacing modes (113 ± 80 vs. 104 ± 108 pg/mL, P = NS). Cardiac output at peak exercise was significantly lower during RVP-max (7.65 ± 3.15 vs. 7.05 ± 2.61 L/min, P < 0.05).

Conclusion
Right ventricular pacing is associated with worsened endothelial function and cardiac reserve.

Keywords
Right ventricular pacing • Endothelial function • BNP • Ventricular dyssynchrony

Introduction
Conventional dual-chamber pacing maintains atrioventricular (AV) synchrony, but may induce dyssynchronous activation of the ventricles, analogous to that associated with left bundle branch block.1 Therefore, any haemodynamic benefits of AV synchrony may be offset by right ventricular pacing-induced ventricular dysynchrony. This hypothesis is supported by results of a meta-analysis of randomized clinical trials comparing ventricular-based pacing with ‘physiological’ atrial-based (mainly dual-chamber) pacing, which found no difference in survival or heart failure, the only benefit of atrial-based pacing being a reduction in atrial fibrillation, and a modest reduction in stroke.2 Additionally, retrospective analyses from pacing and implantable cardioverter-defibrillator (ICD) trials show that adverse outcomes are associated with increased frequency of right ventricular pacing3–5 and the degree of ventricular dyssynchrony induced.6 However, it should be noted that the Danish study7 found beneficial effects on atrial fibrillation, thrombo-embolic events, heart failure, and cardiovascular mortality with single-chamber atrial pacing with no right ventricular pacing when compared with single chamber ventricular pacing. Combining these findings, there is an increasing evidence to suggest that conventional pacing, at the right ventricular apex, per se may be associated with adverse cardiovascular effects, even in the presence of preserved AV synchrony.

The pathophysiological mechanisms underlying the adverse chronic effects of right ventricular pacing are not known and the aim of this study was to investigate the effects of right ventricular apical pacing on different cardiac physiological measures in subjects with dual-chamber pacemakers for sino-atrial node
dysfunction (SND). The cardiac physiological measures were chosen to reflect vascular health, ventricular wall stress, and cardiac reserve. Endothelial function, a powerful predictor of events in a variety of cardiovascular diseases and a measure for vascular health, was determined using reactive hyperaemia peripheral arterial tonometry (RH-PAT), which is highly correlated with coronary endothelial function. B-type natriuretic peptide (BNP) was determined to provide a measure of ventricular wall stress. Cardiac output (CO) at rest and during exercise was determined non-invasively by an inert gas rebreathing method. The CO response to exercise provides a measure of cardiac reserve and is an important prognostic indicator in subjects with heart failure.

Methods

Subjects previously implanted with a dual-chamber pacemaker for SND were recruited from the Ninewells Hospital and Medical School pacemaker clinic. All subjects had the right ventricular lead implanted at the right ventricular apex. No subject was pacemaker dependent and the indication for pacing was intermittent sinus arrest or sinus bradycardia. Subjects with ongoing angina or heart failure symptoms, known AV node disease, bundle branch block, age >80 years, atrial fibrillation, or inability to exercise, were excluded. All subjects gave written informed consent prior to participation. The study was approved by the Tayside Committee for Medical Research Ethics (ref. 05/S1402/46).

Study protocol

This was a blinded crossover study with subjects assigned in a randomized order to two pacing interventions each lasting 7 days: dual-chamber pacing with short AV delay time to produce maximal right ventricular pacing (RVP-max) and a control arm of minimal right ventricular pacing (RVP-min) using dual-chamber pacing with long AV delay to allow intrinsic conduction to the ventricles. Prior to randomization, as pre-study right ventricular pacing was variable among the subjects, pacing was programmed to produce minimal right ventricular pacing (using single-chamber atrial pacing or dual-chamber mode with long AV delay) for a minimal washout period of ≥1 week. Subjects were studied at baseline after washout, and after each 7-day pacing intervention with 7 days washout between the two pacing interventions. Peripheral endothelial function, CO at rest and at peak exercise (rCO and exCO), and BNP were measured by a single investigator who was blinded to the pacing intervention. An independent unblinded investigator performed interrogation and programming of the pacemakers at each study visit. The programmed base heart rate was increased by >5 b.p.m. over the intrinsic heart rate at randomization and was constant in the two arms.

Endothelial function

Endothelial function was determined by RH-PAT (Itamar Medical Ltd, Caesarea, Israel). This is a non-invasive technique used to assess peripheral microvascular endothelial function by measuring changes in digital pulse volume during reactive hyperaemia. The RH-PAT ratio (RH-PAT index) was defined as the ratio of the arterial pulse wave amplitude following a 5 min arterial occlusion in the forearm to that of the pre-occlusion value. It has been has been validated against acetyl-choline-mediated vaso-dilatation of coronary arteries, the gold standard in endothelial function testing and RH-PAT highly correlates with coronary endothelial function, determined in this manner. Importantly, coronary endothelial function has been shown to be an important prognostic indicator. Subjects were asked to fast, drink only water and not take any nitrate medication in the 4 h prior to testing. Testing was performed after 40 min of bed rest, in a thermo-neutral environment (21–24 °C), away from harsh lighting or noise. Two probes placed on the index fingers of both hands measured changes in blood volume using digital pulse amplitude tonometry. Blood flow measurements were taken for >5 min at baseline, then during 5 min of brachial artery occlusion, designed to provide a consistent ischaemic stimuli, and thereafter for 5 min post-occlusion during the reactive hyperaemia caused by the ischaemic stimuli. Ischaemia was achieved by inflating a BP cuff (Hokanson E20 rapid cuff inflator) around the brachial artery to the higher of 200 mmHg or 60 mmHg above systolic pressure up to a maximum of 300 mmHg to ensure full occlusion. Reactive hyperaemia peripheral arterial tonometry index was calculated independently of the investigator, with post-occlusion reactive hyperaemia in the test arm compared with baseline peripheral blood flow, controlling for systemic responses like sympathetic activation observed in the control (opposite) arm. Reactive hyperaemia peripheral arterial tonometry index of <1.67 is considered to indicate a reduced reactive haemodynamic response in the peripheral vessels and, therefore, endothelial dysfunction.

Resting and exercise cardiac output

This was measured non-invasively using the inert gas rebreathing technique (Innocor, Innivation A/S, Odense, Denmark). This method has been validated against the invasive gold standard where blood flow was measured from the pulmonary artery with a Swan-Ganz thermodilution catheter and it has been validated for use in many study populations. After 60 min of bed rest, subjects breathed in N2O (blood soluble gas) and SF6 (blood insoluble gas) at concentrations of 0.5% (V/V) and 0.1% (V/V), respectively through the Innocor rebreathing system. This oxygen-enriched mixture, 28% O2 (V/V) in a pre-filled 3 L anaesthesia bag formed a closed circuit with the subject’s respiratory system. Photo-acoustic analysers measured changes in gas concentrations over a five breath intervals, with two required to perform a successful analysis. The N2O concentration decrease was proportionate to pulmonary blood flow (PBF) and SF6 concentrations allowed for the measurement of the total volume of the closed system, after equilibrium was reached. Measurements of O2 provide VO2 results. PBF = CO in the absence of pulmonary shunt defined as an arterial O2 saturation of >98% measured by pulse oximetry. A standard exercise bicycle (Ergoline, Ergoselect 100P) protocol was used. Stages lasted 3 min starting with 0 watts; resistance was increased by 25 watts after each stage. Re-breathing tests were done at rest, 50 watts, and peak exercise. Subjects were asked to indicate a minute before terminating exercise to allow for the measurement of peak exCO.

Plasma B-type natriuretic peptide

Venous blood samples were taken to measure BNP concentrations before exercise and after the subject had been supine for 60 min and were then aliquoted into appropriate tubes stored on ice. The samples were spun immediately at 3000 rpm for 10 min at 5 °C in a Biofuge 28 RS centrifuge (Heraeus Instruments, UK). The BNP samples were stored at −70 °C. B-type natriuretic peptide was extracted from plasma in C18 columns and then measured in a single batch by radioimmunoassay (Bachem (UK) Ltd, St Helens, Merseyside, UK).
Sample size
The power calculations, based on our previous data, with a mean RH-PAT of 1.6 and standard deviation of 0.3 indicate that in order to have 80% power to detect a 20% change in RH-PAT in similar patients (alpha = 0.05), a sample size of 14 is required.

Statistical analysis
All values are expressed as mean ± SD unless otherwise stated. Statistical analysis was performed with STATA SE 11 (STATA Corp, TX). Comparisons between RVP-max, RVP-min were tested by paired t-test or by Fisher’s exact probability test, as appropriate. A P value of 0.05 was considered statistically significant.

Results
The clinical details of the 22 enrolled subjects are shown in Table 1. Subjects were mostly male and hypertensive. Measured variables in the two modes are shown in Table 2. At baseline, after ‘washout’ with RVP-min pacing at intrinsic heart rate, mean percentage right ventricular pacing was 8.8 ± 14.7%. Right ventricular pacing was greatest in RVP-max mode (Table 2), as these subjects were almost constantly paced in the right ventricle in response to sensed and paced atrial beats. In contrast, mean percentage pacing during RVP-min pacing was lower, as sinus or paced atrial events were allowed to conduct to the ventricle via the intrinsic AV nodal pathway, and thereby inhibiting right ventricular pacing.

Table 1 Baseline clinical characteristics of 22 enrolled subjects with dual-chamber pacemaker for sino-atrial disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RVP-min</th>
<th>RVP-max</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (% male)</td>
<td>22 (77%)</td>
<td>22 (77%)</td>
<td></td>
</tr>
<tr>
<td>Age (years, ± SD)</td>
<td>67.7 ± 8.9</td>
<td>67.7 ± 8.9</td>
<td></td>
</tr>
<tr>
<td>Time since device implant (years ± SD)</td>
<td>5.2 ± 4.5</td>
<td>5.2 ± 4.5</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (µmol/L ± SD)</td>
<td>110 ± 66</td>
<td>110 ± 66</td>
<td></td>
</tr>
<tr>
<td>Serum haemoglobin (g/dL ± SD)</td>
<td>13.3 ± 1.4</td>
<td>13.3 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>8 (36.4%)</td>
<td>8 (36.4%)</td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2 (9.1%)</td>
<td>2 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>2 (9.1%)</td>
<td>2 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (22.7%)</td>
<td>5 (22.7%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (90.9%)</td>
<td>20 (90.9%)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;40%</td>
<td>5 (22.7%)</td>
<td>5 (22.7%)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>10 (45.5%)</td>
<td>10 (45.5%)</td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>11 (50.0%)</td>
<td>11 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>Beta-adrenergic blockers</td>
<td>9 (40.9%)</td>
<td>9 (40.9%)</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>6 (27.2%)</td>
<td>6 (27.2%)</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>9 (40.9%)</td>
<td>9 (40.9%)</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>15 (68.2%)</td>
<td>15 (68.2%)</td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>8 (36.4%)</td>
<td>8 (36.4%)</td>
<td></td>
</tr>
<tr>
<td>Percentage of RVP [mean (SD)]</td>
<td>8.8 ± 14.7</td>
<td>8.8 ± 14.7</td>
<td></td>
</tr>
<tr>
<td>Mean heart rate ± SD</td>
<td>61 ± 4</td>
<td>61 ± 4</td>
<td></td>
</tr>
<tr>
<td>Atrioventricular delay (ms ± SD)</td>
<td>252 ± 54</td>
<td>252 ± 54</td>
<td></td>
</tr>
<tr>
<td>Mean systolic BP (mmHg) ± SD</td>
<td>144 ± 20</td>
<td>144 ± 20</td>
<td></td>
</tr>
<tr>
<td>Mean diastolic BP (mmHg) ± SD</td>
<td>78 ± 10</td>
<td>78 ± 10</td>
<td></td>
</tr>
<tr>
<td>Mean RH-Pat index ± SD</td>
<td>1.93 ± 0.43</td>
<td>1.93 ± 0.43</td>
<td></td>
</tr>
<tr>
<td>Mean resting cardiac output (L/min)</td>
<td>4.87 ± 1.36</td>
<td>4.87 ± 1.36</td>
<td></td>
</tr>
<tr>
<td>Mean exertional cardiac output (L/min)</td>
<td>8.05 ± 2.95</td>
<td>8.05 ± 2.95</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Clinical measurements by pacing mode: minimal right ventricular pacing and maximal right ventricular pacing in subjects with dual-chamber pacemakers

Discussion
The initial promise of physiological dual-chamber pacing over ventricular-based pacing has not been demonstrated by recent outcome data from pacing and ICD trials. In parallel, as the benefits of biventricular pacing in systolic heart failure with

Endothelial function
Endothelial function worsened in 15 subjects. Reactive hyperaemia peripheral arterial tonometry was significantly lower in RVP-max mode compared with RVP-min (Table 2).

Cardiac output and exercise capacity
Cardiac output at rest tended to be lower with RVP-max when compared with RVP-min, but the difference did not reach statistical significance (4.75 ± 1.32 vs. 4.87 ± 1.36, P = NS). However, exCO during RVP-max was significantly lower compared with RVP-min (7.05 ± 2.61 vs. 7.65 ± 3.15, P < 0.05, Table 2).

Plasma B-type natriuretic peptide
There was no significant difference in BNP between the two pacing arms (Table 2).
ventricular dyssynchrony associated with left bundle branch block have been demonstrated.\textsuperscript{22,23} so has a concomitant realization that ‘acquired dyssynchrony’ caused by right ventricular pacing may be harmful and now avoidance of unnecessary right ventricular pacing appears to be increasingly important.\textsuperscript{5} Recent pacemaker and ICD trials of strategies to avoid unnecessary right ventricular pacing have demonstrated the efficacy\textsuperscript{24} and improved outcomes\textsuperscript{25} with this approach. However, the pathophysiological mechanisms that underlie the adverse outcomes of right ventricular pacing have not been previously demonstrated and are not clearly understood. To the best of knowledge, ours is the first study to show that right ventricular pacing per se, with preserved atrioventricular synchrony, results in impaired endothelial function as well as a lower cardiac reserve. Both endothelial dysfunction and a lower cardiac reserve have been associated with poor outcome in patients with cardiovascular disease.\textsuperscript{17,19}

In this study, RVP-max was associated with a lower cardiac reserve, which may reflect a dysynchronous ventricular contraction. Both animal studies as well as clinical studies have shown that pacing from the right ventricular apex causes abnormal myocardial activation and dysynchronous ventricular contraction, akin to dyssynchrony caused by left bundle branch block.\textsuperscript{26–28} With respect to clinical studies, Thambo et al.\textsuperscript{29} examined 23 adult patients with complete congenital atrioventricular block who had ≥ 5 years of right ventricular apical dual-chambered pacing and found that prolonged ventricular dyssynchrony was associated with left ventricular remodelling, dilatation, asymmetrical hypertrophy, and overall lower exercise capacity than controls. More recently, in a study comparing the impact of different ventricular pacing sites on indices of left ventricular function using pressure–volume analysis, Lieberman et al.\textsuperscript{30} demonstrated that acute right ventricular pacing caused potentially deleterious reductions in CO and stroke volume with impaired diastolic relaxation and increased left ventricular end-diastolic pressure in patients with and without impaired left ventricular function. In our study, CO tended to be lower at rest and was significantly lower during peak exercise with RVP-max when compared with RVP-min. It should be noted that the CO response to exercise has been shown to an important prognostic indicator in subjects with heart failure.\textsuperscript{31} In this study, we did not observe a difference in plasma BNP. This might be due to our small sample size, although a previous study by Sadowski and Wozakowska-Kaplon\textsuperscript{32} also failed to show a difference in BNP levels in patients with atrial pacemakers compared with those with dual-chamber systems.

Our findings of an association between right ventricular pacing and worsened endothelial function are novel. In our study, endothelial function was measured by the RH-PAT method, which has been validated against acetyl-choline-mediated vaso-dilatation of coronary arteries, the gold standard in endothelial function.\textsuperscript{16–18} Although the prognostic value of RH-PAT has yet to be established, it correlates highly with coronary endothelial function, which has been shown to be an important prognostic indicator.\textsuperscript{8} The baseline RH-PAT index in our study population was 1.93, which would indicate that they had near-normal endothelial function.\textsuperscript{16} This is likely to reflect the high usage of medications such as ACE inhibitors (50%) and statins (68%), which are known to improve endothelial function. In our study, right ventricular pacing worsened endothelial function with significantly lower RH-PAT value during RVP-max mode compared with RVP-min. The exact mechanism leading to altered peripheral endothelial function remains unclear, and this study was not designed to determine the exact mechanism of impaired endothelial function. Chronic right ventricular pacing has been shown to be associated with increased sympathetic activation\textsuperscript{31,32} as well as increased oxidative stress, which is associated with a reduced nitric oxide production.\textsuperscript{30} These indirect mechanisms can reduce endothelial function and are likely to have a role in the pathological effects of chronic right ventricular pacing. However, in our study, periods of pacing were relatively shorter and arguably other mechanisms in addition to increased sympathetic response could be involved. One speculation is that dysynchronous pacing may cause loss of laminar spiral flow as is reported to occur in coronary artery disease\textsuperscript{33} and heart failure,\textsuperscript{34,35} conditions that are associated with abnormal endothelial function. Decreased NO release occurs in response to non-laminar flow stress and the associated low and reciprocating shear stress up-regulate pro-atherosclerotic genes and proteins that promote the development of atherosclerosis.\textsuperscript{36,37} It should be noted, however, that the impact of pacing on endothelial function has been investigated both in terms of atrial-based vs. ventricular demand pacing and in the setting of biventricular pacing in patients with heart failure. Fak et al.\textsuperscript{38} showed an acute attenuation of flow mediated dilatation in 12 individuals when their pacemakers were programmed to ventricular demand pacing, as opposed to atrial-based pacing and Rubaj et al.\textsuperscript{39} demonstrated that biventricular pacing, which avoids ventricular dyssynchrony, was associated with reduced oxidative stress, NO metabolites and immune activation, and improved tissue perfusion, compared with right ventricular pacing in heart failure patients. More recently, Akar et al.\textsuperscript{39} reported that in patients with heart failure and electrical dyssynchrony as evidenced by QRS duration > 120 ms, a positive response to cardiac resynchronization therapy (CRT) was more likely in patients with endothelial dysfunction before CRT. These same workers have also reported that CRT improves endothelial function in patients with heart failure.\textsuperscript{40} Further studies are clearly required to define the mechanism of endothelial dysfunction resulting from right ventricular pacing.

Limitations of this study

This study had several limitations. This was a small study, but it was adequately powered to detect differences in endothelial function and CO. Although participants were fasted overnight, drank only water and did not take any nitrate medication in the 12 h prior to testing, and their other vaso-active medications were only omitted in the morning of the test, this may have blunted the alterations seen in endothelial function. No definitive conclusion can be drawn regarding the mechanisms between right ventricular pacing and endothelial function. Further studies are needed to elucidate these mechanisms. The potential benefits of alternative right ventricular lead location in patients indicated for brady-pacing is intensely being investigated.\textsuperscript{41–43} Our study protocol did not allow us to investigate the physiological effects of alternative right ventricular pacing sites such as pacing at the right ventricular outflow tract, septal pacing, and direct His bundle pacing.

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Nevertheless, our findings do support the general hypothesis that conventional right ventricular pacing with a high amount of right ventricular apical pacing has deleterious effects.

The appreciation of the potential deleterious effects of right ventricular pacing and pacing-induced dyssynchrony has led to large prospective mortality-driven clinical trials to compare biventricular pacing with conventional right ventricular pacing in subjects with brady-arrhythmia and without heart failure indications for biventricular pacing. Although these trials will determine mortality, they do not measure mechanisms that may underlie the outcomes of these trials. Although current pacemakers have algorithms to avoid unnecessary right ventricular pacing, 40% of pacemaker patients have AV node disease and require chronic ventricular pacing. Many questions remain as to the selection of the optimal pacing mode in subjects with and without structural or functional heart disease, or in young subjects with long-term pacing requirements. A key to answering these concerns is an understanding of the pathophysiology of right ventricular pacing, such as the effect on endothelial dysfunction, which may be used as surrogate endpoints in the evaluation of novel and improved pacing modalities.

Conclusions

Right ventricular apical pacing is associated with worsened endothelial function and cardiac reserve and this should be evaluated in further studies.

Conflict of interest: none declared.

Funding

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