Improvement in cardiac adrenergic function post biventricular pacing for heart failure

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Aims We investigated whether biventricular (BiV) pacing favourably affects cardiac sympathetic activity in heart failure (HF).

Methods and results In 10 HF patients treated with BiV pacing, we assessed cardiac sympathetic activity by metaiodobenzylguanidine (123I-MIBG) imaging. Patients were randomized in a double-blinded cross-over fashion, for two weeks of either inactivation of BiV pacing or BiV pacing, with crossover to the alternate group for a further two weeks. After randomization blocks, cardiac 123I-MIBG imaging and a 6 min walk test were performed. BiV pacing was associated with significant improvements in cardiac 123I-MIBG uptake reflected by increases in early (BiV 1.71 ± 0.09 vs. non-BiV 1.63 ± 0.06, P = 0.03) and late (at 4 h) heart to mediastinal ratio of uptake (BiV 1.54 ± 0.08 vs. non-BiV 1.45 ± 0.06, P = 0.03). Additionally, pulmonary 123I-MIBG uptake, measured as lung to mediastinal ratio, significantly improved (P = 0.009). Six-minute walk and systolic blood pressure tended to improve with BiV vs. non-BiV pacing (P = 0.09).

Conclusion In patients with stable HF, BiV pacing is associated with long-term improvements in cardiac sympathetic nerve activity, as reflected by improvements in cardiac 123I-MIBG uptake. This is a potential mechanism for morbidity and mortality benefits observed in larger studies.

Keywords Biventricular pacing; Heart failure; Sympathetic activity; Cardiac 123I-MIBG scanning

Introduction

Biventricular pacing has become an established therapy for medically refractory heart failure (HF) in appropriately selected patients, with demonstrated positive effects on morbidity and mortality.1–5 There is also data emerging that biventricular (BiV) pacing should be the preferred mode of pacing the ventricle in patients with milder degrees of left ventricular (LV) dysfunction6 and even normal ventricular function.7 This form of cardiac pacing acts to resynchronize myocardial contraction, with beneficial effects on contractile indices in association with a decrease in mitral regurgitation.8 Although these haemodynamic actions may explain the positive outcome effect of BiV pacing, this remains controversial. In this context, it is notable that the interventions that have been best shown to modify the progression of HF are those that attenuate the effects of neurohormonal activation, which accompanies HF independent of their haemodynamic effect.9 Among these, sympathetic nervous system overactivity (particularly that directed to the heart) has been related to mortality and morbidity in HF,10,11 and accordingly beta-adrenoceptor antagonists have been shown to exert beneficial effects in HF.

In this study, we tested the hypothesis that long-term BiV pacing favourably influences cardiac sympathetic tone in HF, therefore providing a possible mechanism for morbidity and mortality benefits observed in larger studies.1–5 Although recent studies of peripheral sympathetic activity demonstrated that BiV pacing acutely reduced muscle sympathetic activity,12–14 the long-term relevance of this finding is unclear, and in contrast studies, plasma norepinephrine levels do not appear to change with BiV pacing.15,16 To assess the effects of BiV pacing on cardiac sympathetic tone, we employed a nuclear imaging approach using the norepinephrine analogue, metaiodobenzylguanidine (123I-MIBG), which is a substrate for the norepinephrine transporter on sympathetic nerves and has been widely employed to non-invasively assess the cardiac adrenergic activity.17

Methods

Assessment of cardiac and pulmonary sympathetic activity to biventricular pacing

We assessed the effects of BiV pacing on cardiac sympathetic tone by cardiac 123I-MIBG scanning in a cohort of 10 HF patients (seven males and three females, average age 60 ± 7 years) recruited...
randomly as outpatients who had BiV pacing (mean atrio-ventricular delay 115 ± 21 ms, 4 ms non-programmable interventricular delay) for a mean of 8 ± 2 months, in addition to maximal anti-failure pharmacotherapy. The indication for BiV pacing in this cohort was HF patients in sinus rhythm with left bundle branch block (QRS > 120 ms), LV ejection fraction < 35%, and New York Heart Association (NYHA) function class III on maximal anti-failure pharmacotherapy. Patients had to have BiV pacing for at least 6 months to be enrolled. This time period allowed leads to mature and patients to stabilize post-implant procedure. All patients had transvenous endocardial pacemaker implants and were in sinus rhythm. LV leads were sited in a lateral cardiac vein via the coronary transvenous endocardial pacemaker implants and were in sinus and patients to stabilize post-implant procedure. All patients had 6 months to be enrolled. This time period allowed leads to mature without modification during the study protocol. Symptomatic decompensation, all patients remained on anti-failure therapy clinically unstable due to other comorbidities. No patients were diabetic or were receiving tricyclic antidepressants.

All patients were on maximal anti-failure pharmacotherapy at the time of enrolment, including beta-blockers and angiotensin-converting enzyme inhibitors (at maximal tolerated dose). During the study, no patients had their medications altered. The aetiology of HF was ischaemic cardiomyopathy in four patients and idiopathic dilated cardiomyopathy in six. To avoid potential haemodynamic decompensation, all patients remained on anti-failure therapy without modification during the study protocol. Symptomatic response was assessed at clinical review during each phase of the protocol by asking the patients if they felt better, worse, or no different. This part of the study complied with the declaration of Helsinki and was also performed in accordance with Alfred Hospital Ethics Committee.

Protocol for cardiac sympathetic assessment

The study was conducted in a double-blinded randomized crossover study, consistent with previous studies, assessing the clinical response to BiV pacing. Patients were entered into a protocol whereby their pacemakers were programmed to either a backup mode of right ventricular pacing (VVI mode) at a rate of 80 bpm or continued BiV pacing for a period of two weeks followed by 123I-MIBG scanning, clinical review, and 6 min walk test. Patients were then crossed over to the opposite pacing protocol for a further two weeks and the 123I-MIBG scanning, 6 min walk test, and clinical review repeated. Previous studies have demonstrated the benefits of BiV pacing dissipation when the pacing is turned off and return with recommencement of pacing. The investigating physicians, data analysts, research staff, and patients were blinded to the pacemaker allocation. Allocation and pacemaker programming was randomly assigned by pacemaker technical staff, who opened an envelope from a series of sealed envelopes with protocol allocation (either backup mode then BiV pacing or vice versa). The pacemaker technical staff was otherwise not involved with the study.

123I-MIBG cardiac scanning

Patients undergoing cardiac 123I-MIBG scanning were advised to abstain from caffeine and tobacco for 24 h. Intravenous cannulae were placed in an antecubital vein while the patients were supine. Patients remained in a quiet room for 45 min to achieve a resting state. Approximately 200 MBq (5 mCi) of 123I-MIBG (Australian Radiosotopes) was then injected intravenously and flushed with normal saline solution. All images were acquired on a large field-of-view gamma camera (General electric Maxxus, Milwaukie, USA) fitted with a low-energy, high-resolution collimator, using a 20% energy window centred at 159 keV and a matrix of size 128 × 128. The first image acquisition (early) began 15 min post-injection with a 15 min planar anterior chest image that included all the myocardium and thyroid in the field of view. Identical images (late) were obtained at 4 h post-injection. All image data were collected for later analysis.

Two nuclear medicine physicians then processed the scans independently and the results averaged; the mean variability between all measured parameters was 3.5%. Both were blinded to pacemaker programming, patient identification, and the results of clinical review and 6 min walk test. Using the images acquired in the anterior projection of the first visit of the patient, the LV 123I-MIBG activity was determined from a manually sized and positioned elliptical region of interest (ROI) fitted closely around the ventricular myocardium. Mediastinal activity was then obtained from an 8 × 8 pixel sized box region of interest placed over the upper portion of the anterior mediastinum. A manually drawn ROI was also placed around the right lung. Identical sized ROIs from the 15 min study were then placed at a similar position on the 4 h study, and the mean value from each ROI data set recorded. This procedure was then immediately repeated for the data set obtained from the second study, two weeks later, using the processed images from the first study to help determine the positioning and size of the second set of ROI. Identical images from the first data pair were not used due to minor variations in patient positioning between the two study days.

The anterior heart to mediastinum ratio (H/M) was calculated using data obtained from images at 15 min and 4 h after I 123I-MIBG injection:

\[
\frac{H}{M} = \frac{[H]}{[M]},
\]

where [H] is the mean count/pixel in LV and [M] the mean count/pixel in upper mediastinum.

The lung to mediastinum ratio was calculated by:

\[
\frac{L}{M} = \frac{[L]}{[M]},
\]

where [L] is the mean count/pixel in lung.

Myocardial washout rate was defined as per cent change in activity from the early and late images within the LV without background subtraction, calculated as:

\[
\text{Lung washout rate} = \frac{[L]_{\text{early}} - (\text{decay corrected})[L]_{\text{late}}}{[L]_{\text{early}}} \times 100\%.
\]

Statistical analysis

Data were presented as mean value ± standard error of the mean, unless otherwise stated. Statistical analysis and graphical presentation was performed using statistical software (SigmaStat, version 2.03, Chicago, IL, USA). Comparison of adrenergic and haemodynamic response between each group was compared using a paired t-test if normally distributed data, and if non-normally distributed data were analysed by a Mann-Whitney test. Nominal or categorical data were compared using a y² test or a Fischer Exact Test where appropriate. A one-way analysis of variance with repeated measures was used to compare responses in all three groups in the acute assessment. A P-value of <0.05 was considered statistically significant.

Results

Baseline heart failure cohort characteristics

Prior to BiV pacemaker implantation, the mean LV ejection fraction in the HF cohort was 25 ± 6%. At enrolment in the study, the mean LV ejection fraction of the cohort was 33 ± 7%. The mean QRS duration was 159 ± 7 ms left bundle branch block morphology during the non-BiV pacing period.
Effect of biventricular pacing on cardiac $^{123}$I-MIBG uptake

The haemodynamic response to BiV pacing compared with left bundle branch block conduction is presented in Table 1. Patients in backup pacing modality had VVI pacing for <10% of the 2 weeks period. Eight patients (of 10) reported better functional capacity and quality of life during BiV pacing in comparison with the non-BiV mode, which was significant ($P = 0.025$). Otherwise there were trends to improvement in 6 min walk test ($P = 0.09$) and mean arterial blood pressure ($P = 0.09$) with BiV pacing over this observation period. One patient was not able to perform the 6 min walk test on each occasion due to peripheral vascular disease. Other haemodynamic parameters and NYHA class did not differ over this observation period.

During BiV pacing, there was a significant improvement in the cardiac adrenergic profile, as assessed by the H/M $^{123}$I-MIBG ratio. In particular, at 4 h post $^{123}$I-MIBG injection, there was a significantly greater H/M ratio during BiV pacing than that during the non-BiV-paced period (1.54 ± 0.08 vs. 1.45 ± 0.06, respectively, $P = 0.03$). Similarly, early post $^{123}$I-MIBG injection scans showed a significantly greater H/M ratio during BiV pacing than that during the non-BiV-paced period (1.71 ± 0.09 vs. 1.63 ± 0.06, respectively, $P = 0.03$). A typical image of cardiac and pulmonary $^{123}$I-MIBG uptake is shown in Figure 1. The myocardial $^{123}$I-MIBG washout was not significantly influenced by BiV pacing (non-BiV 28 ± 2% vs. BiV 29 ± 2%, $P = 0.73$). With BiV pacing, significantly greater pulmonary $^{123}$I-MIBG uptake was found at both early and late scanning (early: non-BiV 1.62 ± 0.07, BiV 1.75 ± 0.09, $P = 0.004$; late: non-BiV 1.52 ± 0.04, BiV 1.64 ± 0.07, $P = 0.009$).

Discussion

The current study was predicated on the well-established principle that neurohumoral activation plays a key role in the pathophysiology of HF and that antagonism of the adrenergic nervous system and renin–angiotensin system exerts beneficial actions. In conjunction, several studies now indicate that BiV pacing improves functional status and possible outcome in HF patients. Despite these observations, there is a lack of complete understanding as to the mechanisms by which this pacing modality exerts positive effects. In the present study, we tested the hypothesis that BiV pacing may exert a modulatory effect on the cardiac sympathetic nervous system. We found that BiV pacing causes a favourable effect on cardiac sympathetic nerve function, as reflected by improvements in cardiac $^{123}$I-MIBG uptake in a well-treated HF cohort at 8 ± 2 months post-implant. Furthermore, this cardiac effect is lost when pacing is discontinued, thereby indicating that ongoing BiV pacing remains essential for ongoing improvements demonstrated in this study. Previous research has also demonstrated a similar effect with peripheral sympathetic activity in responders to BiV pacing.

We assessed the effect of BiV pacing on cardiac sympathetic activity in our study by using the degree of cardiac $^{123}$I-MIBG uptake as an indicator of sympathetic function. $^{123}$I-MIBG is an analogue of norepinephrine sharing the same uptake (uptake-1 transporter) and secretion properties as norepinephrine, but unlike norepinephrine is not active at adrenergic receptors. Furthermore, the $^{123}$I-MIBG H/M ratio has recently been shown in HF patients to correlate significantly with the transcardiac veno-arterial norepinephrine gradient, supporting its utility as an index of cardiac sympathetic activity. Cardiac $^{123}$I-MIBG uptake has been used extensively in HF to characterize the cardiac adrenergic profile and response to HF pharmacotherapy, and an extensive body of data demonstrates increased morbidity and mortality in association with reduced cardiac $^{123}$I-MIBG uptake, typically measured as the 4 h H/M ratio. Moreover, the late or delayed H/M ratio has been shown to be an independent predictor of mortality above other traditional parameters. A recent study has correlated a lower late or delayed H/M ratio with abnormal myocardial contractile reserve in dilated cardiomyopathy.

In addition to the prognostic information afforded by $^{123}$I-MIBG scanning, improvements in H/M uptake have also been shown to precede the functional improvement in LV function. As all the HF patients in our cohort were on angiotensin-converting enzyme inhibitors and beta-blockers, the improvement in cardiac $^{123}$I-MIBG uptake strongly suggests that the benefit is independent of these therapeutic manoeuvres. Although our group has extensively used invasive approaches to study the cardiac sympathetic function, a direct neurochemical approach was not employed because of concerns that coronary sinus cannulation could dislodge the existing LV lead.

The improvements in cardiac $^{123}$I-MIBG uptake demonstrated in this study therefore most likely represent improved sympathetic nerve retention of the tracer secondary to BiV pacing. The precise cellular mechanism by which the $^{123}$I-MIBG H/M ratio improved with BiV pacing, however, cannot be determined from our study. Potential mechanisms include a reduction in the cardiac sympathetic nerve-firing rate or an increase in the activity of the neuronal norepinephrine transporter. Recent research has also demonstrated BiV pacing in HF results in improvements in coronary blood flow and uptake of other markers indicating improved blood flow, which may also have implications for improved cardiac $^{123}$I-MIBG H/M ratio observed here. The magnitude of the improvement in H/M uptake in our study appeared to be modest (6%); this may reflect the short duration assessed and the small numbers in our study. Most studies perform post-intervention $^{123}$I-MIBG cardiac uptake scans at least 6 months post-commencement of therapy, and many show greater changes in H/M ratio than in this study, particularly for carvedilol therapy in HF (20% improvement after 1 year of therapy and 10% after 7 months of therapy) and amiodarone therapy in HF (11%)

Table 1: Effects of biventricular pacing

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BiV off</th>
<th>BiV on</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>62 ± 3</td>
<td>65 ± 1</td>
<td>0.32</td>
</tr>
<tr>
<td>Mean Arterial Pressure (mmHg)</td>
<td>87 ± 2</td>
<td>90 ± 2</td>
<td>0.09</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>122 ± 3</td>
<td>122 ± 4</td>
<td>0.96</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>70 ± 2</td>
<td>74 ± 2</td>
<td>0.12</td>
</tr>
<tr>
<td>Six-minute walk test (m)</td>
<td>452 ± 67</td>
<td>516 ± 46</td>
<td>0.09</td>
</tr>
<tr>
<td>NYHA Functional Class</td>
<td>1.75 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Non-BiV, non-biventricular pacing; BiV, biventricular pacing; NYHA, New York Heart Association.
improvement after 1 year of therapy). Hence, it is possible that the 2 weeks duration of pacing may underestimate the beneficial effect of BiV pacing. However, the degree of underestimation may not be that large as there are also other 6 months studies that have shown changes in H/M ratios of similar magnitudes to ours, including those assessing effect of ACE inhibition (6.5%) and metoprolol in HF or angiotensin II receptor inhibitors (9% each). As 8 of the 10 patients symptomatically deteriorated in the non-BiV pacing phase, there was a concern regarding longer term follow-up of pacing in this phase. Other parameters measured also tended to improve, however, only mean arterial blood pressure and 6 min walk test approached significance, parameters such as NYHA functional class are qualitative and as such are likely to be less sensitive over such a short period. A previous study by Erol-Yilmaz et al. and Higuchi et al. also demonstrated similar degrees of improvement in H/M uptake with BiV pacing in CHF. The study by Erol-Yilmaz et al. demonstrated significant improvements in 6 months late but not early H/M ratio in comparison with the baseline, in a similar sized cohort to our study. This study, however, was not randomized. Similarly, the study by Higuchi et al., which was also not randomized, demonstrated benefit in late H/M ratio at 1 year in patients with BiV pacing who demonstrated resynchronization. Conversely, unlike our current study, Erol-Yilmaz et al. also demonstrated a significant improvement in myocardial washout of H/M. Accelerated myocardial washout of H/M has similarly been used as a prognostic marker in severe HF however, to date, this parameter, unlike H/M ratio, has not been correlated with cardiac adrenergic drive. Changes in the washout rate have also been absent in various other interventional studies, and accordingly the importance of an absence of a change in washout in our study remains unclear.

Pulmonary uptake of H/M has been ascribed to pulmonary endothelial cells, which possess norepinephrine (NE) transporter capacity, and its uptake has been shown to decrease in animal models of pulmonary endothelial damage. Pulmonary H/M uptake has also previously been shown to decrease in response to pulmonary oedema in the setting of altitude sickness and then to recover with treatment. Additionally, in a series of patients with heart and lung disease, unilateral lung to mediastinal uptake ratio decreased in HF patients compared with those without HF by a similar magnitude to that observed in our current study. Although we did not specifically measure the haemodynamic response to BiV vs. non-BiV pacing in the present study, our finding is consistent with a BiV-mediated reduction in filling pressures due to mechanical resynchronization and/or a reduction in mitral regurgitation, with a concomitant improvement in the symptom status of our patients and trend to improvement in 6 min

Figure 1 A representative image of H/M uptake at 4 h in the thyroid, lung, heart, and liver. (A) Demonstrates cardiac and other organ H/M uptake in non-biventricular pacing period. (B) Demonstrates cardiac and other organ H/M uptake in biventricular pacing period, with greater cardiac H/M uptake than (A).

Figure 2 Graph demonstrating individual heart to mediastinal cardiac H/M uptake ratio at 4 h, for non-biventricular pacing vs. biventricular pacing. Dark and light circles represent mean and standard error of the mean for heart to mediastinal cardiac H/M uptake ratio at 4 h, for non-biventricular pacing (dark) and biventricular pacing (light).

Figure 3 Bar graph shows lung to mediastinal H/M uptake ratio at 4 h.
walk test. Our cohort were responders to BiV pacing as evidenced by the improvement in LV ejection fraction and symptoms; however, up to 30% of appropriate candidates do not respond\(^2,4\) often due to factors such as lateral wall fibrosis. Thus, the changes in the pulmonary \(^{123}\text{T-MIBG}\) uptake are also consistent with improvement in haemodynamics due to BiV pacing in HF patients.

**Limitations**

The numbers in our study cohort were modest, limiting the statistical significance of some of our secondary findings. However, the experimental method using a double-blind crossover technique was more robust than those used in a number of other studies\(^12,13,38\) with similar numbers of patients. Thus, meaningful correlation of the changes in \(^{123}\text{T-MIBG}\) uptake with individual changes in clinical parameters could not be performed. Although the use of single photon emission computed tomography (SPECT) imaging in general affords better assessment of regional radiotracer accumulation than the simpler planar method chosen in this study, SPECT has been shown to be relatively inaccurate for \(^{123}\text{T-MIBG}\) imaging due to the low count activity observed in patients with severe HF.\(^44\)

**Conclusion**

Our study suggests that long-term BiV pacing in patients already treated with maximal anti-failure pharmacotherapy remains necessary for the maintenance of improved sympathetic nerve integrity in the heart and lung, as reflected by improvements in cardiac \(^{123}\text{T-MIBG}\) uptake demonstrated in this study. As such, this finding provides further insights into a possible mechanism by which BiV pacing exerts favourable effects in HF. In future, the use of \(^{123}\text{T-MIBG}\) scanning may also be of value in assessing the efficacy of resynchronization therapy and in integrating pacing strategies with pharmacological therapy for patients with HF.

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**Conflict of interest:** none declared.

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