Cardiac resynchronization therapy and AV optimization increase myocardial oxygen consumption, but increase cardiac function more than proportionally

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Background: The mechanoenergetic effects of atrioventricular delay optimization during biventricular pacing (“cardiac resynchronization therapy”, CRT) are unknown.

Methods: Eleven patients with heart failure and left bundle branch block (LBBB) underwent invasive measurements of left ventricular (LV) developed pressure, aortic flow velocity-time-integral (VTI) and myocardial oxygen consumption (MVO₂) at 4 pacing states: biventricular pacing (with VV 0 ms) at AVD 40 ms (AV-40), AVD 120 ms (AV-120, a common nominal AV delay), at their pre-identified individualised haemodynamic optimum (AV-Opt); and intrinsic conduction (LBBB).

Results: AV-120, relative to LBBB, increased LV developed pressure by a mean of 11(SEM 2)%, p = 0.001, and aortic VTI by 11(SEM 3)%, p = 0.002, but also increased MVO₂ by 11(SEM 5)%, p = 0.04. AV-Opt further increased LV developed pressure by a mean of 2(SEM 1)%, p = 0.035 and aortic VTI by 4(SEM 1)%, p = 0.017. MVO₂ trended further up by 7(SEM 5)% , p = 0.22. Mechanoenergetics at AV-40 were no different from LBBB.

The 4 states lay on a straight line for Δexternal work (ΔLV developed pressure × Δaortic VTI) against ΔMVO₂, with slope 1.80, significantly >1 (p = 0.02).

Conclusions: Biventricular pacing and atrioventricular delay optimization increased external cardiac work done but also myocardial oxygen consumption. Nevertheless, the increase in cardiac work was ~80% greater than the increase in oxygen consumption, signifying an improvement in cardiac mechanoenergetics. Finally, the incremental effect of optimization on external work was approximately one-third beyond that of nominal AV pacing, along the same favourable efficiency trajectory, suggesting that AV delay dominates the biventricular pacing effect — which may therefore not be mainly “resynchronization”.

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1. Introduction

Atriobiventricular pacing (cardiac resynchronization therapy, CRT) in heart failure patients with LBBB and EF <35%, has been shown in small pioneering studies to increase arterial blood pressure and cardiac output and increases external ventricular work[1–5] and efficiency[6]. Large randomized controlled trials later demonstrated reductions in morbidity and mortality[7–10]. Some questions remain, however.

First, the effect of atriobiventricular pacing on myocardial oxygen consumption per beat is not certain. One invasive study[6] where heart rate was allowed to vary spontaneously found that myocardial oxygen consumption per minute fell after 2 min of pacing (at 85.8 ± 4.5 bpm), but it is not clear whether oxygen consumption per beat was altered.

Non-invasive measurement of myocardial oxygen consumption, using positron emission tomography (PET), has shown favorable regional redistribution of myocardial oxygen consumption after biventricular pacing at several time points[11–13]. These studies were carried out after 12 months of device implantation[11] (with at least 2 h of fixed heart rate pacing at +10 bpm above sinus rhythm) and they too were at a non-fixed heart rate, 70 ± 12 bpm after 4 months[12] and 65 ± 9 bpm after 13 months[13] of implantation. All suggested a non-significant trend to increase in myocardial oxygen consumption. Moreover, DCM patients with LBBB have lower myocardial oxygen consumption than those without[14].

Second, it is not known whether the pattern of mechanoenergetic effect of AV delay adjustment resembles that of resynchronization itself or has a different profile. AV delay adjustment improves haemodynamic...
parameters acutely [15]. AV optimization increases left ventricular filling time, increasing stroke volume and cardiac output [15]. The impact of AV delay is larger at higher heart rates, during exercise, where diastolic time is shorter [15]. It is not known whether, once the left ventricle has been resynchronized, there is any further mechanoenergetic benefit of AV optimization.

We designed one experiment to answer both questions invasively by monitoring cardiac output, aortic and left ventricular pressures and myocardial oxygen consumption, in a contemporary cohort of patients undergoing biventricular pacing device implantation.

The primary endpoint was the detection with high resolution of the effect of biventricular pacing at nominal AV delay on pressure, flow velocity, and myocardial oxygen consumption. The secondary endpoint was detection of the incremental effect of changing from nominal AV delay to a patient-individualized AV optimum, determined separately beforehand to avoid inadvertent overestimation of effect size [16].

2. Methods

2.1. Study subjects

Sequential patients about to undergo coronary angiography as a routine part of evaluation prior to implantation of a biventricular pacemaker were approached for recruitment in this prospective study which was approved by the local ethics committee. Each subject served as their own control. All twelve patients who were consecutively approached prior to angiography gave consent for this study. Patients were eligible if their coronary angiogram showed no current significant coronary artery stenosis requiring revascularisation. One patient was found to have a significant coronary stenosis and was therefore excluded; the 11 remaining underwent the study. Patient characteristics are displayed in Table 1. All patients were on an ACE inhibitor or angiotensin receptor blocker, ten were on diuretics and none on digitalis. Four patients were not on beta blockers; two had significant chronic restrictive pulmonary disease and two patients had withdrawn from beta blockers due to adverse symptoms they considered unacceptable [17].

2.2. Measurements

2.2.1. Stage I: Establishment of non-invasive haemodynamic AV delay optimum

Non-invasive haemodynamic AV delay optimization was carried out using an alternation algorithm as previously described [19–23]. In brief, a series of AV delays were tested and compared against a reference AV delay (120 ms) using several forward and backward transitions, which allowed the relative systolic blood pressure difference between the AV delays to be determined to a high level of precision [19,24–26]. We tested a range of AV delays for each patient (40, 80, 160, 200, 240, and so forth at 40 ms intervals) until intrinsic conduction was reached. The non-invasive haemodynamic optimal AV value was defined for each individual as the AV delay corresponding to the maximum of the parabola fitted to the measured systolic blood pressure [19,20]. This alternation protocol is semi-automated and an optimal AV delay can be determined within a few minutes as shown in Fig. 2. The curve fitting process identifies the optimum as a continuous variable, without restricting it to being one of the tested settings [27].

2.2.2. Stage II: Invasive measurements at 4 pacing settings

(a) A pressure wire (Volcano PrimeWire 7900) was placed in the LV cavity via a diagnostic catheter and was used to record the LV pressure throughout the cardiac cycle. The diagnostic catheter was withdrawn 4.5 cm into the aorta and kept at this position throughout the study, leaving the pressure wire in the LV cavity. A flow wire (Volcano FloWire 1400) was then inserted into the same diagnostic catheter and carefully positioned in the aorta, approximately 4 cm from the aortic valve to obtain a stable flow velocity signal. The positions of the diagnostic catheter and the pressure and flow wires were confirmed periodically throughout this stage of the procedure.

Measurements of aortic flow velocity and LV pressure were made at a fixed atrial rate (100 bpm) in random order, at 4 pacemaker settings: AVD 40 ms (AV-40); AVD 80 ms (AV-80); AVD 120 ms (AV-120), a commonly programmed nominal AVD; the individual’s predetermined (as described in Stage I above) non invasive haemodynamic optimum (AV-Dop) and AAI (intrinsic ventricular conduction i.e. LBBB).

Note that the AV-Dop was determined during stage I, i.e. using only non-invasive pressure measurements. Therefore the data obtained in stage II with this pacemaker setting does not simply represent the highest value of any stage II measurement, rather it represents the invasive haemodynamic values arising as a consequence of the pacemaker being programmed to the optimal setting identified by non invasive haemodynamics.

Invasive left ventricular pressure and aortic flow velocity were measured after a steady state pacing period of 90 s at all 4 pacing states. The product of aortic flow velocity integral and left ventricular developed pressure (systolic – diastolic) was used as an index of stroke work for each AV delay tested to enable comparison of all four tested pacing states.

(b) For the invasive assessment of myocardial oxygen consumption the flow wire was then repositioned, through a diagnostic catheter, in the left coronary artery in a proximal position where a clear Doppler signal could be recorded. The site was the left main stem in 10 patients, but had to be the proximal circumflex artery in 1 patient. The velocity waveform was traced automatically (by theComboMap console Pressure and Flow system), and this profile of the velocity waveform was digitally acquired by our system for automatic ensemble averaging across beats, to obtain a velocity-time integral for all the four pacing states tested within each patient. Myocardial oxygen consumption was estimated by multiplying arteriovenous oxygen saturation difference, $\Delta VO_2$ (in the left coronary artery and coronary sinus) by coronary flow velocity-time integral.

Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Cause of heart failure</th>
<th>NYHA class</th>
<th>Heart rate (bpm)</th>
<th>Blood pressure (mm Hg)</th>
<th>PR interval (ms)</th>
<th>Ejection fraction (%)</th>
<th>LVEDD (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>52</td>
<td>DCM</td>
<td>III</td>
<td>68</td>
<td>105/65</td>
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<td>7.3</td>
<td>145</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>73</td>
<td>IHD</td>
<td>III</td>
<td>73</td>
<td>135/73</td>
<td>213</td>
<td>6.0</td>
<td>120</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>60</td>
<td>IHD</td>
<td>III</td>
<td>55</td>
<td>156/84</td>
<td>194</td>
<td>4.8</td>
<td>130</td>
</tr>
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<td>4</td>
<td>M</td>
<td>78</td>
<td>DCM</td>
<td>IV</td>
<td>62</td>
<td>131/68</td>
<td>170</td>
<td>4.3</td>
<td>135</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>76</td>
<td>DCM</td>
<td>III</td>
<td>83</td>
<td>135/66</td>
<td>180</td>
<td>5.0</td>
<td>120</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>80</td>
<td>IHD</td>
<td>III</td>
<td>72</td>
<td>112/60</td>
<td>280</td>
<td>4.1</td>
<td>120</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>55</td>
<td>IHD</td>
<td>III</td>
<td>52</td>
<td>104/71</td>
<td>180</td>
<td>6.7</td>
<td>120</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>62</td>
<td>DCM</td>
<td>IV</td>
<td>70</td>
<td>115/58</td>
<td>196</td>
<td>5.4</td>
<td>120</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>68</td>
<td>DCM</td>
<td>III</td>
<td>60</td>
<td>148/90</td>
<td>200</td>
<td>6.5</td>
<td>120</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>42</td>
<td>DCM</td>
<td>III</td>
<td>64</td>
<td>126/55</td>
<td>144</td>
<td>6.4</td>
<td>120</td>
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<tr>
<td>11</td>
<td>M</td>
<td>64</td>
<td>DCM</td>
<td>III</td>
<td>68</td>
<td>132/84</td>
<td>140</td>
<td>8.0</td>
<td>120</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>55</td>
<td></td>
<td></td>
<td>65</td>
<td>189</td>
<td>38</td>
<td>5.9</td>
<td>120</td>
</tr>
</tbody>
</table>

St.Dev. 11
For each pacing state, quintuplicate pairs of arterial and venous blood samples were withdrawn, for saturation assessment, after at least 90 s of pacing in that state [6,28,29].

Coronary flow was defined as the velocity-time integral averaged over the 60 s period of blood sample withdrawal.

2.3. Data acquisition

Aortic and coronary flow velocities and coronary and left ventricular pressures were measured by the sensor-tipped pressure and flow wires. Aortic pressure was measured using a standard fluid-filled catheter which was carefully calibrated before the study measurements, by matching against the pressure wire signal, with the pressure wire and catheter co-located in the aorta. Haemodynamic and ECG data were acquired using a NIDAQ AI-16E-4 analog-to-digital card (National Instruments, Austin, TX) and Labview (National Instruments, Austin, TX). They were analysed with custom software based on the Matlab platform (MathWorks, Natick, MA).

2.4. Statistics

Distributions of baseline characteristics are given as mean and standard deviation. Statements regarding mean effect sizes are given as mean and its uncertainty, i.e. standard error of the mean. Where space permits, both are presented.

Some of the physiological variables did not fit the criteria for normal distribution on the Anderson Darling test and therefore the pressure, flow, MVO2 and cardiac work data were log transformed, which produced variables that passed the normality test. Statistical tests were therefore performed on the log transformed data using standard parametric methods. Comparisons between the 4 pacing states were performed by repeated measures ANOVA (on log transformed values) and where there was evidence of difference between groups this was pursued using individual t-tests.

The p-values were calculated comparisonwise [30,31] and the reader should be aware that the risk of a false positive finding somewhere in the paper as a whole is higher than 5%. Stata version 11.0 for Windows (StataCorp LP, College Station, Texas) was used for statistical analysis.

The protocol was designed to avoid inadvertent exaggeration of effects [32,33] or artificial correlations [34,35].

3. Results

The individual patient data for all measurements made during the study are displayed on Table 2. The changes in these haemodynamic parameters, which occurred during biventricular pacing, at the prespecified three AV delays, are presented on Table 3.

In Table A1 in the Appendix the raw values of all haemodynamic parameters across all patients at the three biventricular pacing states are presented, to permit any alternative form of analysis.

3.1. Effect of biventricular pacing on haemodynamics

Left ventricular developed pressure (systolic minus diastolic) rose from LBBB to AV 120 ms (AV-120) by 11 (SD 8, SEM 2)%,

\[ p = 0.001 \]

and an additional 2 (SD 3, SEM 1)% increase was observed at the optimal haemodynamic AV delay (AV-Opt);

\[ p = 0.035 \] versus AV-120. At AVD 40 ms (AV-40), developed pressure was worse than AV-120 (\[ \Delta = -2 \] (SD 11, SEM 3)%,

\[ p = 0.50 \]).

Aortic velocity time integral (index of stroke volume), measured throughout each individual’s study, rose by 11 (SD 9, SEM 3)% from LBBB to AV-120, \[ p = 0.002 \], rising a further 4 (SD 4 SEM 1)% at AV-Opt, \[ p = 0.017 \] versus AV-120.
At AV-40, aortic VTI was worse than AV-120 ($p < 0.001$) and no different to LBBB ($\Delta = 1$ (SD 10, SEM 3)\%), $p = 0.87)$. All four pacing states are shown in Fig. 3.

During atrioventricular pacing the relationship between $\Delta$ aortic VTI and $\Delta$ LV developed pressure, from LBBB, was characterized by the regression equation, $y = 1.140x - 0.017$. The slope, 1.14, was not statistically different to 1 ($p = ns$); i.e. both parameters changed by equal proportions.

Compared with LBBB, external cardiac work (indexed by aortic VTI × LV developed pressure) increased at AV-120 by 24 (SD 20,

### Table 2

AV conduction and haemodynamic parameters at an atrially paced rate (AAI) of 100 bpm.

<table>
<thead>
<tr>
<th>Patient</th>
<th>PR interval with AAI pacing (ms)</th>
<th>Optimal AV delay (ms)</th>
<th>Coronary flow VTI (cm)</th>
<th>A-V oxygen saturation (%)</th>
<th>Myocardial oxygen cons. index (au)</th>
<th>LV developed pressure (mm Hg)</th>
<th>Aortic VTI (cm)</th>
<th>Cardiac work index (au)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>220</td>
<td>155</td>
<td>12</td>
<td>63</td>
<td>753</td>
<td>83</td>
<td>22</td>
<td>1859</td>
</tr>
<tr>
<td>2</td>
<td>250</td>
<td>187</td>
<td>41</td>
<td>51</td>
<td>2092</td>
<td>128</td>
<td>12</td>
<td>1473</td>
</tr>
<tr>
<td>3</td>
<td>253</td>
<td>176</td>
<td>33</td>
<td>48</td>
<td>1622</td>
<td>140</td>
<td>22</td>
<td>3019</td>
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<td>118</td>
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<td>972</td>
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<td>270</td>
<td>211</td>
<td>20</td>
<td>61</td>
<td>1229</td>
<td>112</td>
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<td>211</td>
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<td>46</td>
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<td>114</td>
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<td>11</td>
<td>285</td>
<td>213</td>
<td>24</td>
<td>70</td>
<td>1684</td>
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<td>15</td>
<td>1849</td>
</tr>
<tr>
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<td>23</td>
<td>58</td>
<td>1303</td>
<td>114</td>
<td>16</td>
<td>1784</td>
</tr>
<tr>
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<td>26</td>
<td>9</td>
<td>11</td>
<td>523</td>
<td>20</td>
<td>5</td>
<td>652</td>
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<tr>
<td>SEM</td>
<td>13</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>158</td>
<td>6</td>
<td>1</td>
<td>197</td>
</tr>
</tbody>
</table>
3.2. Myocardial oxygen consumption

The myocardial oxygen consumption increased from LBBB to AV-120 by 11 (SD 16, SEM 5)% \( p = 0.04 \) and to AV-Opt by 18 (SD 16, SEM 5)% \( p = 0.003 \); there was no significant difference in the myocardial oxygen consumption between AV-120 and AV-Opt, \( p = 0.22 \). The myocardial oxygen consumption between AV-40 and LBBB was not significantly different; \( \Delta = 0 \) (SD 14, SEM 2) %, \( p = 0.83 \), Fig. 4.

3.3. Mechanoenergetic effect of biventricular pacing

The 4 states lay on a straight line, because the (resynchronization) increment from LBBB to AV-120 had the same direction as the effects of adjustment of AV delay (between AV-40, AV-120, AV-Opt). This common direction had a slope (percentage increment in external cardiac work done per percentage increment in \( \Delta \) myocardial oxygen consumption) of 1.80, significantly greater than 1 (\( p = 0.02 \)), Fig. 5.

4. Discussion

While biventricular pacing at AVD 120 ms (a common nominal setting of biventricular pacing devices) increased external cardiac

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**Table 3**

Relative changes (%) in haemodynamic parameters at 100 bpm, with LBBB as reference.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Myocardial oxygen cons. (% change from LBBB)</th>
<th>LV developed pressure (% change from LBBB)</th>
<th>Aortic velocity time integral (% change from LBBB)</th>
<th>Cardiac work (% change from LBBB)</th>
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<td>1</td>
<td>-7 1 3</td>
<td>-4 5 4</td>
<td>-3 11 13</td>
<td>-7 16 18</td>
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<td>-10 26 29</td>
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<td>2 10 17</td>
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<td>-10 3 3</td>
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<tr>
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<td>0.9 11.3 14.9</td>
<td>0.0 24.3 31.1</td>
</tr>
<tr>
<td>Stand. Dev.</td>
<td>14 16 16</td>
<td>11 8 8</td>
<td>10 9 11</td>
<td>21 20 22</td>
</tr>
<tr>
<td>SEM</td>
<td>4 5 5</td>
<td>3 2 2</td>
<td>3 3 3</td>
<td>6 6 7</td>
</tr>
</tbody>
</table>
work delivered, it did so at the expense of some increase in myocardial oxygen consumption. Fortunately, the proportionate increase in external cardiac work was 80% more than that in oxygen consumption, which indicates that the increment had a higher efficiency than baseline LBBB function.

Second, moving from AVD 120 ms to the individual's predetermined AV optimum significantly increased external cardiac work delivered by approximately one-third with a trend to a further increase in myocardial oxygen consumption. The trajectory of this further increment from optimization was similar to that of switching the biventricular pacemaker on at AVD 120 ms.

Finally, setting a universally unfavourable AV delay (40 ms) put the mechanoenergetic profile of biventricular pacing back to values closely resembling LBBB, i.e. unfavourable AV delay alone fully reversed the entire mechanoenergetic benefit of cardiac resynchronisation.

4.1. Impact of biventricular pacing on myocardial oxygen consumption

Our study demonstrates that, when heart rate is kept fixed and therefore not influencing mechanoenergetics, biventricular pacing with a nominal AV delay of 120 ms increases the myocardial oxygen consumption per beat. In principle, the acute effect of biventricular pacing only affects the timing of activation and cannot directly manipulate the internal metabolism of sarcomeres or mitochondria [36]. Poorer synchrony means wall movement is occurring at times that are more different between sites. As a result, cavity pressure developed is delayed and overall lower. If inward wall movement at each local site is the same, then the total energy consumed by inward movement over the whole (dysynchronous) chamber must be less. Of course, it is possible that the sum of local inward movements is larger in a dysynchronous heart, but it has to be larger by more than the degree of fall in pressure developed, before their mutual product – the leading determinant of metabolic cost – can be higher than in the synchronous heart.

Resynchronization of the ventricular walls prevents substantial segments from escaping with light duties [37] (i.e. contracting early, at lower pressure and therefore lower metabolic cost, but without usefully ejecting blood). This might be why biventricular pacing increases myocardial oxygen consumption.

Positron emission tomography scanning data at fixed heart rate suggested that biventricular pacing raises oxidative metabolism in the septum by 15%, with no significant changes in the lateral or anterior walls [11]. It is the septum which has the opportunity to contract early at lower cavity pressures – and therefore at lower metabolic cost – during LBBB. Canine MRI tagging studies also indicate that at the site of pacing, early local contraction dramatically reduces local work done [30].

Many interventions that increase work done by the heart, do so at the expense of increasing myocardial oxygen consumption [38,39]. The concept that biventricular pacing might be unique, increasing work done while reducing oxygen consumption [6], has therefore been very attractive. The biventricular pacing element of that study was conducted in 5 of 10 invasively studied patients (having started with 11 and set aside one in whom sufficient systolic pressure response was not obtained). The characteristics of those patients were typical of patients being considered for biventricular pacing at that time (2000), namely almost exclusively non ischaemic dilated cardiomyopathy, long PR interval (mean PR 196.5 ± 13.6 ms); wide QRS (mean QRS 179.1 ± 3.4 ms) and very low ejection fraction (mean EF 19.7 ± 2.6%). Such patients are – even now – widely considered to be ideal candidates for biventricular pacing. Our own study's patients are more typical of current cohorts undergoing implantation, namely a mixture of ischaemic and non ischaemic cardiomyopathies, Table 1. That study also differed from ours in that it allowed heart rate to change naturally and attempted a statistical correction to simulate the effect of there being no reflex fall in heart rate with biventricular pacing. In contrast our study fixed heart rate at 100 bpm. The previous approach gives the answer to a question which might be argued to be more clinically important: net effect (with reflex heart rate response); in contrast our current approach gives the answer to a more specific mechanistic question: pure direct cardiac effect (without reflex heart rate response). Together with the difference in patient populations, this procedural difference may explain the superficially different results of the two studies.

Although it may seem disappointing that biventricular pacing did not reduce myocardial oxygen consumption, it should be remembered that fall in myocardial oxygen consumption is not essential to make the heart more efficient. Nor should an intervention that makes the walls of the left ventricle contract more simultaneously, against a higher cavity pressure, automatically be expected to reduce oxygen consumption.

4.2. Commonalities between biventricular pacing and adjustment of AV delay

In our study, initiation of biventricular pacing raised cardiac work by 24 (SD 20, SEM 6)% for an increment in myocardial oxygen consumption of only 11(SD 16, SEM 5)%. This means that the
incremental change had a trajectory –180% as efficient as the behaviour of the myocardium in the native LBBB state. Beyond biventricular pacing at the nominal AV delay of 120 ms, programming AV delay to the noninvasively determined haemodynamic optimum gave a further significant increment in cardiac work of 7 (SD 8, SEM 2)% (approximately an additional one-third of the effect of AV-120), and a non-significant increase in myocardial oxygen consumption (Fig. 5).

Initiation of biventricular pacing has a combination of effects: shortening AV delay and ventricular resynchronisation. Adjusting programmed AV delay also has both potential effects because it not only changes the timing of the ventricular pacing, but also the time relationship between that ventricular pacing and any native conduction contributing to ventricular activation. The presence of ventricular fusion, is sometimes obvious from a visible change in surface ECG, but is sometimes occult. For this reason we cannot be sure that improvements in acute haemodynamic measurements occurring with adjustment of AV delay are not partly acting through changes in ventricular synchronization.

Another mechanism which may explain the effects of biventricular pacing is the minimization of the negative effect of diastolic ventricular interaction. Ventricular resynchronization has been shown to improve left ventricular diastolic volume and effective left ventricular end diastolic pressure by decreasing the external constraint caused by the diastolic ventricular interaction in heart failure [40]. This reduction of constraint led to an improved preload-dependent stroke volume. AV delay optimization may also play a part in improving haemodynamics by (a) improving synchronization further by allowing fusion of biventricular pacing and native conduction, leading to a lesser external constraint and (b) by maximizing the volume of blood filling the left ventricle therefore raising the stroke volume by the Starling mechanism.

Regardless of the precise mechanism of effect of AV delay changes on haemodynamics, an increase in cardiac performance with anything less than a fully corresponding increment in oxygen consumption is welcome.

Moreover, it is striking that setting the AV delay too short, at 40 ms, effectively annuls all the mecanoeenergetic effects of biventricular pacing, back to a state equivalent to LBBB.

4.3. Clinical implications

First, the impact of AV optimization on the measured parameters in this study was about one-third the effect of switching on biventricular pacing a fixed AV delay of 120 ms. This estimate is statistically unbiased because the effect size was measured invasively entirely separately from the previous collected non-invasive data used for identification of the optimal AV delay [19]. Thus, the finding that invasive pressure is higher at the optimum is not simply selection of the highest amongst random variation [24] since, had this occurred, the subsequent invasive measurements would not on average have been any higher than the AV 120 values.

Second, the effect of optimization had the same balance of haemodynamic effects (and same inclination to improved efficiency) as nominal-programmed pacing itself, although smaller (an additional increment of one-third of that of nominal pacing), and so we should expect the same balance of morbidity–mortality benefits but an endpoint trial to verify this would need to be much larger (×9) than the landmark biventricular pacing trials. A smaller effect size does not mean lower cost-effectiveness, since optimization can be much cheaper than the implant procedure.

Third, this study shows that selecting the wrong AV delay does very large harm to haemodynamics. Although extreme mis-selection (AV 40 ms) is required to systematically abolish the haemodynamic effect of biventricular pacing across the whole population, milder mis-selection (i.e. getting only close to the true optimum) may still substantially downgrade haemodynamic benefit. The downgrade of the benefit resulting from a mis-selection of the ‘optimal’ AV delay, would be larger at higher than lower heart rates. Increasing heart rate drastically reduces left ventricular filling time, making precise timing of activation more crucial [20]. Current evidence suggests that adjustment of AV delay with exercise improves the cardiac
output and the functional capacity of patients with DDD pacemakers [41] and also in the biventricular pacing population [42]. The findings from our study complements existing evidence by demonstrating for the first time that optimization of the AV delay at a higher heart rate (100 bpm) further improves cardiac mechanics, along the same favourable efficiency trajectory of biventricular pacing at a nominal AV setting.

4.4. Study limitations

Our study was an invasive study and the number of subjects was not large. However, it was sufficient to address the physiological question being considered. Patients were heterogeneous in terms of aetiology and drug therapy but we believe they are representative of contemporary biventricular pacing device recipients.

In this study we did not assess dyssynchrony using echocardiographic measures. This was based on our analysis of the reports of prediction of response, which can be seen to exceed the mathematically plausible limit [43]. The strong positive claims arose entirely in studies lacking formal enrolment or blinding, and are contradicted by formally-designed studies [43]. The ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 also now recognize that mechanical dyssynchrony assessment is not a useful addition in the selection process. We recruited patients undergoing clinical device implantation based on LBBB.

All participants were atrially paced. This prevented reflex reduction in heart rate which is a feature of biventricular pacing but had the advantage that it allowed the direct mechanoenergetic consequences of resynchronization and AV optimization on the cardiac cycle to be studied unconfounded by changes in heart rate.

Our study, like others [6], focuses on measurements of flow in the left coronary artery and not the right coronary artery, and on measurements of saturation in the coronary sinus which drains almost all of the left coronary artery territory but not all of the right coronary artery territory (a considerable part of which drains directly into the chambers). Therefore the impact on oxygen consumption in the right coronary artery territory is not assessed by this study and – because of its significant direct drainage – may be difficult to assess. This may not be a trivial concern, but PET scan studies which can measure global blood flow have suggested a trend to an overall increase in the total blood flow during biventricular pacing [11–13].

We have not attempted, and do not intend, to assess improvement in mortality from optimization. The data showed that the mechanoenergetic effect of optimization (away from AVD 120) is about one-third of that elicited by implantation of the device. Therefore the most likely impact on survival would be one-third of the 29% benefit seen in CARE-HF, i.e. ~10%. However an optimization endpoint trial adequately powered to confirm this would need to be approximately 32 = 9 times the size of an implantation endpoint trial.

5. Conclusions

Biventricular pacing increases useful cardiac energy output by ~80% more than the increase in myocardial oxygen consumption, i.e. the increment has an improved efficiency. Optimization further increases both, and in the same proportion. The trajectories of effect on haemodynamic measurements of AV optimization and of institution of nominal-AV biventricular pacing are therefore very similar, to the extent that mis-selection of AV completely abolishes the haemodynamic effects of biventricular pacing, rendering the patient back to a mechanoenergetic status equivalent to intrinsic LBBB. This suggests that AV delay is an important contributor to the haemodynamic (and therefore clinical) benefit of biventricular pacing and AV optimization appears to extend this improvement by approximately one-third.

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Conflict of interest disclosures

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