Improvement in Coronary Blood Flow Velocity With Acute Biventricular Pacing Is Predominantly Due to an Increase in a Diastolic Backward-Travelling Decompression (Suction) Wave

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Background—Normal coronary flow is principally determined by a backward-traveling decompression (suction) wave in diastole. Dyssynchronous chronic heart failure may attenuate suction, because regional relaxation and contraction overlap in timing. We hypothesized that biventricular pacing, by restoring left ventricular (LV) synchronization and improving LV relaxation, might increase this suction wave, improving coronary flow.

Method and Results—Ten patients with chronic heart failure (9 males; age 65±12; ejection fraction 26±7%) with left bundle-branch block (LBBB; QRS duration 174±18 ms) were atrioventricularily paced at 100 bpm. LV pressure was measured and wave intensity calculated from invasive coronary flow velocity and pressure, with native conduction (LBBB) and during biventricular pacing at atrioventricular (AV) delays of 40 ms, 120 ms, and separately preidentified hemodynamically optimal AV delay. In comparison with LBBB, biventricular pacing at separately preidentified hemodynamically optimal AV delay (BiV-Opt) enhanced coronary flow velocity time integral by 15% (7%–25%) (P=0.007), LV dP/dt max by 15% (10%–21%) (P=0.005), and neg dP/dt max by 17% (9%–22%) (P=0.005). The cumulative intensity of the diastolic backward decompression (suction) wave increased by 26% (18%–54%) (P=0.005). The majority of the increase in coronary flow velocity time integral occurred in diastole (69% [41%–84% ]; P=0.047). The systolic compression waves also increased: forward by 36% (6%–49%) (P=0.022) and backward by 38% (20%–55%) (P=0.022). Biventricular pacing at AV delays of 120 ms generated a smaller LV dP/dt max (by 12% [5%–23% ], P=0.013) and neg dP/dt max (by 15% [8%–40% ]; P=0.009) increase than BiV-Opt, against LBBB as reference; BiV-Opt and biventricular pacing at AV delays of 120 ms were not significantly different in coronary flow velocity time integral or waves. Biventricular pacing at AV delays of 40 ms was no different from LBBB.

Conclusions—When biventricular pacing improves LV contraction and relaxation, it increases coronary blood flow velocity, predominantly by increasing the dominant diastolic backward decompression (suction) wave. (Circulation. 2012;126:1334-1344.)

Key Words: biventricular pacing ▪ cardiac resynchronization therapy ▪ coronary flow ▪ heart failure ▪ wave intensity

Clinical Perspective on p 1344

One study6 reported that acute resynchronization pacing in patients with dilated cardiomyopathy and LBBB resulted in a nonsignificant trend to fall in mean coronary blood flow measured by intracoronary Doppler. Another study showed no change in global myocardial blood flow measured by 11C-acetate positron emission tomography in patients with ischemic or nonischemic cardiomyopathy at 4 months after...
implantation, although there was evidence of redistribution of coronary blood flow to the septal wall. No study has reported the instantaneous phasic changes in coronary blood flow over the cardiac cycle, and, additionally, because the intracoronary pressure was not measured, it was not possible to establish the hemodynamic mechanisms of any changes in flow.

The coronary bed is unique among systemic arteries, because flow occurs predominantly during diastole. The reason is that the intramural coronary arteries are compressed during systole, and during diastole, when this compression is released, pressure falls faster at the microcirculatory end of the vessel than at the aortic end. The difference in pressure timecourse in diastole causes a suction wave that travels from the distal to the proximal end of the coronary arterial tree, accelerating coronary artery blood flow.

With the use of modern hemodynamic monitoring equipment, it is possible to measure directly the waves associated with the differential pressure changes at each end of the vessel. This allows a detailed quantification of the interaction between the myocardium, coronary artery, and the aorta in determining blood flow along the coronary artery. Formal identification and quantification of these waves is called wave intensity analysis. In human coronary arteries, the most important waves responsible for accelerating blood flow are the backward decompression wave during left ventricular (LV) relaxation (diastole) and the forward compression wave during LV contraction (systole). These waves have been found to have abnormal patterns in conditions such as LV hypertrophy, coronary artery disease, and aortic stenosis.

Dysynchrony is often conceptualized as failure of the contraction to be synchronized across different segments of the LV, but equally might be viewed as failure of relaxation to be synchronized. Because it is the act of relaxation that generates the backward decompression wave that is responsible for the majority of coronary flow, dysynchrony could be attenuating the backward decompression wave and thereby reducing coronary flow. The vigor of contraction can be quantified by using the maximal systolic rate of rise of LV pressure (dP/dt max) and that of relaxation by using the maximal diastolic rate of fall of LV pressure (neg dP/dt max).

To test this hypothesis that cardiac resynchronization, and alteration of atrioventricular (AV) delay, can affect the backward decompression wave and thereby coronary flow, we measured invasively the effects of biventricular pacing on the cardiac cycle, and, additionally, because the intracoronary hemodynamics and used wave intensity analysis to establish the origin of any changes.

### Methods

#### Study Subjects

Twelve sequential patients with heart failure in sinus rhythm with no significant valve disease scheduled for coronary angiography as a prelude to cardiac resynchronization therapy implantation were recruited for this study. Patients only entered the measurement phase if they were found to have visually unobstructed coronary arteries. One patient was found to have a significant coronary stenosis and was therefore excluded. In 1 patient, it was not possible to position the flow wire in the left main stem in a position that provided a consistent stable velocity trace. Therefore, 10 patients underwent this study. Three had left-dominant coronary circulations, and 7 had right-dominant coronary circulations.

Patient characteristics are displayed in Table 1. All patients gave previous written informed consent for this study, which was approved by the local ethics committee.

#### Measurements

**Patient Preparation**

Temporary biventricular pacing was achieved by placement, via the femoral route, of 1 quadripolar electrode catheter (Josephson Curve, Bard Vikings) in the high right atrium, 1 pentapole electrode catheter (Josephson Curve, Bard Woven) in the right ventricle apex, and through an AL1 and/or a Channel sheath positioned in the coronary sinus, an ATW wire was placed posterolaterally for LV pacing.

The stability of the pacing wires was periodically confirmed during the study to ensure consistent atrioventricular pacing. The right atrium, right ventricle, and LV pacing leads were connected via custom-made connectors to a standard cardiac resynchronization therapy pacemaker (Medtronic InSync III 8042). All patients were studied at a controlled atrial rate of 100 bpm.

#### AV Delay Optimization

Optimization of the AV delay was performed with the use of a noninvasive beat-to-beat blood pressure measurement device (Finapres Medical Systems, Amsterdam, Netherlands) applied to the patient’s finger. An algorithm of alternations, as previously described was used to identify the optimal AV delay. This algorithm involves a series of tested AV delays each separately compared with a reference AV delay (120 ms) using several forward and backward transitions, as shown in the online-only Data Supplement Figure 1. This permits the relative systolic blood pressure difference between the tested AV delay and reference AV to be determined to high precision. The AV delays tested for each patient ranged from 40, 80, 160, 200, 240 ms, and so forth, until intrinsic AV conduction was reached with evidence of LBBB. Parabolic curve fitting was used to improve the precision of determination of the optimum. The AV delay identified by parabolic interpolation corresponding to the maximum change in blood pressure from AV 120 ms was considered to be the optimal delay.
Invasive Coronary Measurements at 4 Pacing States

Left main coronary artery pressure and flow velocity were recorded by a sensor-tipped solid state pressure wire (Volcano PrimeWire 7900) and a sensor-tipped solid state flow wire (Volcano FloWire 1400), both positioned through a 6F Judkins left catheter (JL4). To permit a stable state that could be continued throughout the prolonged duration of all measurements without discomfort to the patient, no nitrate was administered. The diagnostic fluid-filled catheter measured the aortic systolic pressure. Wave intensity analysis could then be applied (Figure 1).

Recordings were made for up to 2 minutes at 4 pacemaker settings: biventricular pacing AV delay 40 ms (BiV-40); reference biventricular pacing AV delay 120 ms (BiV-120, manufacturer’s nominal AV delay), individual’s noninvasive hemodynamic biventricular AV optimum (BiV-Opt) and at LBBB (intrinsically ventricular conduction during atrial [AAI] pacing). The 4 settings were tested in random order determined by a random number generator.

Data Acquisition and Analysis

Hemodynamic and ECG data were acquired by using a NIDAQ AI-16E-4 analog-to-digital card (National Instruments, TX) and Labview (National Instruments, TX). They were analyzed with custom software written in Matlab (MathWorks, MA). The aortic pressure and coronary pressure and flow velocity data were filtered and ensemble averaged, and wave intensity analysis was performed as previously described. The analyses of LV $dP/dt_{\text{max}}$, neg$dP/dt_{\text{max}}$, coronary flow velocity time integral, coronary pressure, and analysis of wave intensity magnitudes were performed in Matlab using automated algorithms. Velocity time integral was defined in the following way, where $t$ represents time during the cardiac cycle from $t_{\text{start}}$ to $t_{\text{end}}$, $V_i$ the instantaneous flow velocity at time $t$, and $\delta t$ the interval between successive measurements which was 1 ms:

$$\text{Velocity time integral} = \sum_{i=t_{\text{start}}}^{t_{\text{end}}} V_i \delta t$$

Individual Patient Data

To assist researchers planning future work in this field, and to permit alternative analyses, we provide in the online-only Data Supplement Material the individual data (online-only Data Supplement Table I) for each variable in each patient in each state, from which Figure 2 to 4 were derived.

Scientific Integrity

All authors confirm that the study was designed to make measurements without bias, to all be held individually responsible for procedural deficiency, and to retract the article if any is suspected. We are aware of no reason why the study, if reproduced in independent hands by these described methods, should give different results. Patients were recruited only by the method described. Measurements were made blinded and uniformly. No data were deleted, nor remeasured to favor 1 result over another. The authors are committed to conducting and presenting research reliably and, without precondition, welcome collaboration with others seeking to confirm, develop, or contradict these findings.

Statistics

Descriptions of the spectrum of baseline patient characteristics are given as mean and SD explicitly.

The results were tested with nonparametric statistics, so that the conclusions would not be dependent on an assumption that the coronary measurements were normally distributed. Continuous variables are presented as median and interquartile range. Data from the 4 pacing states were tested by using the Friedman test, the nonparametric equivalent of repeated-measures ANOVA. Where the Friedman test was significant ($P<0.05$), comparisons between pairs of states were made by using the Wilcoxon signed rank test, with probability values calculated comparison-wise and the number of potential comparisons stated so that readers may balance the possibility of type I error against that of type II error. Under the null hypothesis, to have a 5% probability of a false-positive result anywhere among $4 \times 3/2 = 6$ potential comparisons, i.e., the Bonferroni correction, would require the individual comparison-wise probability value threshold to be 0.05/6, i.e., 0.0083. To have a 5% probability of a false-positive result in any particular individual comparison, the probability value threshold would be 0.05.

Correlation between continuous variables was quantified by Spearman rank correlation coefficient rho. SPSS V16 (IBM Corporation) was used for statistical analysis.

Results

The baseline hemodynamic data of all patients studied are shown in Table 2.

Increase in Coronary Flow Velocity Time Integral With Biventricular Pacing at a Fixed Heart Rate

Coronary flow velocity time integral (VTI) increased with biventricular pacing by 21% (5%–27%) ($P=0.013$) at BiV-120 and by 15% (7%–25%) ($P=0.007$) at BiV-Opt, with respect to LBBB (Figure 2). Coronary flow VTI was not increased by biventricular pacing at the very short AV delay of BiV-40 (1% [-6% to 18%], $P=0.58$) in comparison with LBBB.
Of the increase in flow VTI from LBBB to biventricular pacing, the diastolic increase contributed the most: 70% (62%–87%) \((P=0.007)\) at BiV-120, and 69% (41%–84%) \((P=0.047)\) at BiV-Opt.

Across all pacing states the median contribution of diastolic flow to the total flow VTI ranged from 77% to 80%.

Increase in Ventricular Contractility and Relaxation With Biventricular Pacing at a Fixed Heart Rate

Biventricular pacing increased LV \(dP/dt_{\text{max}}\) by 14% (7%–20%) \((P=0.007)\) at BiV-120, and by 15% (10%–21%) \((P=0.005)\) at BiV-Opt, with LBBB as reference. LV \(\text{neg}dP/dt_{\text{max}}\) was enhanced by 13% (6%–17%) \((P=0.009)\) at BiV-120 and by 17% (9%–22%) \((P=0.005)\) at BiV-Opt.

BiV-40 was not significantly different from LBBB in terms of LV \(dP/dt_{\text{max}}\) (2% [6% to 7%]; \(P=0.799\)), nor of LV \(\text{neg}dP/dt_{\text{max}}\) (5% [2% to 10%]; \(P=0.203\)), as shown in Figure 3. BiV-Opt showed a small but statistically significant greater LV \(dP/dt_{\text{max}}\) (by 13% [3%–20%]; \(P=0.013\)) and LV \(\text{neg}dP/dt_{\text{max}}\) (by 11% [8%–27%]; \(P=0.009\)) than BiV-120 (Figure 3).

Across all 4 pacing states, LV \(dP/dt_{\text{max}}\) and \(\text{neg}dP/dt_{\text{max}}\) correlated well \((r=0.86, P<0.001)\).

Increase in Intracoronary Waves With Biventricular Pacing at a Fixed Heart Rate

The wave intensity of the major intracoronary waves throughout the cardiac cycle for the 4 pacing states is shown in Table 3.

The systolic forward compression wave, increased by 26% (9%–38%) \((P=0.017)\) at BiV-120 and by 36% (6%–49%) \((P=0.022)\) at BiV-Opt, against LBBB as a reference (Figure 4). The opposing systolic total backward compression waves increased by almost identical amounts: by 27% (3%–62%) \((P=0.013)\) at BiV-120 and by 38% (20%–55%) \((P=0.005)\) at BiV-Opt.

The dominant wave in diastole, backward decompression wave, was increased by 25% (11%–60%) \((P=0.013)\) at BiV-120 and by 38% (20%–55%) \((P=0.022)\) at BiV-Opt.

The dominant wave in diastole, backward decompression wave, was increased by 25% (11%–60%) \((P=0.013)\) at BiV-120 and by 26% (18%–54%) \((P=0.005)\) at BiV-Opt, at a time in the cardiac cycle when there were no net opposing waves.

At BiV-40 the forward compression, backward compression, and backward decompression waves were not different from LBBB: \(-5\%\) (−15% to 26%); \(P=0.386, 1\%\) (−42% to 36%); \(P=0.799\) and \(-1\%\) (−13% to 22%); \(P=0.799\), respectively.

There were significant correlations between the systolic waves (forward and backward compression) and LV \(dP/dt_{\text{max}}\): \(r=0.54 (P<0.001)\) and \(r=0.66 (P<0.001)\), respectively (Figure 5). There was also a significant positive correlation between the backward decompression wave and LV \(\text{neg}dP/dt_{\text{max}}\) \((r=0.46, P=0.003)\).
For the backward decompression wave, the values are 40%, 32%, 24%, giving a root-mean-square of 32%. In a 10-patient group this gives 80% power at a 5% significance level to detect changes of 28%.

In practice, the tests were conducted with nonparametric statistics whose relative efficiency might be slightly different from the above-stated values. The probability values shown in the article are comparison-wise. Had they been experiment-wise, then (say) allowing for 6 comparisons, ie, comparison-wise \(\alpha\) of 5%/6, would give \(Z_{\text{significance}} = 2.64\), so that the corresponding sizes of effect detectable would be 15% for flow velocity, 15% for LV \(dP/dt_{\text{max}}\), and 35% for the backward decompression wave.

**Discussion**

In this invasive study of patients with systolic heart failure, we found that, in patients with heart failure and LBBB, biventricular pacing increases the flow VTI in the left main coronary artery through enhancement of ventricular relaxation, which increases the diastolic backward-traveling decompression (suction) wave.

**Impact of Biventricular Pacing on Left Coronary Artery Flow**

Total left coronary artery flow VTI increased during biventricular pacing at AV 120 and optimal AV in comparison with LBBB. This finding may be explained by the change in the pattern of ventricular contraction and relaxation during pacing.

The impact of LBBB and resynchronization on myocardial metabolism and consequently demand for blood flow is likely to be mediated by the change in the pattern of contraction and relaxation during the cardiac cycle. The dysynchrony of LBBB causes LV wall segments to contract at different times, reducing the rate of active stress generation and limiting the rise in pressure developed. For example, because septal and posterolateral wall segments do not contract simultaneously, the contraction of each segment is not against the full pressure developed by the others, and so the work needing to be done by the segment is smaller than would be the case without LBBB. Resynchronization improves synchrony of contraction of ventricular wall segments and thereby increases both LV pressure and stroke volume. The external work done per individual wall segment is therefore likely to be higher, which may explain the raised metabolic demands on blood supply, as indicated in Figure 6.

MRI tagging in the canine model has shown that, at the site of pacing, early local contraction (in comparison with the rest of the ventricle, which therefore results in a lower rise in chamber pressure) dramatically reduced local external work done with a corresponding increase in local external work performed in more remote regions. Local mechanical work correlates positively with changes in myocardial oxygen demand and may explain the finding of the reduction of myocardial perfusion in LBBB, which is magnified with increasing heart rates. In the absence of a change in the myocyte mechanical efficiency, the increase in external cardiac work done with acute biventricular pacing would therefore be expected to increase myocardial blood flow, as was found in our study.
Table 3. Cumulative Wave Intensity of Major Left Coronary Artery Waves in All 4 Pacing States

<table>
<thead>
<tr>
<th>Wave Intensity (AUC) $\times 10^3$ W m$^{-2}$ s$^{-1}$</th>
<th>LBBB</th>
<th>Biv-40</th>
<th>Biv-120</th>
<th>Biv-Opt</th>
<th>$P$ (Biv-Opt vs LBBB)</th>
<th>$P$ (Biv-40 vs LBBB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Forward compression</td>
<td>9.9 (4.1 to 13.8)</td>
<td>7.6 (3.4 to 12.6)</td>
<td>11.4 (4.0 to 17.9)</td>
<td>12.9 (4.8 to 18.2)</td>
<td>0.02</td>
<td>0.39</td>
</tr>
<tr>
<td>2 Backward compression</td>
<td>6.2 (5.6 to 7.8)</td>
<td>7.7 (2.5 to 9.9)</td>
<td>9.3 (6.2 to 11.2)</td>
<td>9.3 (8.0 to 9.9)</td>
<td>0.02</td>
<td>0.80</td>
</tr>
<tr>
<td>Net wave contribution to forward flow (1 – 2)</td>
<td>0.6 (–2.1 to 5.5)</td>
<td>0.5 (–0.1 to 1.6)</td>
<td>2.6 (0.8 to 4.2)</td>
<td>1.4 (–1.9 to 4.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Forward decompression</td>
<td>1.5 (1.0 to 3.1)</td>
<td>2.8 (1.8 to 4.9)</td>
<td>3.3 (1.3 to 5.8)</td>
<td>3.0 (2.8 to 3.4)</td>
<td>0.09</td>
<td>0.33</td>
</tr>
<tr>
<td>4 Late forward compression</td>
<td>2.0 (1.3 to 5.3)</td>
<td>1.3 (0.8 to 2.7)</td>
<td>2.6 (1.4 to 3.4)</td>
<td>1.7 (1.1 to 3.6)</td>
<td>0.72</td>
<td>0.39</td>
</tr>
<tr>
<td>5 Backward decompression (suction)</td>
<td>7.7 (4.8 to 10.3)</td>
<td>6.2 (4.9 to 11.0)</td>
<td>8.2 (6.3 to 14.0)</td>
<td>8.8 (6.2 to 12.2)</td>
<td>0.005</td>
<td>0.80</td>
</tr>
<tr>
<td>Net wave contribution to forward flow (5 + 4 – 3)</td>
<td>7.4 (4.7 to 12.0)</td>
<td>5.8 (3.9 to 9.8)</td>
<td>7.6 (3.8 to 13.3)</td>
<td>9.2 (5.3 to 11.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of diastolic contribution to total wave contribution to forward flow</td>
<td>85%</td>
<td>93%</td>
<td>75%</td>
<td>86%</td>
<td>0.95</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as median and interquartile range. The Wilcoxon signed rank test was used for the pairwise comparisons between LBBB and Biv-Opt and Biv-40. Comparison between all pacing states was performed by the Friedman test. LBBB indicates left bundle-branch block; AV, atrioventricular; Biv-40, biventricular pacing at AV delays of 40 ms; Biv-120, biventricular pacing at AV delays of 120 ms; Biv-Opt, biventricular pacing at separately preidentified hemodynamically optimal AV delay; and AUC, area under the curve.

The only previous study in humans that examined left coronary flow and LV mechanoenergetics reported that biventricular pacing, in comparison with LBBB, caused an increase in work and (when matched for heart rate) had no significant effect on oxygen consumption or average coronary flow. However, that study differed from ours in design; it permitted reflex-driven variation in heart rate, whereas ours fixed atrial rate at 100 bpm.

At both AV 120 and optimal AV, the biventricular pacemaker is resynchronizing ventricular contraction (and thereby also resynchronizing ventricular relaxation). The difference between them is principally in the relative timing of atrium and ventricle. At AV 120, the interval between atrial and ventricular activation is set at a constant value for all patients, whereas, at optimal AV, each patient has an individually programmed AV delay calculated beforehand to be likely to deliver the most effective cardiac function as assessed by the largest increment in peripherally measured systolic pressure. Resynchronization by biventricular pacing had a much larger effect than any difference between AV 120 and optimal AV, but selection of a very poor AV delay was able to counteract the increased flow VTI of resynchronization. We cannot be certain whether there was a subtle undetected difference between AV 120 and optimal AV, but the ability of a very poor AV delay to eliminate the benefits of biventricular pacing suggests that AV delay cannot be irrelevant.

Biventricular Pacing-Mediated Increase in Diastolic Coronary Flow VTI

We found that both the systolic and diastolic components of coronary flow VTI increased when biventricular pacing was introduced at an AV delay that improved LV $dP/dt_{\text{max}}$ and $\text{neg}dP/dt_{\text{max}}$, these improvements were observed at AV 120 and at the individual’s optimal AV delay. Proportionally, the systolic and diastolic flow VTIs appeared to be elevated by similar magnitudes; 10% to 15% and 16% to 21%, respectively ($P=0.54$). However, the increased diastolic flow VTI contributed $\approx 70\%$ of the total increase in coronary flow VTI.

Driving Forces Behind Changes in Coronary Flow VTI During Biventricular Pacing

Optimal (and near-optimal, BiV-120) biventricular pacing improves electric synchronization and ventricular filling, which improve ventricular contractility and relaxation as demonstrated by the effects on the LV pressure’s first derivatives in Figure 3. This raises myocardial oxygen demand, leading to an increased myocardial blood supply, but the mechanisms underlying this increase in blood supply have yet to be identified.

Mechanisms of Coronary Flow VTI Rise During Biventricular Pacing: Waves From Aorta and Microcirculation

Both the systolic forward-traveling and backward-traveling compression waves increased in magnitude when the ventricle was biventricularly paced at both optimal AV delay and near-optimal, BiV-120 (Figure 5). This finding is reassuring from a mechanistic perspective and demonstrates the interrelationship between increasing ventricular contractile performance with biventricular pacing (measured by the increase in $dP/dt_{\text{max}}$) and the magnitude of these systolic waves. Biventricular pacing intensifies not only contraction but also relaxation and therefore enhances not only the systolic compression waves but also the diastolic backward decompression wave that is dominantly responsible for increasing coronary flow velocity.

Although similar findings have been demonstrated by increasing heart rate in animals, our study appears to be the first in humans to identify a chain of causation from purely increasing ventricular contraction and relaxation (at constant heart rate) to improved coronary hemodynamics manifested by the backward decompression wave (Figure 7).

Under normal pressure load conditions, the coronary microcirculation is subject to transmission of the pressure loads...
from the LV cavity. A simplified analogy would be to consider the microcirculation behaving somewhat like a sponge. During systole, the coronary microcirculation is squeezed, displacing a volume of blood, measured as a backward-traveling compression wave. During diastole, as microcirculatory compression is relieved; a suction wave is generated in proportion to the increase in microcirculatory volume. The greater the degree of compression during systole, the greater is the capacity for decompression during diastole. In this way blood flow within the coronary arteries can be closely regulated by compression and decompression in addition to vasodilatory mechanisms.

Conditions that alter this normal relaxation pattern, such as LV hypertrophy, or those that lead to excessive LV pressure loading, such as those in severe aortic stenosis, can disrupt the normal relationship between LV contraction–relaxation and detrimentally change coronary hemodynamics.

In systole, although there is a sizeable forward compression wave, it is opposed by a similarly sized and simultaneous backward compression wave. Therefore the net effect on
forward coronary flow VTI in systole is much smaller (Table 2) than in diastole, where the backward decompression wave is unopposed for much of its duration, leading to a large diastolic increase in coronary blood flow.

**Insight From Very Suboptimal AV Delay During Biventricular Pacing**

The effect of varying the AV delay during biventricular pacing on coronary and ventricular physiology has never been studied to this detail. The effects of optimal AV (and near-optimal AV delay of 120ms) have been discussed above.

A very undesirable AV delay of 40 ms, despite still being a biventricularly paced state, did not improve any of the hemodynamic parameters (ventricular pressure derivatives, coronary flow velocity, and wave intensity) above the LBBB state. This indicates that, despite ventricular resynchronization, which itself improves ventricular hemodynamics, programming AV delay to a value that compromises ventricular filling can offset the effects on ventricular contraction and relaxation, coronary flow velocity, and coronary waves.

Our interpretation of these findings is that the LV (via contraction and relaxation) regulates its own coronary flow, and these mechanisms are readily visible in the coronary waves. During biventricular pacing, improvements in contraction and relaxation depend on 2 factors: co-ordination of ventricular activation and adequacy of preload (which undesirable AV delay can impair), as outlined in Figure 8.

**Clinical Implications**

Resynchronization, and optimization of AV delay, increases the ability of the heart to develop pressure (which is of use in predicting outcomes) and also increases coronary blood flow velocity. The increase in coronary blood flow arises principally through an increase in microcirculatory suction driven by an improvement in myocardial relaxation.

**Study Limitations**

The 10 patients we studied are a small number to make definitive conclusions for all patients, although they were not selected for any particular clinical characteristics and are representative of a contemporary cohort of patients without obstructive coronary disease undergoing biventricular pacing. This experimental protocol is complex and demanding for patients; it is neither necessary nor suitable for routine clinical practice. Although it was able to explore phenomena in the acute ventricular and coronary physiological consequences of biventricular pacing and AV delay optimization, it was not designed to cover subtler questions such as the differential effects of age and sex on coronary physiology during biventricular pacing. In addition, variability between causes of heart failure with differing degrees of myocardial microcirculatory impairment may alter the magnitude of response to biventricular pacing.

We did not allow natural variations of heart rate during the experiment. However, the decision to fix the atrial rate permitted us to assess the direct effect of biventricular pacing on important aspects of ventricular physiology and its consequences on coronary hemodynamics by avoiding confounding by reflex heart rate regulation.

We cannot be certain whether there was a contribution from microvascular resistance to our findings, or how large it was, because we did not give adenosine to make microcirculatory resistance minimal and constant. Instead, we can only conclude that biventricular pacing at AV 120 or AV optimum, which increases indices of myocardial systolic and diastolic function, also increases coronary flow velocity and wave intensity. An associated concern is that, in patients with macrovascular coronary stenoses, the early diastolic suction wave in individual diseased vessels is affected by the state of anastomoses (collaterals) with adjacent territories. To minimize this, we did not recruit patients with obstructive macrovascular disease and, furthermore, made measurements very proximally, in the left main stem rather than within
individual vessels. Consequently, our study casts no light on the impact of anastomoses.

We did not perform measurements of fractional flow reserve or coronary flow reserve to ethically minimize experimental burden on patients of time and adenosine infusion. We did not recruit patients who had any lesions that any of our interventional consultants would have considered as possibly needing fractional flow reserve or coronary flow reserve.

Left ventricular pressure first derivatives can be criticized as measuring an effect of contractility that is loading dependent, rather than measuring a conceptual ideal of loading-independent contractility. However, in the case of biventricular pacing, which improves ventricular synchrony and ventricular preload, $dp/dt_{\text{max}}$ and $negdP/dt_{\text{max}}$ are credible markers of the combined effect.

Left main stem diameter has been reported to be unchanged by biventricular pacing, and measuring it at each stage of the protocol would have introduced measurement error that may be larger than the any very small genuine underlying change induced by change in pacing state. Furthermore, this error would have been squared during estimation of volume flow rate, and the patients would have had to receive additional radiation and contrast at each stage. For these reasons, we confined ourselves to measuring and reporting changes in coronary flow VTI. Readers concerned that increased VTI might be consistently accompanied by reduced cross-sectional area should take special care not to consider increase in flow VTI to be synonymous with increase in flow.

Conclusions
Biventricular pacing at an AV delay that increases ventricular contractility and relaxation, also improves myocardial blood supply. Wave intensity analysis indicates that the mechanism for the improved coronary blood flow VTI is principally an increase in the intensity of the diastolic backward decompression (suction) wave driven by the improved relaxation. For resynchronization with nominal AV delay, and with additional AV optimization, increases in contractile performance, hemodynamics, coronary waves, and coronary flow VTI appear to go hand in hand.

Figure 7. A schematic presentation of the action of the main waves on the direction of blood flow during the cardiac cycle. During systole, the 2 main waves, the forward compression and backward compression waves, act in opposing directions and as a result the systolic net wave contribution to forward coronary flow is small. In diastole, the backward decompression (suction) wave is largely unopposed, and, therefore, the net wave contribution to forward flow is considerably larger than during systole. LV indicates left ventricular.
Ventricular synchrony

Optimal AV delay

Left Ventricular contractility and relaxation

Backward decompression (suction) wave

Coronary flow

Figure 8. Relationship between ventricular contractility and relaxation and coronary flow during acute biventricular pacing. Left ventricular contraction and relaxation improve during acute biventricular pacing as a result of ventricular resynchronization and AV optimization. This improvement causes an increase in the diastolic backward decompression suction wave with an increase in coronary flow. AV indicates atrioventricular.

Biventricular pacing has multiple effects on cardiac and coronary physiology and should not be assumed to be purely resynchronization, because a substantial component arises from AV delay optimization if performed with high precision.

Acknowledgments

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Disclosures

Imperial College London has filed a patent for a method of hemodynamic optimization of AV delay of biventricular pacemakers, which was the approach used in this study because reproducibility was important.

References


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**CLINICAL PERSPECTIVE**

Biventricular pacing is known to improve cardiac contractility. This study shows that, equally, it improves cardiac relaxation and the resultant suction effect from the distal circulation that enhances coronary flow velocity. Both ventricular resynchronization and better-timed filling (atrioventricular optimization) have this effect. Pressure and flow velocity changes that occur in the coronary artery may originate proximally (traveling forward from the aorta) or distally (traveling backward from the microcirculation). Wave intensity analysis is a tool used to identify the origins of any changes, even when they are occurring simultaneously. In systole, myocardial contraction creates a forward compression wave but also an opposing backward compression wave. In contrast, in diastole, myocardial relaxation causes a backward decompression (suction) wave that is not opposed by such a matching forward-traveling wave (because the aortic valve closes). The ability of myocardial relaxation to suck blood into the coronary tree appears to be the predominant drive for coronary perfusion, and this drive can be quantified in the form of the backward-traveling decompression wave. Biventricular pacing increases this wave by enhancing myocardial relaxation, as observed in this study. Increases in ventricular pressure responses, brought about by biventricular pacing or optimization of atrioventricular delay, correspond with increases in coronary flow velocity.
Improvement in Coronary Blood Flow Velocity With Acute Biventricular Pacing Is Predominantly Due to an Increase in a Diastolic Backward- Travelling Decompression (Suction) Wave
Andreas Kyriacou, Zachary I. Whinnett, Sayan Sen, Punam A. Pabari, Ian Wright, Richard Cornelussen, David Lefroy, D. Wyn Davies, Nicholas S. Peters, Prapa Kanagaratnam, Jamil Mayet, Alun D. Hughes, Darrel P. Francis and Justin E. Davies

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Supplemental Figure 1. Example patient whereby the forward and backward transitions AV optimization algorithm was used

To minimise the noise we performed an algorithm of forward and backward transitions (generating a number of replicate datasets) from a reference AV delay of 120 ms to a tested AV delay such as AV 40 ms, as shown in the top panel. A number of transitions were performed for each tested pacemaker setting (tested AV settings ranged from AV 40ms until, but not including, intrinsic LBBB). By using both “forward” and “backward” transitions the effect of any drift within the haemodynamic trace is cancelled out. The optimal AV delay was calculated using parabolic interpolation.
Supplemental Table 1. Individual patient data for coronary flow, contractility, relaxation and for the main systolic and diastolic waves

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