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

Running title: Kyriacou et al; Coronary diastolic blood suction improves with biventricular pacing

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Abstract:

**Background** - Normal coronary blood flow is principally determined by a backward-travelling decompression (suction) wave in diastole. Dyssynchronous chronic heart failure may attenuate suction, as 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 CHF patients (9 male; age 65±12; EF 26±7%) with left bundle branch block (LBBB, QRS duration 174±18 ms) were atrio-biventricularly paced at 100bpm. 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 40ms (BiV-40), 120ms (BiV-120), and separately pre-identified haemodynamically-optimal AV delay (BiV-Opt). Compared against LBBB, BiV-Opt enhanced coronary flow VTI by 15(7-25)% (p=0.007), LV dP/dtmax by 17(9-22)% (p=0.005) and negdP/dtmax 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 VTI 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). BiV-120 generated a smaller LV dP/dtmax (by 12(5-23)%, p=0.013) and negdP/dtmax (by 15(8-40)% p=0.009) increase than BiV-Opt, against LBBB as reference; BiV-Opt and BiV-120 were not significantly different in coronary flow VTI or waves. BiV-40 was no different from LBBB.

**Conclusions** - When biventricular pacing improves left ventricular contraction and relaxation, it increases coronary blood flow velocity, predominantly by increasing the dominant diastolic backward decompression (suction) wave.

**Key words:** biventricular pacing; cardiac resynchronization therapy; coronary; heart failure; wave intensity
Introduction

Atrio-biventricular pacing (cardiac resynchronization therapy, CRT) in heart failure patients with left bundle branch block (LBBB) and ejection fraction (EF) <35% was originally shown to increase arterial blood pressure, cardiac output and external work achieved by the heart.\textsuperscript{1,2,3,4,5,6} These pioneering small studies paved the way for large randomized controlled trials which demonstrated reductions in morbidity and mortality in heart failure.\textsuperscript{7,8,9,10,11,12,13} Surprisingly, the effects of biventricular pacing on coronary blood flow have been little studied.

One study\textsuperscript{6} reported that acute resynchronization pacing in patients with dilated cardiomyopathy and LBBB resulted in a non-significant trend to fall in mean coronary blood flow measured by intra-coronary Doppler. Another study showed no change in global myocardial blood flow measured by \textsuperscript{11}C-acetate positron emission tomography (PET) in patients with ischemic or non-ischemic cardiomyopathy at 4 months following implantation, although there was evidence of redistribution of coronary blood flow to the septal wall.\textsuperscript{14,15} No study has reported the instantaneous phasic changes in coronary blood flow over the cardiac cycle and additionally, since 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 amongst systemic arteries, as 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 gradient in diastole causes a suction wave which travels from the distal to the proximal end of the coronary arterial tree, accelerating coronary artery blood flow.

Using modern haemodynamic 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.16,17,18,19

In the human coronary arteries, the most important waves responsible for accelerating blow 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 hypertrophy16, coronary artery disease20 and in aortic stenosis.21

Dyssynchrony is often conceptualized as failure of the contraction to be synchronized across different segments of the left ventricle, but equally might be viewed as failure of relaxation to be synchronized. Since it is the act of relaxation that generates the backward decompression wave which is responsible for the majority of coronary flow, dyssynchrony could be attenuating the backward decompression wave and thereby reduce coronary flow. Vigor of contraction can be quantified using the maximal systolic rate of rise of LV pressure (dP/dtmax) and that of relaxation using the maximal diastolic rate of fall of LV pressure (negdP/dtmax).

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

Methods

Study Subjects

Twelve sequential heart failure patients in sinus rhythm with no significant valve disease
scheduled for coronary angiography as a prelude to CRT implantation were recruited for this study. Patients only entered the measurement phase of the study 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 one 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 seven right-dominant.

Patient characteristics are displayed in Table 1. All patients gave prior 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 one quadripolar electrode catheter (Josephson Curve, Bard Vikings) in the right atrium (RA), one pentapole electrode catheter (Josephson Curve, Bard Woven) in the right ventricular apex and, through an AL1 and/or a Channel sheath positioned in the coronary sinus, an ATW wire was placed posterolaterally for LV pacing.22

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

Atrioventricular (AV) delay optimization

Optimization of the AV delay was carried out using a non-invasive 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\textsuperscript{23,24,25,26,27}, was used to identify the optimal AV delay. This algorithm involves a series of tested AV delays each separately compared against a reference AV delay (120 ms) using several forward and backward transitions, as shown in the \textbf{Supplemental Figure 1}. This permits the relative systolic blood pressure difference between the tested AV delay and reference AV to be determined to high precision.\textsuperscript{23,28} 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.\textsuperscript{29,30} 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.\textsuperscript{23,24}

\textbf{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). In order 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\textsuperscript{6,31,32} at 4 pacemaker settings: AV delay 40 ms (BiV-40); reference AV delay 120 ms (BiV-120, manufacturer’s nominal AV delay), individual’s non-invasive haemodynamic optimum (BiV-Opt) and at LBBB (intrinsic ventricular conduction during atrial (AAI) pacing). The four settings were tested in random order determined by a random number generator.\textsuperscript{28}
Data acquisition and analysis

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 written in Matlab (MathWorks, Natick, MA). The aortic pressure and coronary pressure and flow velocity data were filtered and ensemble averaged, and wave intensity analysis performed as previously described. The LV $dP/dt_{\text{max}}$, $\text{neg}dP/dt_{\text{max}}$, coronary flow velocity time integral, coronary pressure and analysis of wave intensity magnitudes was performed in Matlab (MathWorks, Natick, MA) 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 $t_{\text{end}}$, $v_t$ the instantaneous flow velocity at time $t$, and $\delta t$ the interval between successive measurements which was 1 ms:

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

Individual patient data

To assist researchers planning of future work in this field, and to permit alternative analyses, we provide in the Supplemental Material the individual data (Supplemental Table 1) for each variable in each patient in each state, from which Figures 2-4 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 paper 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 one 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 standard
deviation (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 (IQR). Data from the 4
pacing states were tested using Friedman’s test, the nonparametric equivalent of repeated-measures ANOVA. Where Friedman’s test was significant (p<0.05) comparisons between pairs of states were made using the Wilcoxon signed rank test, with p values calculated
comparsionwise\textsuperscript{34,35} 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 amongst 4×3/2=6 potential comparisons, i.e. the
Bonferroni correction, would require the individual comparisonwise p 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 p value threshold would be 0.05.

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

Results

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

Increase in coronary flow VTI with biventricular pacing at a fixed heart rate
Coronary flow velocity time integral (VTI) increased with biventricular pacing by 21(5 to 27)% (p=0.013) at Biv-120 and by 15 (7 to 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) compared against LBBB.

Of the increase in flow VTI from LBBB to biventricular pacing, the diastolic increase contributed the most: 70 (62 to 87)% (p=0.007) at BiV-120; and by 69 (41 to 84)% (p=0.047) at BiV-Opt.

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

Increase in ventricular contractility and relaxation with biventricular pacing at a fixed heart rate

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

BiV-40 was not significantly different from LBBB in terms of LV dP/dt_{max} (2 (-6 to 7)%, p=0.799), nor of LV_{neg}dP/dt_{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_{max} (by 13 (3 to 20)% , p=0.013) and LV_{neg}dP/dt_{max} (by 11 (8 to 27)%, p=0.009) than BiV-120 (Figure 3).

Across all 4 pacing states, LV dP/dt_{max} and _negdP/dt_{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 to 38)% (p=0.017) at BiV-120 and by 36 (6 to 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 to 62)% (p=0.139) at BiV-120 and by 38 (20 to 55)% (p=0.022) at BiV-Opt.

The dominant wave in diastole, backward decompression wave, was increased by 25 (11 to 60)% (p=0.013, Figure 4) at BiV-120 and by 26 (18 to 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 to 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/dtmax: r=0.54 (p<0.001) and r=0.66 (p<0.001), respectively (Figure 5). There was also a correlation between the backward decompression wave and LV negdP/dtmax (r=0.46, p=0.003).

Retrospective power calculations

In our data, between patients the standard deviations of the percentage change in flow velocity from LBBB to each of the paced states were 17% (LBBB to AV 40), 14% (to 120), and 12% (to Optimal AV), giving a root-mean-square of 14%. For 80% power, Zpower=0.84. For a significance level of 5%, Zsignificance=1.96. Thus the size of difference detectable in a 10-patient group is (0.84+1.96)/\sqrt{10} \times 14\% , i.e. 12\%, if a parametric test were used.

For LV dP/dtmax, the standard deviation of the percentage change from LBBB to paced were 14% (to AV 40), 13% (to AV 120), and 13% (to Optimal AV), giving a root-mean-square of 14%. In a 10-patient group this gives 80% power at a 5% significance level to detect changes.
of 12%.

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 carried out with nonparametric statistics whose relative efficiency might be slightly different from the above stated values. The $p$ values shown in the manuscript are comparisonwise. Had they been experimentwise, then (say) allowing for 6 comparisons, i.e. comparisonwise 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-travelling 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, when compared with LBBB. This finding may be explained by at least 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 dyssynchrony 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 simultaneity of contraction of ventricular wall segments\textsuperscript{37}, 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 to the rest of the ventricle which therefore results in a lower rise in chamber pressure) dramatically reduced local external work done\textsuperscript{37} with a corresponding increase in local external work performed in more remote regions. Local mechanical work correlates positively with changes in myocardial oxygen demand\textsuperscript{38}, and may explain the finding of the reduction of myocardial perfusion in LBBB\textsuperscript{39,40} which is magnified with increasing heart rates\textsuperscript{41,42}. 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.

The only previous study in humans\textsuperscript{6} that examined left coronary flow and left ventricular mechanoenergetics reported that biventricular pacing, compared 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, permitting reflex-driven variation in heart rate, while 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 that selecting 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 which improved left ventricular 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; 10-15% and 16-21%, respectively (p=0.54). However, the increased diastolic flow VTI contributed ~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 electrical synchronization and ventricular filling, which improve ventricular contractility and relaxation as demonstrated by the effects on the left ventricular 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-travelling and backward-travelling 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 inter-relationship 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 which 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 haemodynamics manifest 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-travelling 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 which alter this normal relaxation pattern such as left ventricular hypertrophy\textsuperscript{16}, or those which 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 haemodynamics.\textsuperscript{21,43}

In systole, although there is a sizeable forward compression wave, it is opposed by a similar-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 haemodynamic parameters (ventricular pressure derivatives, coronary flow velocity and wave intensity) above the LBBB state. This indicates that, despite ventricular resynchronization, which itself improves ventricular haemodynamics, programming AV delay to a value which 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 left ventricle (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 two 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\textsuperscript{44,45,46}) 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 ten 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, and 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 differential effects of age and gender on coronary physiology during biventricular pacing. In addition, variability between heart failure aetiologies 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 haemodynamics, by avoiding confounding by reflex heart rate regulation.

We cannot be certain whether there is 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 minimise 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 carry out measurements of FFR or CFR in order to ethically minimise experimental burden on patients of time and adenosine infusion. We did not recruit patients who had any lesions which any of our interventional consultants would have considered as possibly needing FFR or CFR.

Left ventricular pressure first derivatives can be criticised as measuring an effect of contractility which 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, \( \frac{dp}{dt_{max}} \) and \( \text{neg} \frac{dP}{dt_{max}} \) are credible markers of the combined effect.

Left main stem diameter has been reported to be unchanged by biventricular pacing\(^6\) 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 have 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 which increases ventricular contractility and relaxation also improves the 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 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, haemodynamics, coronary waves and coronary flow VTI appear to go hand in hand.

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

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<th>Table 1. Baseline characteristics.</th>
<th>n (%) or mean and SD</th>
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<td>Male</td>
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<td>Age (years)</td>
<td>65.5 SD 12</td>
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<td>β-blockers</td>
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</tr>
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<td>ACE-I/ARB</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>α-blockers</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Digitalis</td>
<td>0</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>2 (20%)</td>
</tr>
</tbody>
</table>
Table 2. Haemodynamic data of all the patients during intrinsic ventricular conduction (LBBB) when atrially paced at 100 bpm. Data are presented as median and interquartile range.

<table>
<thead>
<tr>
<th>Haemodynamic parameter</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>122 (117 to 137)</td>
</tr>
<tr>
<td>LV dP/dt$_{\text{max}}$ (mmHg/s)</td>
<td>1044 (1032 to 1098)</td>
</tr>
<tr>
<td>LV negdP/dt$_{\text{max}}$ (mmHg/s)</td>
<td>986 (929 to 1040)</td>
</tr>
<tr>
<td>Total coronary flow VTI (cm)</td>
<td>19.7 (17.0 to 23.0)</td>
</tr>
<tr>
<td>Systolic coronary flow VTI (cm)</td>
<td>4.0 (3.5 to 5.5)</td>
</tr>
<tr>
<td>Diastolic coronary flow VTI (cm)</td>
<td>16.0 (13.2 to 17.5)</td>
</tr>
</tbody>
</table>
Table 3. Cumulative wave intensity of major left coronary artery waves in all four pacing states. Data are presented as median and interquartile range. Wilcoxon’s sign rank test was used for the pairwise comparisons between LBBB (left bundle branch block) and BiV-Opt and BiV-40. Comparison between all pacing states was carried out by Friedman’s test.

<table>
<thead>
<tr>
<th>Wave Intensity (AUC) x 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-value (BiV-Opt Vs LBBB)</th>
<th>P-value (Biv-40 Vs LBBB)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systole</strong></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><em>Net wave contribution to forward flow (1 minus 2)</em></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><strong>Diastole</strong></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><strong>0.005</strong></td>
<td>0.80</td>
</tr>
<tr>
<td><em>Net wave contribution to forward flow (5 plus 4 minus 3)</em></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><strong>Proportion of diastolic contribution to total net wave contribution to forward flow</strong></td>
<td>85%</td>
<td>93%</td>
<td>75%</td>
<td>86%</td>
<td></td>
<td><strong>0.95</strong></td>
</tr>
</tbody>
</table>
Figure Legends:

Figure 1. Wave intensity analysis of proximal left coronary artery in a heart failure patient. This is an example patient included in this study, paced at a constant heart rate of 100bpm at the optimal AV delay. Shown on the top diagram are the main waves isolated by wave intensity analysis. The most dominant waves are the forward compression wave in systole and the backward decompression or suction wave in diastole. In the bottom panel the pressure (red) and flow velocity (black) in the proximal left coronary artery are shown, throughout the cardiac cycle.

Figure 2. Impact on coronary flow of biventricular pacing. Changes in total, systolic and diastolic left coronary flow VTI from LBBB to the three tested AV delays. These are shown as box plots which display the median (dark horizontal line), interquartile range (box) and full range. The nonparametric repeated measures comparison between states was carried out by Friedman’s test. The total coronary flow VTI was significantly increased at BiV-Opt (p=0.007) and BiV-120 (p=0.013) when compared to LBBB. There was no difference in total flow VTI between BiV-40 and LBBB (p=0.58).

Figure 3. Effect of biventricular pacing on left ventricular contraction and relaxation. The changes in LV dP/dt\text{max} and LV negdP/dt\text{max} from LBBB to the three tested AV delays are presented as box plots. The Friedman test was used to assess a difference between all states. Both the LV dP/dt\text{max} and LV negdP/dt\text{max} enhanced from LBBB to BiV-120 (p=0.007 and p=0.009, respectively) and by slightly, but statistically significantly, more at BiV-Opt (p=0.013 and
p=0.009, respectively). There was no significant difference between LBBB and BiV-40 for both the LV dP/dt\text{max} (p=0.80) and LV negdP/dt\text{max} (p=0.20).

**Figure 4.** Impact of biventricular pacing on the main left coronary waves. Changes in the diastolic backward decompression and systolic forward compression waves are presented as median (dark horizontal line), interquartile range (box) and full range. The nonparametric repeated measures comparison between states was carried out by Friedman’s test. The Wilcoxon sign rank test was used to compare pairs of pacing states. Both the forward compression and backward decompression waves are significantly increased at BiV-Opt (p=0.022 and p=0.005, respectively) when compared to LBBB. The intensities of the waves at BiV-40 were not different to LBBB (p=0.386 and p=0.799, respectively).

**Figure 5.** Impact of LV dP/dt\text{max} and LV negdP/dt\text{max} on their temporally corresponding coronary waves. In each part of the cardiac cycle, the peak rate of intraventricular pressure change (LV dP/dt\text{max} for systole, and LV negdP/dt\text{max} for diastole) correlated (Spearman’s Rho) with the corresponding waves, consistent with myocardial compression and decompression of the coronary microcirculation generating the waves.

**Figure 6.** A conceptualized diagram illustrating the pressure difference between LBBB and resynchronization during contraction for each of three myocardial wall segments. During LBBB, wall segment 1 contracts first and 3 contracts last. Both of these segments contract at times of very low ‘off peak’ LV pressures; with only segment 2 contracting against peak LV pressure, which is itself low. When these three wall segments are resynchronized, they contract
simultaneously, each working to generate higher LV pressure (long black arrows) than they did during LBBB. With each segment contracting against a higher pressure, there may be greater demand for myocardial blood flow.

**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 two 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.

**Figure 8.** Relationship between ventricular contractility and relaxation and coronary flow during acute biventricular pacing. Left ventricular contraction and relaxation improves 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.
Regional wall activation during CRT

Early

Late

time

Regional wall activation during LBBB

1. against high peak cavity pressure

2. against low peak cavity pressure

3. against very low cavity pressure

1. against very low cavity pressure

2. against low cavity pressure

3. against very low cavity pressure
**Systole**

- Forward compression wave
- Backward compression wave

**Diastole**

- Backward decompression (suction) wave

Muscular compression of microcirculation causes backward compression wave

Muscular decompression of microcirculation causes backward decompression (suction) wave

LV $\frac{dP}{dt}_{\text{max}}$

Diastole

Schematic magnification of myocyte–microvascular interface

LV $\frac{dP}{dt}_{\text{max}}$

Systole
Ventricular synchrony  Optimal AV delay

Left Ventricular contractility and relaxation

Backward decompression (suction) wave

Coronary flow
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 Material

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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Systolic VTI (cm)</th>
<th>% change from LBBB</th>
<th>Diastolic VTI (cm)</th>
<th>% change from LBBB</th>
<th>Total VTI (cm)</th>
<th>% change from LBBB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>during LBBB</td>
<td>BV-40</td>
<td>BV-120</td>
<td>BV-Opt</td>
<td>during LBBB</td>
<td>BV-40</td>
</tr>
<tr>
<td>1</td>
<td>0.03</td>
<td>-13.2</td>
<td>-0.2</td>
<td>-3.3</td>
<td>0.09</td>
<td>-4.2</td>
</tr>
<tr>
<td>2</td>
<td>0.06</td>
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<td>-14.0</td>
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<td>0.18</td>
<td>-6.9</td>
</tr>
<tr>
<td>3</td>
<td>0.12</td>
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<td>+14.6</td>
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<td>-4.2</td>
</tr>
<tr>
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</tr>
<tr>
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<td>+31.4</td>
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<td>-3.2</td>
<td>0.16</td>
<td>+27.8</td>
</tr>
<tr>
<td>6</td>
<td>0.03</td>
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<td>+33.1</td>
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<tr>
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<td>+14.8</td>
<td>+16.2</td>
<td>0.14</td>
<td>+2.8</td>
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<tr>
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<tr>
<td>10</td>
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<td>+4.5</td>
<td>+39.5</td>
<td>0.11</td>
<td>+25.5</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient</th>
<th>LV dP/dt max</th>
<th>% change from LBBB</th>
<th>LV max dP/dt max</th>
<th>% change from LBBB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>during LBBB</td>
<td>BV-40</td>
<td>BV-120</td>
<td>BV-Opt</td>
</tr>
<tr>
<td>1</td>
<td>491</td>
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</table>

<table>
<thead>
<tr>
<th>Patient</th>
<th>Forward Comp. wave (AUC) x 10^8 W m^-3 s^-1</th>
<th>% change from LBBB</th>
<th>Backward Decomp. wave (AUC) x 10^8 W m^-3 s^-1</th>
<th>% change from LBBB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>during LBBB</td>
<td>BV-40</td>
<td>BV-120</td>
<td>BV-Opt</td>
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<tr>
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