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Effects of Epicardial and Endocardial Cardiac Resynchronization Therapy on Coronary Flow: Insights From Wave Intensity Analysis

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Background—The increase in global coronary flow seen with conventional biventricular pacing is mediated by an increase in the dominant backward expansion wave (BEW). Little is known about the determinants of flow in the left-sided epicardial coronary arteries beyond this or the effect of endocardial pacing stimulation on coronary physiology.

Methods and Results—Eleven patients with a chronically implanted biventricular pacemaker underwent an acute hemodynamic and electrophysiological study. Five of 11 patients also took part in a left ventricular endocardial pacing protocol at the same time. Conventional biventricular pacing, delivered epicardially from the coronary sinus, resulted in a 9% increase in flow (average peak velocity) in the left anterior descending artery (LAD), mediated by a 13% increase in the area under the BEW ($P=0.004$). Endocardial pacing resulted in a 27% increase in LAD flow, mediated by a 112% increase in the area under the forward compression wave (FCW) and a 43% increase in the area under the BEW ($P=0.048$ and $P=0.036$, respectively). There were no significant changes in circumflex parameters. Conventional biventricular pacing resulted in homogenization of timing of coronary flow compared with baseline (mean difference in time to peak in the LAD versus circumflex artery: FCW 39 ms [baseline] versus 3 ms [conventional biventricular pacing], $P=0.008$; BEW 47 ms [baseline] versus 8 ms [conventional biventricular pacing], $P=0.004$).

Conclusions—Epicardial and endocardial pacing result in increased coronary flow in the left anterior descending artery and homogenization of the timing of waves that determine flow in the LAD and the circumflex artery. The increase in both the FCW and the BEW with endocardial pacing may be the result of a more physiological activation pattern than that of epicardial pacing, which resulted in an increase of only the BEW. (*J Am Heart Assoc.* 2015;4:e002626 doi: 10.1161/JAHA.115.002626)

Key Words: cardiac resynchronization therapy • coronary flow • endocardial pacing • wave intensity

Cardiac resynchronization therapy (CRT) is an effective treatment for patients with systolic heart failure and electrical dyssynchrony, resulting in improvements in both symptoms and mortality.¹ Depending on the end point assessed, between 30% and 40% of patients fail to improve with CRT.² Metrics created to improve patient selection and to predict response have often appeared encouraging in small

single-center studies but have lacked reproducibility when extrapolated to multicenter trials.³ Consequently, interest has been increasing in both the pathophysiology of dyssynchronous heart failure, in an attempt to understand the mechanical sequelae of electrical dyssynchrony, and new methods of ventricular stimulation such as endocardial and multipoint pacing to improve CRT response.^{4–8} An area of research is the effect of impaired electrical activation and CRT on coronary hemodynamics and physiology; recent data from animal models have indicated the importance of blood flow in CRT response.⁹

The coronary vasculature is unique in the human body in that the majority of flow occurs during diastole. Using advanced invasive techniques, it has been possible to demonstrate that flow is mediated principally by the forward propulsion of blood through the coronary tree in systole (a dominant forward compression wave [FCW]) and by a relatively larger backward expansion wave (BEW; suction wave) generated by relaxation of the ventricle in diastole.¹⁰ Current evidence shows that the amplitude and wavelengths

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of these waves are affected by CRT when measured in the left main coronary artery¹¹; however, relative workload and myocardial stress are not homogenous in the dyssynchronous left ventricle. Ventricular activation with left bundle branch block results initially in septal contraction with delayed activation and contraction of the lateral wall. This early contraction occurs prior to development of tension in the lateral wall, resulting in reduced septal work compared with normal contraction. Conversely, the lateral wall contracts against a pressure-loaded ventricle, causing an increase in lateral wall work compared with synchronous activation.^{12,13}

Conventional biventricular pacing (BIVCS) delivered epicardially from the coronary sinus can increase left anterior descending artery (LAD) coronary flow, and acute changes in LAD flow may predict response to CRT, but little is known about the effects of BIVCS on the wave energy that determines coronary flow in the left-sided coronary system.^{14,15} Similarly, although data are increasing regarding the beneficial acute effects of left ventricular (LV) endocardial pacing on cardiac work and acute contractility, no data describe the effects of LV endocardial pacing on coronary blood flow.^{16,17} Given the heterogeneity of regional work in the dyssynchronous ventricle, a more detailed examination of the individual epicardial arteries may give insights into the regional effects of myocardial contraction on the different constituents of coronary blood flow during both epicardial and endocardial LV pacing.

We sought to describe the effects of both standard CRT via LV epicardial pacing from the coronary sinus and biventricular endocardial pacing (BIVEN) on coronary flow. By applying wave intensity analysis to simultaneously obtained coronary pressure–Doppler flow data, we sought to describe the effect of pacing from different sites (epicardial and endocardial) on coronary physiology in both left-sided epicardial arteries.

Methods

The study received approval from the local research ethics committee and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. We obtained simultaneous electrophysiological and hemodynamic measurements from 11 patients with a previously implanted standard CRT device with an epicardial LV lead in the lateral/posterolateral wall. Arterial access was gained in both the femoral and radial arteries. A 0.014-cm Doppler wire (ComboWire model 9500; Volcano Corp) was advanced to the proximal LAD and then to a central location within the proximal LAD at which a high signal-to-noise ratio was obtained. A PrimeWire pressure guide wire (Volcano Corp) was placed in the LV cavity to allow measurement of acute contractility by the maximal rate of rise of LV pressure (dP/dt_{max}).¹⁸

To study the effects of LV endocardial pacing on coronary flow, 5 of the 11 patients agreed to undergo a more comprehensive study in which a roving endocardial pacing catheter was placed in the left ventricle to perform LV endocardial pacing. Several endocardial positions (mean of 4 [2 for each artery]) were tested in the 5 patients, and the site with the highest average peak velocity (APV) in each artery was selected for analysis. Patients underwent an acute pacing protocol with assessment of different pacing configurations. The study was then repeated with the ComboWire moved from the LAD to the circumflex artery (Cx). In 5 cases, the Cx was assessed before the LAD. Intracoronary adenosine was given as a bolus dose of 36 microgrammes to induce hyperemia for further investigation of the effect of pacing from different sites on coronary hemodynamics.

Baseline measurements were taken from patients in sinus rhythm in AAI mode. For patients with atrial fibrillation or complete heart block, the baseline comparator rhythm was right ventricular pacing with atrial synchronous pacing in the latter group. When comparisons were made between baseline and right ventricular pacing, those whose baseline required right ventricular pacing were omitted from analysis. All studies were performed with pacing at 10 beats above the intrinsic rate or at 70 beats per minute in the case of patients with underlying atrioventricular block to control for the Bowditch effect.¹⁹ Atrio- and ventriculoventricular delays were set, as per previous standard clinical echo optimization using the Doppler mitral inflow and LV outflow tract velocity time integral metrics, respectively. Baseline measures were reassessed for different pacing configurations to control for possible drift.

Patients received dual antiplatelet therapy prior to the procedure in case of the need for emergency percutaneous intervention and received boluses of heparin to keep an activated clotting time >300 seconds.

The first 3 to 5 beats recorded after a change in pacing protocol were selected for analysis according to the following criteria, which are similar to those used by other groups¹¹:

1. Lapse of an initial 10 seconds to stabilize the new pacing parameter
2. Exclusion of the beat preceding and the 3 beats following an ectopic ventricular beat
3. Determination that the signals were of sufficient quality for analysis, made by a physician who was blinded to the study hypotheses

Data analysis involved 2 stages. The raw data were analyzed using the StudyManager program (Volcano Corp). Wave intensity analysis was applied to the coronary data using a custom-made program, Cardiac Waves (King's College London). Data were sampled at 250 Hz. Details of the methodology used to perform wave intensity analysis for data

analysis have been described previously.^{20,21} Briefly, a Savitzky–Golay convolution method was adopted using a polynomial filter to refine the derivatives of the aortic pressure and velocity signals.^{21,22} The selected 3 to 5 consecutive cardiac cycles were gated to the ECG R wave peak, with ensemble averaging of aortic pressure, coronary pressure (P_d), APV, and heart rate. Net coronary wave intensity (dI in the equation) was calculated from the time derivatives (dt in the equation) of ensemble-averaged coronary pressure and flow velocity (dU in the equation), as follows: $dI = dP_d/dt \times dU/dt$.^{10,21} Coincident backward (micro-circulation-derived) and forward (aorta-derived) propagating waves were separated, assuming blood density to be 1050 kg/m^3 and estimating coronary wave speed using the sum of squares method.^{21,23} The areas beneath the 2 most prominent wave energies identified were analyzed and included in this report. These were the positive (aorta-derived) FCW, occurring at the onset of systole, and the BEW, the first negative wave occurring at the onset of ventricular relaxation, identified by the onset of diastole. An example of the data following analysis are demonstrated in graphic form in Figure 1.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 22.0 (IBM Corp). Rather than assume normality, coronary flow data were analyzed as nonparametric variables using the Friedman test (the nonparametric equivalent of ANOVA for repeated measures).²⁴ If the Friedman test was significant, comparisons between pairs of states were made using the

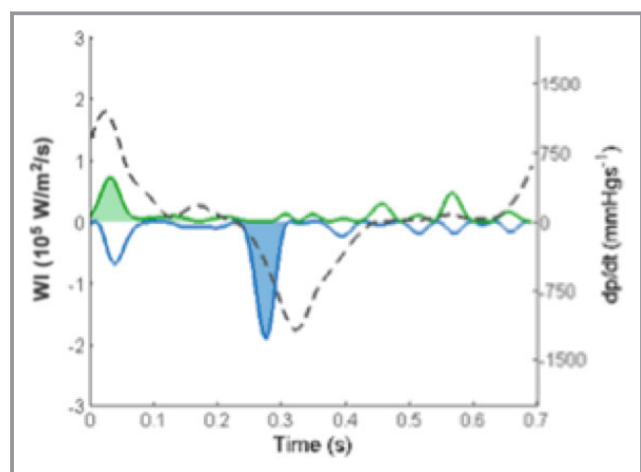


Figure 1. Acute contractility data measured by dP/dt (black dashed line) and the constituent waveforms (forward-traveling waves are shown in dark green, and backward-traveling waves are shown in blue). The large shaded green area is the forward compression wave; the larger blue area is the backward expansion wave. dP/dt , rate of rise of LV pressure; WI, wave intensity.

Wilcoxon signed rank test, with probability values calculated comparisonwise. For normally distributed data, paired 2-sided Student t tests were used to compare means. Demographic data are presented as means with standard deviations. Data regarding the atrio- and ventriculoventricular delays are presented as medians and ranges to provide clinically interpretable data. To allow for correlation of repeated measures in the same patient, linear mixed-effect models were used to explore the relationship between coronary flow and acute changes in LV contractility.

Results

Twelve patients consented to take part in the study. The protocol could not be completed in 1 patient because of problems getting a stable signal from the ComboWire, and this patient was excluded from further analysis. Patient demographics for the remaining 11 patients are shown in Table. There were no complications as a result of the acute procedure. The median atrioventricular delay was 125 ms (range 100 to 140 ms), and the median ventriculoventricular delay was left ventricle ahead by 30 ms (range 0 to 40 ms).

Table. Demographic Data

Characteristics	Mean (SD)
Age, y	59.9 (9.38)
Sex	
Male	9
Female	2
Etiology	
NICM	9
ICM	2
QRS morphology	
LBBB	8
NSIVCD	2
RBBB	1
QRS duration, ms	156.6 (20.1)
EF before implant (%)	24 (10.5)
Sinus rhythm	8/11
Time since implant (days)	1027 (967)
ACEIs	11/11
Beta blockers	11/11
Aldosterone antagonists	9/11

ACEIs indicates angiotensin-converting enzyme inhibitors; EF, ejection fraction; ICM, ischemic cardiomyopathy (previous infarct or flow-limiting coronary disease at angiography); LBBB, left bundle branch block; NICM, nonischemic cardiomyopathy; NSIVCD, nonspecific intraventricular conduction delay; RBBB, right bundle branch block.

Effect on Coronary Flow With Different Pacing States

There was no change in LAD flow when intrinsic conduction was compared with right ventricular pacing (-4.5% , $P=0.123$). BIVCS from the chronically implanted epicardial LV lead increased LAD flow significantly from baseline ($+8.7\%$; $P=0.033$) and was further increased with the optimal endocardial pacing site (BIVEN; $+27.0\%$; $P=0.021$) (Figure 2). BIVEN pacing resulted in an increase in LAD flow from BIVCS, but this was not significant ($+6.6\%$; mean increase from baseline in 5 patients: BIVCS $+20.2\%$ versus BIVEN $+27.0\%$; $P=0.748$). APV from the Cx showed no significant variation among baseline, BIVCS, right ventricle, and BIVEN ($P=0.615$) (Figure 2).

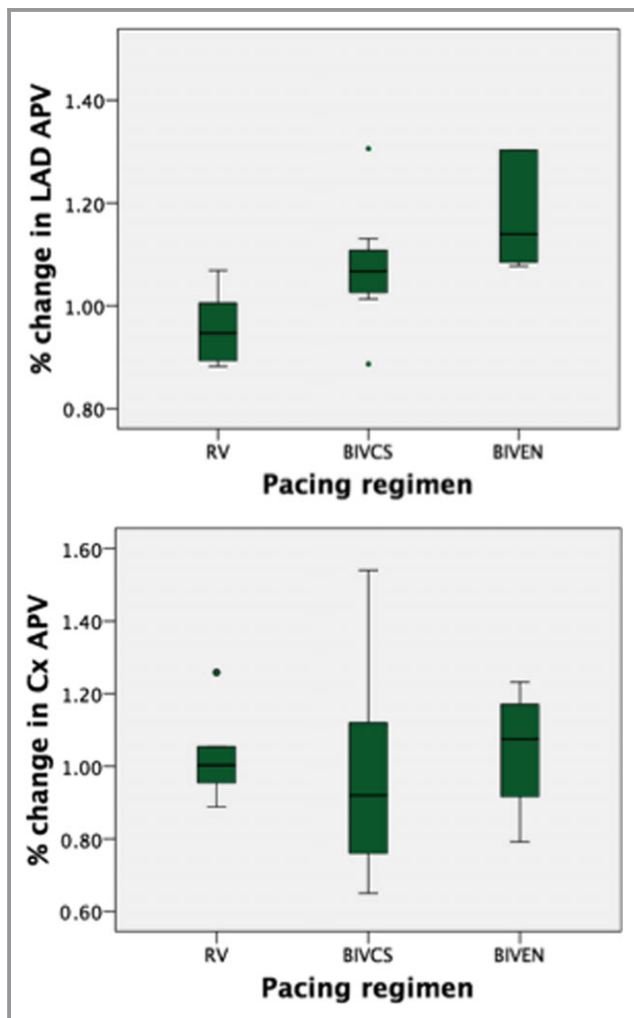


Figure 2. Percentage changes from baseline of coronary flow (APV) in the LAD and the Cx with different forms of pacing. APV indicates average peak velocity; BIVCS, conventional biventricular pacing; BIVEN, biventricular endocardial pacing; Cx, circumflex artery; LAD, left anterior descending artery; RV, right ventricle.

Analysis of the 8 patients with left bundle branch block demonstrated a significant increase in LAD flow with BIVCS from baseline ($+10.2\%$, $P=0.034$) with no significant change in Cx flow ($P=0.917$). Analysis of the 8 patients in sinus rhythm demonstrated a significant increase in LAD flow with BIVCS from baseline ($+10.1\%$, $P=0.005$) with no significant change in Cx flow ($P=0.6$).

Relationship Between Coronary Flow and Acute Myocardial Contractility (dP/dt_{max})

The change in LAD (APV) and acute hemodynamic response, as measured by dP/dt_{max} , was significantly correlated with a Pearson correlation coefficient of 0.449 when all pacing states in all patients were assessed ($P=0.015$). The relationship between the 2 variables remained significant in the mixed model, which allowed for correlation within repeated measures from the same participant ($\beta=1.006$ [95% CI 0.09 to 1.92]; $P=0.033$) (Figure 3). The change in acute hemodynamic response was poorly correlated with the change in Cx flow, and there was no evidence of association using the mixed model when all pacing states were assessed ($\beta=-0.215$ [95% CI -0.797 to 0.357]; $P=0.44$).

Effect of Pacing on Wave Intensity Analysis Energy Profile

There was a significant increase in the magnitude of the BEW in the LAD with BIVCS compared with baseline (mean area 6422.8 W/m^2 per second at baseline increased to

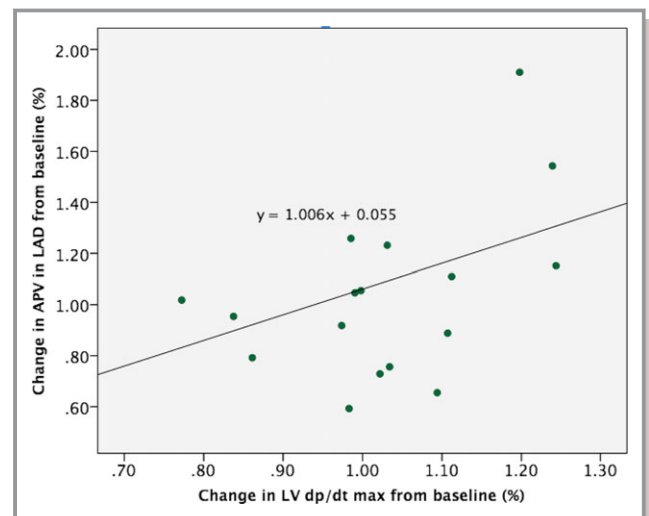


Figure 3. Correlation between change in LAD coronary flow (APV) from baseline and change in acute contractility (dP/dt_{max}) from baseline. APV indicates average peak velocity; dP/dt_{max} , maximal rate of rise of LV pressure; LAD, left anterior descending artery; LV, left ventricular.

7281.9 W/m² per second with BIVCS [13% mean increase]; $P=0.004$). BIVEN facilitated a significant increase in the area above the wave to a mean of 8200.3 W/m² per second versus 5744.1 W/m² per second ($P=0.036$). The difference in BEW between BIVEN and BIVCS for the artery was 1594.0 W/m² per second, but this was not significant ($P=0.139$) (Figures 4 and 5).

There was no difference in the area under the FCW in the LAD with a mean increase from 2668.5 W/m² per second at baseline to 3027.0 W/m² per second with BIVCS (P value not significant). The optimal BIVEN position, however, also resulted in a significant increase in the energy of the FCW (mean area 1984.18 W/m² per second to 4220.4 W/m² per second [112% mean increase]; $P=0.048$) (Figures 4 and 5).

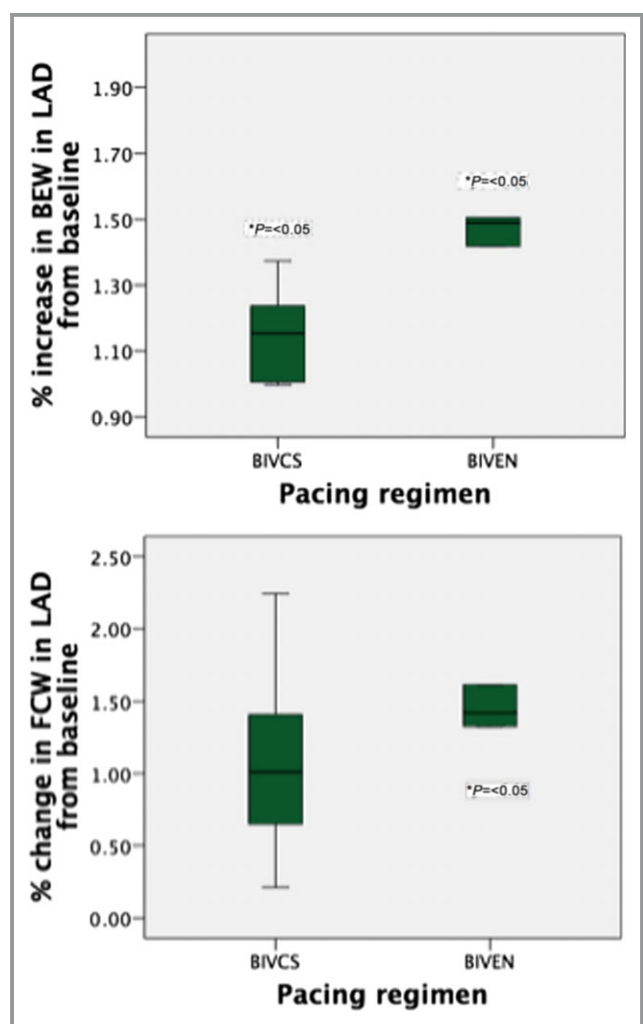


Figure 4. Percentage change from baseline of the area above the BEW and below the FCW in the LAD with different pacing regimens. BEW indicates backward expansion wave; BIVCS, conventional biventricular pacing; BIVEN, biventricular endocardial pacing; FCW, forward compression wave; LAD, left anterior descending artery.

There was no difference in the magnitude of the BEW in the Cx with BIVCS compared with baseline (mean 11 047.2 W/m² per second at baseline reduced to 8666.6 W/m² per second; $P=0.237$). There was a nonsignificant reduction in the size of the BEW for the patients who underwent the endocardial procedure (mean area under the BEW at baseline was 13 704.68 W/m² per second versus largest BIVEN 5825.5 W/m² per second; $P=0.053$). With regard to the area under the dominant FCW, there was no change in the energy from baseline with BIVCS (baseline 4501.648 W/m² per second versus BIVCS 3229.2 W/m² per second; $P=0.123$) and the best BIVEN (baseline 4548.48 W/m² per second versus BIVEN 1910.3 W/m² per second; $P=0.176$) (Figure 6).

Change in Timing of Coronary Waves With Application of Biventricular Pacing: Coronary Resynchronization

The time to the peak of the dominant BEW was significantly delayed between the LAD and the Cx at baseline in patients with a nonischemic etiology (284 ms in the LAD versus 331 ms in the Cx; $P=0.01$) (Figure 7). This was corrected by BIVCS (mean LAD 289 ms versus mean Cx 297 ms; $P=0.566$). The reduction of the difference between the time to peak of the BEW in the LAD versus the Cx by BIVCS was significant (mean 47 ms at baseline versus 8 ms; $P=0.004$) (Figure 7).

In assessing the FCW in a similar manner, the time to peak of the FCW at baseline was significantly different between the LAD and the Cx (30 versus 69 ms; $P=0.03$), with a reduction in the difference of this timing with BIVCS (56 ms [LAD] versus 53 ms [Cx]; $P=0.715$). The reduction of the difference to peak of the FCW was also significant (39 versus 3 ms; $P=0.008$) (Figure 7).

Coronary Flow Velocity Reserve in the LAD and the Cx

Hyperemia was induced at baseline and with BIVCS. There was a significant difference between the baseline LAD coronary flow velocity reserve (CFVR; mean 2.35) and CFVR with BIVCS (mean 2.05; $P=0.02$). Conversely, there was a nonsignificant increase in the CFVR in the Cx from 2.1 to 2.46 with BIVCS pacing ($P=0.349$) (Figure 8).

Discussion

To our knowledge, this study was the first to comprehensively analyze the effect of epicardial and endocardial pacing on the constituent waveforms of coronary flow in the LAD and the Cx.

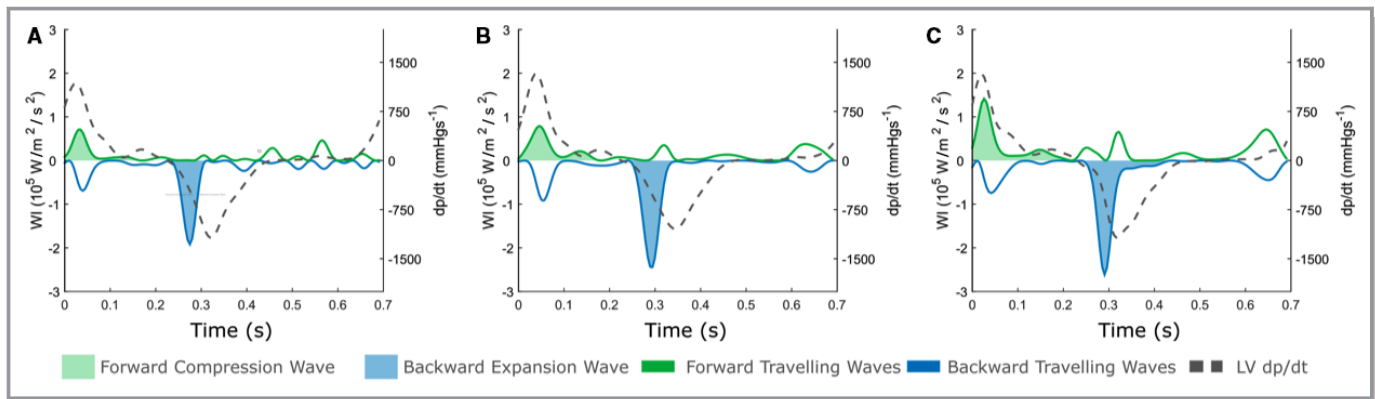


Figure 5. An example of wave intensity analysis in the left anterior descending artery of 1 patient: (A) baseline, (B) BIVCS, (C) BIVEN. Note the increase in the BEW in BIVCS and the increase in both the BEW and forward compression wave with BIVEN. Key as per Figure 1. BEW indicates backward expansion wave; BIVCS, conventional biventricular pacing; BIVEN, biventricular endocardial pacing; WI, wave intensity.

The principal findings were as follows:

1. Increased flow in the LAD with BIVCS and BIVEN was the result of an increase in the BEW.
2. In addition to an increase in the BEW, BIVEN increased coronary flow with a significant increase in the FCW in the LAD.
3. The time to the peak of the FCW and the BEW is homogenized between the LAD and the Cx following CRT.
4. Cx flow and the constituent determinants of flow did not alter with BIVCS or BIVEN.

The effect of biventricular pacing on coronary flow and physiology has been an area of inquiry for many years, with discussion as to whether the changes noted are merely the result of restoration of synchronous mechanical activation or related to changes in underlying myocardial oxygen supply and demand.^{25,26} In recent years, there has been gradual refinement of our understanding of how coronary physiology is affected by the dyssynchronous ventricle^{11,27}; however, significant disagreement remains within the literature as to the effect of pacing on coronary flow.^{15,18,28} Our findings provide new insight into the effect of epicardial and LV endocardial pacing on coronary physiology.

Coronary Flow: Comparison With Previous Studies

The significant increase in flow in the LAD with BIVCS accords with recent studies.^{14,27} The neutral effect on coronary flow in the Cx, however, differs with the findings of Itoh et al, who found that biventricular pacing increased both LAD and Cx flow, but this was in the acute setting soon after device implant. Our data may offer some explanation with regard to the differing results of studies looking at regional and global myocardial blood flow noninvasively: These results demon-

strate either no change in regional myocardial blood flow or correction of a septal perfusion defect with CRT.^{29–32} Our findings of minimal changes in the Cx combined with an increase in the LAD with BIVCS and BIVEN may explain these apparently divergent findings. If we accept that CRT increases global (left main coronary artery) flow velocity, as per Kyriacou et al, our findings suggest that this increase in flow preferentially affects the LAD, namely, there is an increase in flow to the LAD with unchanged Cx flow rather than redistribution of an unchanged global blood flow toward the LAD.²⁴ This may explain why imaging modalities do not report redistribution of flow (ie, there is none) even though CRT has been noted to reverse septal perfusion abnormalities (through increased LAD flow secondary to increased global flow).

Equally, the noted significant reduction in CFVR in the LAD with BIVCS and the nonsignificant increase in CFVR in the Cx contrast with other studies showing increased CFVR in the LAD with CRT.^{27,28} Our findings may appear counterintuitive; one might expect more physiological electrical activation to have a positive effect on parameters such as CFVR. Nevertheless, our reported reduction in CFVR with BIVCS may reflect the multifaceted etiology of the impaired septal flow at baseline and during hyperemia in this cohort of patients with chronically implanted biventricular devices.

CFVR levels in the LAD and the Cx were below those seen in health, suggesting a generalized blunted hyperemic response reflecting microvascular dysfunction that cannot be overcome by CRT. Components of microvascular dysfunction that CRT is likely unable to overcome include the anatomical disruption of the microvasculature by fibrosis and extracellular matrix, decreased myocardial capillary density, and impaired capillary vasodilation.^{33–36} The only component of microvascular resistance that seems likely to be altered by CRT is the effect of compressive forces related to high end-diastolic pressures.²⁵

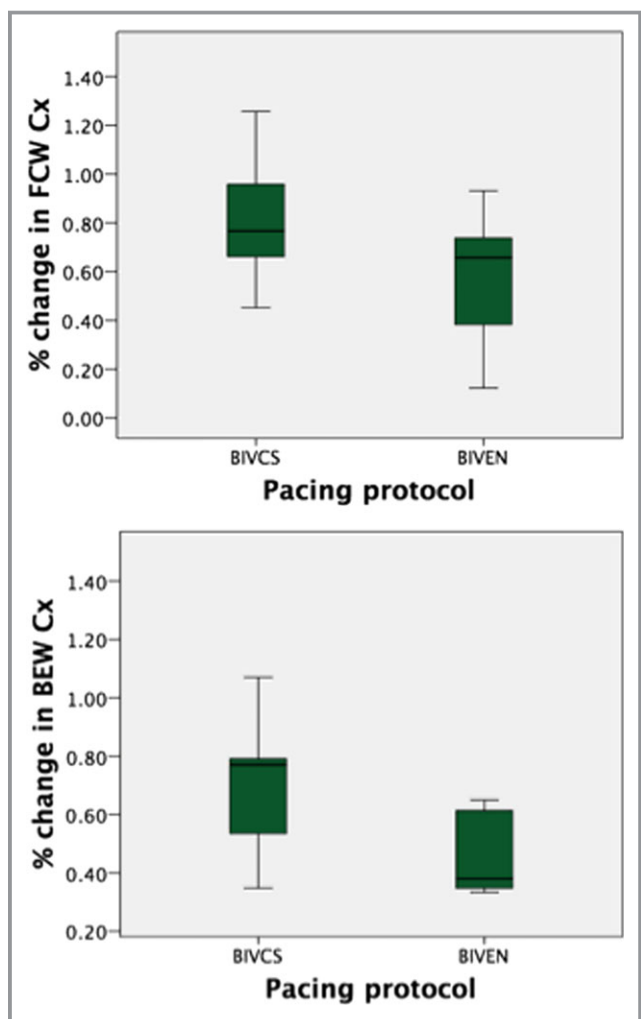


Figure 6. Percentage change from baseline of area above the BEW and below the FCW in the Cx with different pacing regimens. BEW indicates backward expansion wave; BIVCS, conventional biventricular pacing; BIVEN, biventricular endocardial pacing; Cx, circumflex artery; FCW, forward compression wave.

It is important to interpret our findings within the context of our studied population, namely, patients who had chronically received CRT and thus potentially undergone ventricular remodeling. It is suggested that the sudden withdrawal of BIVCS results in new-onset mechanical dyssynchrony and thus acts as potential and sudden mechanical obstruction to LAD flow with attendant increases in diastolic pressures.³⁷ When BIVCS is reintroduced, this obstruction is relieved, resulting in an increase in flow. Conversely, this mechanical obstruction can be overcome during hyperemia both at baseline and with BIVCS as a result of the chronic remodeling process, resulting in similar hyperemic flows. The net effect is a reduction in CFVR when BIVCS is compared with baseline. Conversely, the flow in the Cx is relatively unaffected by the cessation of BIVCS (with a trend toward reduction in flow). In the presence of a fixed hyperemic flow, this will manifest as

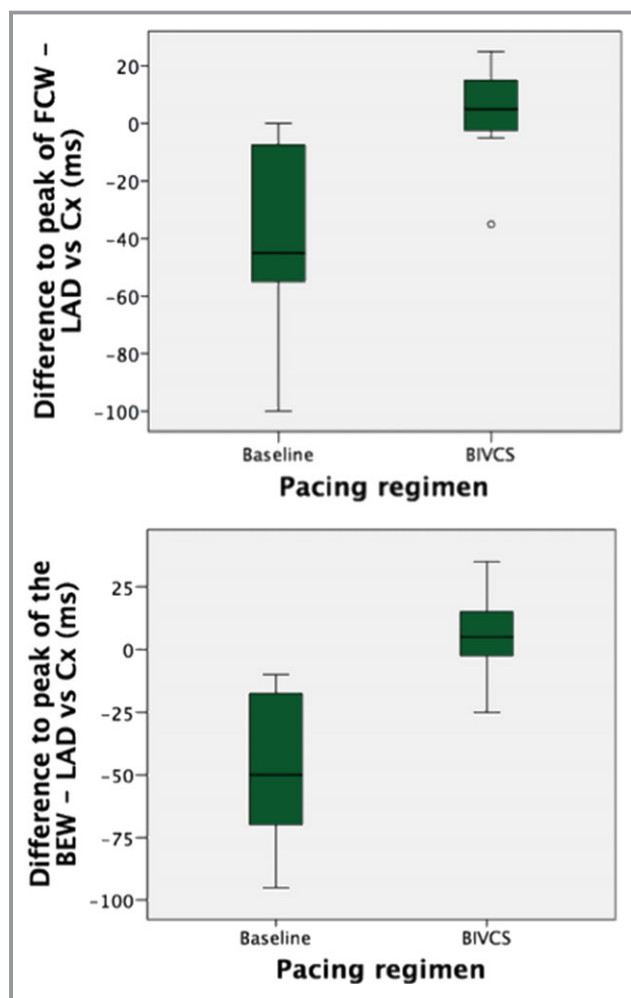


Figure 7. Coronary resynchronization: Delay between the time from R wave to peak of the FCW and BEW in the LAD artery and circumflex artery corrected by biventricular pacing. BEW indicates backward expansion wave; BIVCS, conventional biventricular pacing; Cx, circumflex artery; FCW, forward compression wave; LAD, left anterior descending artery.

the nonsignificant trend toward an increase in the CFVR with BIVCS.

The potential explanation for the increase in LAD flow with BIVCS may relate to the noted correlation between LAD APV and dP/dt_{max} . The finding is biologically attractive and accords with the work of Kyriacou et al on the effect of CRT on myocardial oxygen demand.²⁴ The increase in flow in the LAD from baseline to BIVCS could represent a physiological increase in blood flow to help meet the increased myocardial oxygen consumption required as a result of the increased contractility and septal work. Our findings, however, do not preclude a second possibility that the increase in LAD APV with BIVCS is the result of changes in microvascular resistance secondary to correction of mechanical dyssynchrony, and the wave intensity data are consistent with the hypothesis that these local factors may play an important role.

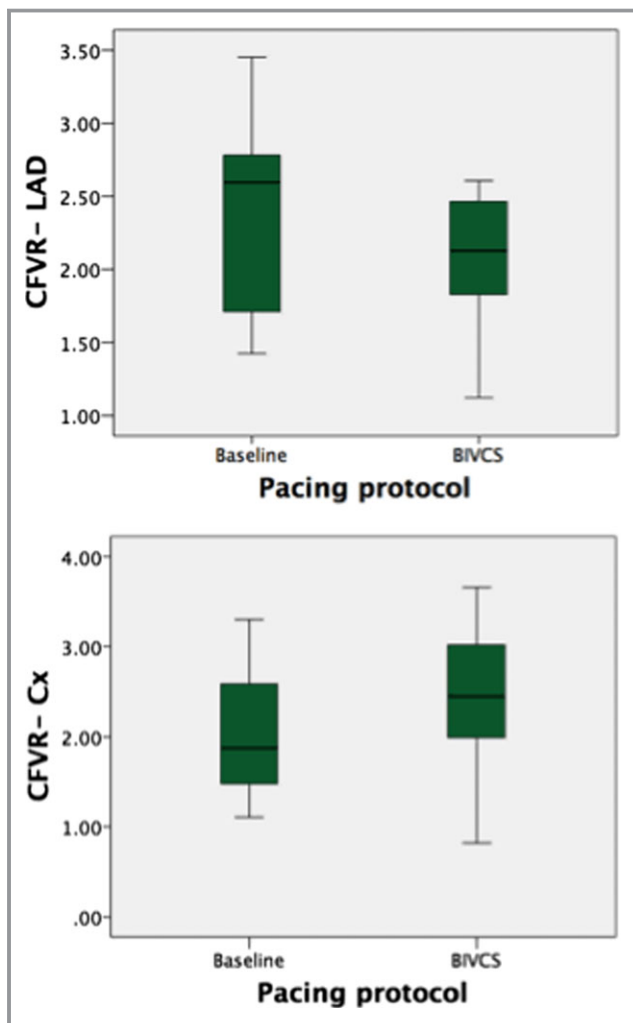


Figure 8. The effect of withdrawal of CRT on CFVR in chronically implanted CRT patients. BIVCS indicates conventional biventricular pacing; CFVR, coronary flow velocity reserve; CRT, cardiac resynchronization therapy; Cx, circumflex artery; LAD, left anterior descending artery.

Wave Intensity Analysis of Left-Sided Coronary Circulation

The increase in LAD flow with BIVCS was significantly related to an increase in flow mediated by the BEW, suggesting increased suction by improved regional relaxation of the microvasculature. The increase in LAD flow during BIVEN was related to an increase in both the FCW and the BEW. Although the reason for the increase in the BEW with BIVEN is likely similar to that proposed for BIVCS, it is suggested that the increase in the FCW in the LAD is likely related to global effects of forward propulsion and, importantly, to changes in the septal microvasculature; no increase was noted in the FCW in the Cx. This change in microvasculature might be the result of the more physiological activation pattern that LV

endocardial pacing is thought to be able to achieve by early activation of the specialized Purkinje network.³⁸

With regard to the Cx, we found a nonsignificant trend toward reduction in both the FCW and the BEW. With regard to the BEW, this would conform to the hypothesis that BIVCS reduces work in the lateral wall and thus that the local intramyocardial pressure generated to create the suction for the BEW is reduced. This combined assessment of the changes in the FCW and the BEW with different pacing regimens demonstrates that both regional and global mechanisms are involved in determining coronary flow to different parts of the myocardium. This duality is further developed considering the synchronization of timing of the FCW and the BEW in the LAD and the Cx following CRT.

Coronary Resynchronization

By measuring the time to the peak of the FCW and the BEW in both the LAD and the Cx at baseline and with BIVCS, we are able to demonstrate for the first time in humans that there is a difference between the timing of flow in the LAD and the Cx in dyssynchronous heart failure. Furthermore, we have shown that this is corrected significantly with regard to the time to peak of both the FCW and the BEW. The implications are 2-fold. First, such homogenization is suggestive of generalized cardiac resynchronization. Second, it has been recognized previously that in patients with normal coronary arteries, the waves measured in coronary flow are generated by the global effects of cardiac contraction and relaxation causing propulsion of blood forward (FCW) and suction of blood backward (BEW), respectively. Changes in the sizes of waves have been correlated to wall thickness in concentric hypertrophy, suggesting that waves are dependent on the myocardium and microvasculature per se and are not just generated by the intracavity pressure gradients.¹⁰

Our findings relating to dyssynchronous heart failure and the effect of BIVCS are the first to demonstrate the effect of both regional and global forces on the coronary waves. It is proposed that the ability of CRT to homogenize this timing suggests that dyssynchrony causes regional changes in the microvascular energetics that can be corrected with biventricular pacing. With regard to the FCW, timing is homogenized to a time point between the time to peak of the LAD and the Cx at baseline. This accords with the concept that the FCW is generated by the forward propulsion of blood down the coronary arteries as a result of LV systolic contraction. Conversely, the homogenization of the larger BEW is achieved largely by a reduction in the time to peak of the BEW in the Cx rather than a significant change in LAD timing. This is biologically attractive because any negative pressure generated in the LV cavity in diastole relies on the microvasculature as a conduit to create the suction for the BEW. Consequently,

delayed lateral wall relaxation before resynchronization of this conduit will result in a delayed time to peak in the BEW in the Cx and reduction of the time to peak of the BEW that we observed following CRT.

From the clinical perspective, our study offers potentially new explanations of how conventional CRT may exert its benefit. It is suggested that changes in coronary blood flow and wave energy need to be investigated in prospective studies at the time of implant to determine whether they may offer a role in patient selection. As noted, neither electrical resynchronization nor correction of mechanical dyssynchrony have been found to be accurate predictors of response to CRT.³ Although changes in coronary hemodynamics are also unlikely to be single predictors of response, it may be that they have roles in a more integrated patient-selection pathway in difficult cases or can be used as a target for optimization in nonresponders using emerging noninvasive techniques.^{3,39} Further dedicated studies are required to assess these potential clinical applications.

There is evidence that BIVEN has an acute effect on LV function beyond conventional CRT, but further research is necessary to determine the mechanisms by which this occurs. It is again suggested that this be performed at the time of device implant, with attention paid to coronary wave energetics as a component of such studies.¹⁷ Such research is increasingly required as device manufacturers begin to market BIVEN systems.⁴⁰ It is highly desirable that we have an understanding of the mechanistic effects of such systems before their use in the clinical environment becomes routine.

Study Limitations

The patients studied were not selected for any particular clinical characteristics and reflect a real-world CRT population; however, our sample size was small, and it is important that we remain guarded about the generalizability of our results to the whole CRT population. Nevertheless, the number of patients studied is equivalent to other similar invasive studies.^{11,41} The invasive procedural burden for patients is very high and is not suitable for routine clinical practice; however, emerging noninvasive techniques to measure wave intensity are increasingly being described and may allow larger studies to be performed.³⁹ All patients studied were chronically implanted with CRT devices. This makes extrapolation of our findings to preimplant patients difficult, although many of the findings could be amplified in the preimplant population. The prolonged time between implantation of the device and study participation means that any association of blood flow changes, wave energetics, and response to CRT is unclear. As noted, further studies at the time of implant are required. By fixing the heart rate, we controlled for the effect that changes in chronotropy can

cause to inotropy (the Bowditch effect); however, this does prevent reflex heart rate regulation to changes in inotropy.

Conclusions

The data presented develop our understanding of coronary physiology in dyssynchronous heart failure with biventricular pacing beyond the left main coronary artery and give new insight into the effect of regional and global mechanics as well as coronary wave energies on coronary flow. BIVCS and BIVEN increased the microcirculation-derived BEW in the LAD with no change in the Cx. The time to peak of the BEW was homogenized in the LAD and the Cx following CRT. These findings suggest that the coronary BEW is susceptible to changes in local forces rather than dependent solely on increased global LV systolic and diastolic function, as was reported previously.¹¹ The demonstrated increase in LAD coronary flow with an increase in the LAD FCW with endocardial rather than epicardial pacing offers an exciting mechanism to further increase coronary flow and may be mediated by a more favorable and physiological activation pattern of the left ventricle.

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Disclosures

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**Effects of Epicardial and Endocardial Cardiac Resynchronization Therapy on Coronary Flow:
Insights From Wave Intensity Analysis**

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