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FETO is a minimally invasive procedure in which a tiny balloon is inserted into the fetus to plug the trachea. The balloon is inflated, left in place for several weeks to allow the fetus’ lungs to grow, then removed a few weeks prior to delivery.
Regional and Global Strain Changes During Biventricular Pacing in a Porcine Model of Acute Left Ventricular Volume Overload

Alice Wang, BA, Santos E. Cabrera, MBA, T. Alexander Quinn, PhD, Marc E. Richmond, MD, Bin Cheng, PhD, Henry M. Spotnitz, MD

Objectives—Biventricular pacing may ameliorate symptoms of acute heart failure. Speckle-tracking echocardiography can assess cardiac function to elucidate mechanisms of benefit. Accordingly, radial and circumferential strain and radial and circumferential strain synchrony were measured with speckle-tracking echocardiography during biventricular pacing in a model of left ventricular (LV) volume overload.

Methods—Heart block was established in 4 open-chest anesthetized pigs. Left ventricular volume overload was induced with an ascending aorta-LV apex conduit. Measurements included cardiac output by an aortic flow probe, the maximum derivative of LV pressure versus time \( (dP/dt_{max}) \), and transseptal pressure synchrony. Biventricular pacing was performed for combinations of 3 interventricular delays and 3 LV pacing sites. Speckle-tracking echocardiographic analysis was applied to short-axis images at the midpapillary LV for 9 pacing combinations. Strain and synchrony parameters were correlated with hemodynamics.

Results—Increased cardiac output correlated with improved global circumferential strain \( (P = .002) \) but not changes in global radial strain or radial strain synchrony. Increased LV \( dP/dt_{max} \) was associated with improved circumferential strain in the septum \( (P < .001) \) and radial strain in the lateral wall \( (P = .046) \). Improved transseptal pressure synchrony was associated with improved global circumferential strain, but primarily in the septum \( (P < .001) \). Aortic valve closure occurred before peak radial strain in 62% of beats and before peak circumferential strain in 6%.

Conclusions—During acute LV volume overload, hemodynamic improvement with biventricular pacing was associated with improved circumferential strain primarily in the septum. Radial strain and radial strain synchrony did not correlate with improvement, possibly due to delayed systolic contraction. An increase in circumferential strain in the septum associated with optimum transseptal pressure synchrony suggested improvement by interventricular assist from the right ventricle.

Key Words—biventricular pacing; speckle-tracking echocardiography; volume overload

Cardiac resynchronization therapy, or permanent biventricular pacing, is commonly used to treat patients with chronic heart failure from systolic dysfunction with a prolonged QRS duration. This therapy improves symptoms and systolic function and may not increase myocardial oxygen consumption. Several recent studies have investigated the role of biventricular pacing for acute-on-chronic myocardial dysfunction, suggesting that...
Temporary biventricular pacing may improve outcomes in selected patients undergoing open heart surgery. The response to both temporary and permanent biventricular pacing, however, is unpredictable, necessitating a better understanding of the mechanism of improvement to derive optimal benefit for the maximum number of patients.

To achieve this goal, studies of biventricular pacing have been conducted in pure acute heart failure animal models. Our laboratory studied optimized biventricular pacing in acute right ventricular (RV) failure due to pressure overload. Our initial attempts to model left ventricular (LV) failure with aortic stenosis were unstable, and mitral regurgitation models resulted predominantly in dysfunction of the RV. A modification of the model of LV failure due to volume (LV volume overload) described by Welch et al. finally proved useful. In this model, optimized biventricular pacing with LV paced first improved cardiac output, transseptal pressuresynchrony, and ventricular systolic function.

Global LV function appeared improved through interventricular assist, but regional analysis of cardiac function was not available to confirm. Speckle-tracking echocardiography, a relatively novel strain imaging technique, quantifies regional LV deformation and synchrony without limitations of angle dependence and tethering that occur with tissue Doppler imaging. Speckle-tracking echocardiographic analysis of strain and synchrony has shown promise in predicting the response to biventricular pacing and has been used to investigate the mechanism of benefits of biventricular pacing. The effects of temporary biventricular pacing on LV global or regional strain and synchrony in our acute LV volume overload model, as well as the relationship between these indices and hemodynamic parameters, were not previously assessed. Accordingly, we used speckle-tracking echocardiography to analyze echocardiograms obtained previously to examine the mechanism of the benefits of biventricular pacing in acute LV volume overload.

Materials and Methods

Studies were performed according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The experimental protocol was approved by the Columbia University Institutional Animal Care and Use Committee. The experimental protocol has been previously described in detail. Briefly, 6 male Yorkshire pigs (40–50 kg) underwent proper anesthesia, mechanical ventilation, median sternotomy, and pericardiotomy. To stabilize the preparation, a 0.008-ml/kg/h intravenous drip of vasopressin was initiated. Four of the 6 pigs had adequate echocardiograms for speckle-tracking echocardiographic analysis. A solid-state pressure transducer catheter (5F; Millar Instruments, Houston, TX) was inserted into the RV through the apex to measure instantaneous pressures. Pressure in the LV was monitored by a similar catheter, inserted retrograde across the aortic valve via the left carotid artery. An ultrasonic flow probe (24-mm diameter; Transonic Systems, Ithaca, NY) was placed around the ascending aorta to measure instantaneous aortic volume flow. Bipolar temporary epicardial pacing leads (Medtronic, Houston, TX) were clipped to the right atrial appendage and sewn onto the anterior surface of the RV. To vary the LV pacing site, a custom multielectrode temporary pacing array composed of bipolar pacing leads (Capsure Epi 4968; Medtronic) sutured to a Gore-Tex patch (W. L. Gore & Associates, Newark, DE) was placed within the pericardial space posterior to the LV and secured in place. This apparatus allowed rapid testing of biventricular pacing from the obtuse margin and posterior descending artery. An additional pacing lead was sewn onto the surface of the LV at the apex.

A modified version of a preparation described by Welch et al. was used for induction of acute LV volume overload (Figure 1A). This process involved creation of an ascending aorta-to-LV apex conduit from a DLP cannula (12F; Medtronic) with the midsection replaced by a segment of the thoracic aorta harvested from another animal and stored in lactated Ringer and formalin (2.0%) solution. An ultrasonic flow probe was placed around the tissue segment of the conduit (10-mm diameter; Transonic Systems) to measure backward flow from the aorta to the LV.

Biventricular Pacing Protocol

The pacing leads were connected to a custom temporary external biventricular pacing unit containing a shock-mounted permanent biventricular pacing device (InSync III 8042; Medtronic). Dual-chamber RV pacing was initiated with a heart rate of 100 beats/min and an atrioventricular delay of 150 milliseconds. A complete atrioventricular block was established by atrioventricular node ablation with injection of 0.1-mL aliquots of 100% ethanol into the region of the bundle of His, which allowed complete control of the myocardial activation sequence. The surgical tubing clamps were gradually released until flow through the aortic-LV conduit was 30% of total LV output.

After 1 hour of overload, the pacing mode was converted to atrioventricular synchronous biventricular pacing, and the presence of the atrioventricular block and proper sensing and pacing function of the leads and pacing array was confirmed. Interventricular pacing delay was tested at +80, 0, and –80 milliseconds (positive interventricular pacing.
delay indicates RV-first pacing). For each interventricular pacing delay, the LV pacing site was tested at the obtuse margin, posterior descending artery, and LV apex with 9 total combinations. Each combination was tested for 10 seconds. Animals were humanely killed at the conclusion of the experiment.

**Hemodynamic Data Acquisition and Analysis**

Hemodynamic signals were sampled by an analog-to-digital converter (ADInstruments, Milford, MA) and recorded on a personal computer (Apple Computer, Cupertino, CA). Offline analysis was performed using custom routines implemented in MATLAB (The MathWorks, Natick, MA). Briefly, end diastole in each ventricle was defined as the point immediately before the rate of ventricular pressure change exceeded 10% of the maximum derivative of LV pressure versus time \((dP/dt_{\text{max}})\). Cardiac output was calculated by integrating the aortic flow signal over each cardiac cycle, which included all flow (effective forward flow plus retrograde flow), as the flow probe was placed proximal to the conduit. Ventricular systolic function was assessed by \(dP/dt_{\text{max}}\). Transseptal pressure synchrony was calculated as the area enclosed by the normalized RV-LV pressure diagram as a measure of global mechanical interventricular synchrony. This parameter expressed synchrony based on RV-LV pressure during the complete cardiac cycle, with a value of 0 indicating complete synchrony and a maximum value of 1 indicating complete asynchrony. Variables were averaged over the entire testing interval, excluding any ectopic cardiac cycles.

**Echocardiographic Analysis**

Short-axis echocardiograms at the midpapillary muscle level were obtained with a handheld 5.0-MHz transducer (GE-Vingmed Ultrasound AS, Horten, Norway) applied gently to the epicardium by an experienced echocardiographer. Echocardiograms were taken after each of the 9 biventricular pacing combinations with ventilation held to eliminate effects of respiration. Images were analyzed using commercially available speckle-tracking software (EchoPac; GE-Vingmed Ultrasound AS). Only images of high quality with adequate views of all myocardial segments were analyzed. Frame rates were set to a range between 50 and 90 Hz, allowing for adequate temporal resolution and frame-by-frame tracking of stable patterns of natural acoustic markers. The region of interest was carefully drawn by a manual point-and-click method along the endocardial border at end systole. The region of interest was inspected over a single beat and was adjusted if any of the segments did not properly track during any portion of the cardiac cycle. Results were averaged over 3 consecutive beats. Aortic valve closure was defined as the frame coincident with the smallest cross-sectional area, and end diastole was defined as the frame coincident with the largest cross-sectional area. Global radial and circumferential strain were calculated as the greatest average percent change in strain compared to end diastole for anteroseptal, septal, lateral, and posterior segments to focus on the interventricular septum and free wall. Regional strain in the septum was calculated as the average of anteroseptal and septal segments, and regional strain in the free wall was calculated as the average of lateral and posterior segments. Radial strain synchrony and circumferential strain synchrony were calculated as the standard deviation of the time to peak strain of the 4 sections. Thirty-six segments per pig were processed and reported.

**Figure 1.** An ascending aorta (Ao)-to-LV apex conduit created volume overload. An ultrasonic flow probe on the ascending aorta and on the conduit measured flow, and pressure micromanometers measured LV and RV pressure generation (A). Long-axis LV echocardiograms in systole (B) and diastole (C) show diastolic regurgitation. Short-axis LV echocardiograms at baseline (D) and after 10 minutes of volume overload (E) show 48% dilatation.
Statistical Methods

All associations were analyzed under linear mixed effects models in which random subject effects were included to account for within-subject correlations. \( P < .05 \) was considered statistically significant.

Results

Echocardiographic data were recorded in 6 pigs in LV volume overload. Average hemodynamics before, immediately after, and 1 hour after LV volume overload are listed in Table 1. Long-axis images of the LV in systole and diastole (Figure 1, B and C) reveal diastolic regurgitation. Representative short-axis images of the LV at baseline and after 10 minutes of aorta-to-LV conduit flow show a 48% increase in end-diastolic area (Figure 1, D and E). Image quality was adequate for speckle-tracking echocardiographic analysis, with full visualization of epicardial borders, in 4 pigs. A total of 144 segments were analyzed. Left ventricular \( \frac{dP}{dt_{\text{max}}} \) and transseptal pressure synchrony data were available in 4 pigs and cardiac output in 3.

Peak radial strain occurred after aortic valve closure in 62% of beats analyzed, whereas peak circumferential strain occurred after aortic valve closure in only 6% of beats analyzed. Figure 2 illustrates representative radial strain waveforms for pacing combinations of an apex/interventricular pacing delay of −80 milliseconds (Figure 2A) and a posterior descending artery/interventricular pacing delay of −80 milliseconds (Figure 2B). There was improvement in both global radial strain and radial strain synchrony with the apex/interventricular pacing delay of −80 milliseconds, but improvement in the synchrony of peak strain occurred predominantly after aortic valve closure, which may explain the lack of hemodynamic improvement. Figure 3 illustrates representative circumferential strain waveforms for pacing combinations of an obtuse margin/interventricular pacing delay of 0 milliseconds (Figure 3A) and a posterior descending artery/interventricular pacing delay of 0 milliseconds (Figure 3B). There was greater global circumferential strain with the combination of the obtuse margin/interventricular pacing delay of 0 milliseconds compared to the posterior descending artery/interventricular pacing delay of 0 milliseconds before aortic valve closure and also a better correlation with improvements in cardiac output.

Global speckle-tracking echocardiographic indices analyzed included global radial and circumferential strain and radial and circumferential strain synchrony. Estimated coefficients of the associations between global speckle-tracking echocardiographic indices against hemodynamics during the 9 biventricular pacing combinations are listed in Table 2. Improvements in global radial strain are reflected by more positive values; thus, a positive coefficient indicates correlation with improved global radial strain. Improvements in global circumferential strain are reflected by more negative values; thus, a negative coefficient indicates correlation with improved global circumferential strain. Improvement in global circumferential strain was significantly associated with increases in cardiac output and optimized transseptal pressure synchrony. The coefficient, however, was positive between global circumferential strain and transseptal pressure synchrony (and negative between global radial strain and transseptal pressure synchrony), as a transseptal pressure synchrony value of 0 indicates complete mechanical interventricular synchrony. Changes in global radial strain and radial strain synchrony were not significantly associated with improvement in hemodynamics.

Regional speckle-tracking echocardiographic indices analyzed included radial and circumferential strain in the septum and free wall. Estimated correlations between regional speckle-tracking echocardiographic indices and hemodynamics during the 9 biventricular pacing combinations are listed in Table 2. Radial strain in the lateral wall and circumferential strain in the septum were correlated with LV \( \frac{dP}{dt_{\text{max}}} \). Improvement in circumferential strain in the septum was associated with improvement in transseptal pressure synchrony. Again, this coefficient was positive because improved negative circumferential strain was associated with improved transseptal pressure synchrony, where 0 indicates complete mechanical interventricular synchrony.

Discussion

Echocardiography has been used in attempts to define the mechanisms of action of biventricular pacing and to elucidate indices of ventricular dysfunction likely to respond to both temporary and permanent biventricular pacing. Standard 2-dimensional, pulsed Doppler, tissue Doppler, and M-mode echocardiography have been equivocal in predicting the response to biventricular pacing when compared to current ejection fraction and QRS duration criteria. More recently, speckle-tracking echocardiography has shown promise in defining strain and synchrony parameters that predict the response to biventricular pacing. Speckle-tracking echocardiography has also been useful in detecting subclinical dysfunction and elucidating myocardial mechanics. This study further shows the benefit of speckle-tracking echocardiography in defining the association between regional myocardial strain and synchrony and LV systolic function during acute LV volume overload.
Table 1. Average Hemodynamics Before, Immediately After, and After 1 Hour of Volume Overload

<table>
<thead>
<tr>
<th>Hemodynamic Index</th>
<th>Baseline</th>
<th>Acute</th>
<th>After 1h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>101 (0)</td>
<td>101 (0)</td>
<td>101 (0)</td>
</tr>
<tr>
<td>Aortic pressure, mm Hg</td>
<td>85.0 (12.2)</td>
<td>81.4 (14.5)</td>
<td>72.1 (74)</td>
</tr>
<tr>
<td>Flow, L/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aorta</td>
<td>2.3 (0.6)</td>
<td>3.1 (0.3)</td>
<td>2.4 (0.8)</td>
</tr>
<tr>
<td>Graft</td>
<td>NA</td>
<td>0.7 (0.4)</td>
<td>0.6 (0.36)</td>
</tr>
<tr>
<td>LV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-diastolic pressure, mm Hg</td>
<td>7.6 (3.5)</td>
<td>8.4 (3.7)</td>
<td>7.2 (1.5)</td>
</tr>
<tr>
<td>Peak LV pressure, mm Hg</td>
<td>102.6 (18.0)</td>
<td>101.1 (20.6)</td>
<td>90.4 (12.6)</td>
</tr>
<tr>
<td>dP/dt\text{max}, mm Hg/s</td>
<td>729.2 (147.5)</td>
<td>759.1 (157.2)</td>
<td>674.1 (151.0)</td>
</tr>
<tr>
<td>RV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-diastolic pressure, mm Hg</td>
<td>3.4 (1.6)</td>
<td>3.5 (1.7)</td>
<td>2.8 (1.5)</td>
</tr>
<tr>
<td>Peak RV pressure, mm Hg</td>
<td>15.8 (2.4)</td>
<td>171 (3.0)</td>
<td>15.6 (2.0)</td>
</tr>
<tr>
<td>dP/dt\text{max}, mm Hg/s</td>
<td>151.0 (34.1)</td>
<td>155.4 (37.3)</td>
<td>1479 (28.6)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD). NA indicates not applicable.

Figure 2. Representative waveforms of radial strain with pacing combinations of the apex LV pacing site with the LV paced first (interventricular pacing delay, –80 milliseconds; A) and posterior descending artery LV pacing site with the LV paced first (interventricular pacing delay, –80 milliseconds; B). In this example, the apical pacing site with the LV paced first yielded a cardiac output of 3.48 L/min, whereas the posterior descending artery with the LV paced first yielded a cardiac output of 3.52 L/min. There was improvement in both synchrony and global strain with the pacing combination shown in A, which did not, however, greatly affect hemodynamics.

Figure 3. Representative waveforms of circumferential strain with pacing combinations of the obtuse margin pacing site/interventricular pacing delay of 0 milliseconds (A) and posterior descending artery pacing site/interventricular pacing delay of 0 milliseconds (B). The obtuse margin/interventricular pacing delay combination had greater systolic global circumferential strain, represented by the dotted white line.
Global indices such as cardiac output and LV $dP/dt_{\text{max}}$ alone cannot provide this insight. We demonstrate the use of speckle-tracking echocardiography to elucidate the mechanism of benefit of temporary biventricular pacing on myocardial mechanics during acute LV volume overload.

Our results reveal interesting patterns in LV strain and synchrony with biventricular pacing during LV volume overload. Work in the radial direction is shown to be inefficient, with peak radial strain frequently occurring after aortic valve closure. Postsystolic shortening has been reported as a possible early indicator of ischemia. In this model of acute LV volume overload, radial strain may be a more sensitive indicator of myocardial dysfunction than circumferential strain.

Improvements in global circumferential strain correlate with increases in cardiac output from biventricular pacing, but global radial strain did not despite clear improvements. The minimal correlation of global radial strain with hemodynamics may reflect substantial contraction after aortic valve closure. Qualitative improvements in peak radial strain thus lead to ineffective myocardial work against a closed valve. When using a global strain parameter to assess hemodynamic function, attention should thus be given to the degree of postsystolic strain. In this model of LV volume overload, circumferential strain corresponds better to hemodynamic changes.

Neither radial strain synchrony nor circumferential strain synchrony correlated with hemodynamic improvement. Ng et al. reported no significant correlation between radial strain synchrony and the ejection fraction in healthy volunteers. The relationship between radial and circumferential strain synchrony and hemodynamics has not been established in a model of LV volume overload. In particular, the effect of regurgitation through the LV apex on the timing of myocardial strain has not been well characterized. Improvement in radial strain synchrony was also seen frequently after aortic valve closure, possibly explaining why qualitative improvement in radial strain synchrony also did not correlate with improvement in hemodynamics. In addition, we defined synchrony as the standard deviation of the time to peak strain to focus on the relationship of peak function between the ventricular segments. The relationship between systolic or diastolic synchrony and hemodynamics would thus be an interesting target for future studies.

Although global changes in radial strain did not contribute to hemodynamics, regional radial strain in the free wall significantly correlated with LV $dP/dt_{\text{max}}$ during biventricular pacing. This increase predominantly in free wall radial strain has also been observed in an RV pressure overload model created by our laboratory. Both models used similar pacing protocols with an epicardial lead placed in the posterior aspect of the LV, which may account for the improvement in free wall radial strain.

The data from this study support our previously published view that the acutely failing LV can be assisted by RV work transmitted through the interventricular septum during biventricular pacing in LV volume overload. This hypothesis is supported by the demonstration of improved regional circumferential strain in the septum concomitant with improved LV $dP/dt_{\text{max}}$ and transseptal pressure. Although optimum transseptal pressure synchrony correlated with improved global circumferential strain, regional analysis showed that this correlation was only significant with improvement of circumferential strain in the septum. Other investigators have also studied septal strain and function during cardiac dysfunction: Hayabuchi et al. showed that circumferential strain was greater in the septum in a pediatric population with RV

### Table 2. Comparison of Speckle-Tracking Echocardiographic Indices and Hemodynamics

<table>
<thead>
<tr>
<th>Index</th>
<th>Cardiac Output, L/min</th>
<th>LV $dP/dt_{\text{max}}$, mm Hg/s</th>
<th>Transeptal Pressure Synchrony</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial strain, %</td>
<td>1.32 (.626)</td>
<td>0.011 (.130)</td>
<td>−1.65 (.810)</td>
</tr>
<tr>
<td>Radial strain synchrony, SD</td>
<td>0.59 (.963)</td>
<td>0.001 (.991)</td>
<td>30.39 (.335)</td>
</tr>
<tr>
<td>Circumferential strain, %</td>
<td>−0.96 (.022)</td>
<td>−0.006 (.124)</td>
<td>4.26 (.003)</td>
</tr>
<tr>
<td>Circumferential strain synchrony, SD</td>
<td>−14.91 (.557)</td>
<td>−0.068 (.619)</td>
<td>65.82 (.127)</td>
</tr>
<tr>
<td>Regional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral wall radial strain, %</td>
<td>2.54 (.417)</td>
<td>0.016 (.046)</td>
<td>3.36 (.655)</td>
</tr>
<tr>
<td>Septal wall radial strain, %</td>
<td>0.09 (.971)</td>
<td>0.006 (.419)</td>
<td>−6.62 (.315)</td>
</tr>
<tr>
<td>Lateral wall circumferential strain, %</td>
<td>−0.64 (.118)</td>
<td>0.001 (.903)</td>
<td>0.27 (.893)</td>
</tr>
<tr>
<td>Septal wall circumferential strain, %</td>
<td>−1.35 (.287)</td>
<td>−0.009 (.001)</td>
<td>796 (&lt;.001)</td>
</tr>
</tbody>
</table>

$P$ values are given in parentheses; $P < .05$ indicates a significant correlation.
pressure overload than in controls; Serri et al. showed that biventricular pacing improved septal radial strain with a corresponding decrease in free wall radial strain; and Gimelli et al. showed that cardiac resynchronization therapy improved perfusion predominantly in the septum in patients with volume overload. Our study correlates an increase in septal circumferential strain with direct hemodynamic measurements.

Results of this analysis shed additional light on the mechanism of temporary biventricular pacing in LV volume overload and the importance of postsystolic strain and its relationship with hemodynamics. The study was limited by the small sample size, which was due in part to the technical difficulty of the surgery and in part to the difficulty obtaining complete epicardial borders with echocardiography in the dilated LV. Due to the low sample size, we were not sufficiently powered to analyze the effects of the interventricular pacing delay and pacing site combination on strain or synchrony, which would be an objective for future studies.

In conclusion, the correlation of circumferential strain with cardiac output is superior to radial strain and radial strain synchrony in assessing the response to biventricular pacing in a model of acute LV volume overload, possibly because peak radial strain occurs mainly after aortic valve closure. Improved circumferential strain in the interventricular septum during biventricular pacing correlates with improvements in LV \( \frac{dp}{dt}_{\text{max}} \) and transseptal pressure synchrony, consistent with the concept that interventricular assist by the RV can support LV function during acute failure due to LV volume overload.

References


