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RABKIN, D.G., ET AL.: Mechanisms of Optimized Biventricular Pacing in Pulmonary Stenosis: Effects on Left Ventricular Geometry in Swine. We tested the hypothesis that optimized biventricular pacing (BiVP) enhances cardiac output (CO) during critical pulmonary stenosis (PS) by attenuating distortions in left ventricular (LV) geometry. Following median sternotomy in six anesthetized pigs, heart block was induced by ethanol ablation. During epicardial, DDD BiVP, atrioventricular delay (AVD) was varied from 60 ms to 180 ms in 30 ms increments. At the AVD with the highest CO right-left delay (RLD) was varied from (+) 80 ms (RV first) to (−) 80 ms (LV first) in 20 ms increments. At each pacing setting, aortic flow, ECG, and LV diameter were measured in the control state (CON) and during PS, created by snaring the pulmonary artery until CO decreased 50%. Short axis LV echocardiograms were obtained at (+) and (−) 80 ms. In CON, RLD had no effect on function or geometry. During PS optimum BiVP resulted in significant increases in CO (1.12 L/min ± 0.13 SEM at RLD = +40 ms versus 0.92 ± 0.12 at RLD = 0 and 0.73 ± 0.08 at RLD = −80), and LV fractional shortening (8.97% ± 0.51% at RLD = +40 ms versus 7.34% ± 0.58% at RLD = 0 and 6.21% ± 0.66% at RLD = −80). In addition, LV eccentricity with (−) RLD was significantly different versus CON at both end-diastole (0.79 ± 0.07 vs 1.02 ± 0.03, P = 0.011 Student’s t-test) and end-systole (0.83 ± 0.05 vs 1.00 ± 0.02, P = 0.017). However, with (+) RLD differences versus CON were not significant at either end-diastole (0.88 ± 0.06 vs 0.99 ± 0.03) or end-systole (0.92 ± 0.03 vs 1.01 ± 0.03). In swine hearts with PS, optimized BiVP increases CO, fractional shortening, and LV symmetry. BiVP warrants further study as treatment for acute postoperative heart failure. (PACE 2004; 27:1060–1071)

biventricular pacing, heart failure, ventricular geometry, pig, pulmonary stenosis, echocardiography

Introduction

Cardiac resynchronization therapy (CRT), also known as biventricular pacing (BiVP), attempts to normalize the atrioventricular activation sequence and abnormal ventricular contraction patterns often seen in dilated cardiomyopathies by simultaneous stimulation of both ventricles or by advanced stimulation of a late activated region. One significant advantage of this therapy is the improvement of myocardial performance without increases in myocardial energy metabolism.1 This allows for improvements in myocardial efficiency, unlike the use of inotropes, which exacerbate discrepancies between the supply and demand of energy.2 Traditionally, BiVP has been advocated for the treatment of chronic heart failure. This therapy might also be useful in the perioperative setting during weaning from cardiopulmonary bypass after cardiac surgery at which time different forms of heart failure are commonly encountered.

Data from the INSYNC III trial indicate that optimization of the right-left pacing delay (RLD) doubles the improvement in stroke volume (SV) obtained by BiVP versus control.3 However, although many patients derive impressive clinical benefit from CRT, results are inconsistent, selection criteria are not fully developed, and effects are unpredictable. The current experiment examines the mechanism of BiVP optimization of cardiac output (CO) in acute pulmonary stenosis (PS) by testing the hypothesis that the mechanism is related to improvements in left ventricular (LV) geometry.

Materials and Methods

All animals received humane treatment in compliance with the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources, National Research Council, and published by the National Academy
EXPERIMENTAL BIVENTRICULAR PACING

Press, revised 1996. In addition, the experiment was approved by the Institutional Animal Care and Use Committee of Columbia University.

Nine male domestic pigs weighing 35–45 kg were anesthetized with atropine sulfate (1-2 mg intramuscularly), ketamine hydrochloride (20 mg/kg intramuscularly), and xylazine (0.5 mg/kg). Animals were intubated, placed on mechanical ventilation and maintained on isoflurane (1.5%–2.5%) mixed with 100% oxygen. A heating pad was used to maintain body temperature, and the ECG recorded. The peripheral arterial pressure was monitored via the femoral artery. Arterial blood gases and serum electrolytes were periodically checked to monitor oxygenation and optimize ventilation. During the experiments, 0.9% saline solution was administered through an 18 gauge angiocatheter in an ear vein at 10 mL/kg per hour for the first hour and then decreased to 5 mL/kg per hour for the duration of the study.

After midline sternotomy and longitudinal pericardiotomy, animals were systemically heparinized (100 U/kg) and instrumented with a right ventricular (RV) micromanometer (Millar Instruments, Houston, TX, USA) and a transit-time ultrasonic flow probe (Transonic Systems Inc., Ithaca, NY, USA) placed around the ascending aorta. A pair of ultrasonic crystals (Triton, San Diego, CA, USA) was placed on the anterior and posterior epicardial surfaces of the LV at midventricle to measure LV anterior-posterior diameter. A snare was placed around the main pulmonary artery (PA). A bipolar right atrial (RA) sensing lead (Medtronic Inc., Houston, TX, USA) was split such that each proximal electrode was connected to a different temporary external pacemaker (5388, Medtronic). Bipolar epicardial pacing leads were then placed on the anterior surface of the RV and posterior surface of the LV. The atrioventricular delay (AVD) was defined as the interval from atrial depolarization to the earliest ventricular activation. In other words, the pacemaker for the ventricle that was to be paced first was set with a shorter AVD. The pacemaker for the ventricle to be paced second was set with a longer AVD, thus, the RLD was determined by the difference in AVDs between the two temporary pacemakers (i.e., AVD = 150, RLD = +40 is established by the RV pacemaker set at AVD of 150 ms and the LV pacemaker at 190 ms). The pacemakers were programmed to asynchronous ventricular sensitivity to prevent inhibition of the second pacemaker during biventricular pacing with an RLD.

Once proper function of the pacemaker leads was confirmed, complete heart block (CHB) was established by injection of 0.5 mL aliquots of 100% ethanol into the region of the Bundle of His using the surgeon’s (DGR) finger through a right atrial purse-string suture to guide the needle. In two of the animals, while attempting to establish CHB, the RV promptly dilated and became akinetic resulting in hemodynamic instability; these animals were excluded from the study. Another animal was lost as the result of a ventilator failure. In the remaining six animals, after establishment of CHB, during epicardial, DDD BiVP, AVD was varied between 60 and 180 ms in 30 ms increments. At the optimal AVD (defined by CO), RLD was varied from +80 ms (RV first) to −80 ms (LV first) in 20 ms increments at the animals’ atrial sinus rate. Representative ECG tracings along with RV pressure and systemic arterial pressure are shown while the RLD is being varied from (+) 60 ms to (−) 60 ms (Fig. 1).

After data were collected in CON, the snare around the main PA was tightened such that the baseline CO declined by 50% to induce critical PS. After several minutes to allow normalization of hemodynamics, the pacing protocol was repeated for PS. Once data were collected, the snare was released and hemodynamics were allowed to normalize over a period of 5 minutes. CO was again recorded to be certain that the induction of critical PS did not result in sustained alterations in myocardial performance. When baseline CO was achieved in the steady state the pericardial well was filled with water-soluble echocardiography gel (Ultraphonic scanning gel, Pharmaceutical Innovations, Inc., Newark, NJ, USA). Echocardiograms were obtained (Vingmed CFM 800, GE Medical, Milwaukee, WI, USA) for LV cross-sectional short-axis measurements using a handheld 5.0 MHZ ultrasound transducer during both CON and critical PS at (+) 80 ms and (−) 80 ms RLD. The snare was then released and CO measured to assess the stability of the model. Animals were humanely sacrificed at the conclusion of the experiment. Representative data during both CON and critical PS are shown in Figure 2.

Data Acquisition and Analysis

ECG, peripheral arterial pressure, RV pressure, LV anterior-posterior diameter, and aortic flow velocity were sampled at 200 Hz and transferred through a 16-channel analog to digital converter (MacLab, ADInstruments Inc, Milford, MA, USA) to a personal computer (iMac, Apple Computer, Cupertino, CA, USA). CO was determined by integrating aortic flow velocity over time during one complete respiratory cycle free of arrhythmias at each experimental phase. A statistical modeling procedure (described below) was used to determine the effects of AVD and RLD on CO. Fractional shortening (FS) was calculated using the ultrasonic crystal
Figure 1. Representative ECG tracing, RV pressure and systemic arterial pressure as right-left delay (RLD) is changed in 20 ms increments from (+) 60 ms to (−) 60 ms. Note decreases in systemic arterial pressure without changes in RV pressure as RLD becomes more negative. RVP = right ventricular pressure; MAP = mean atrial pressure.

Figure 2. Representative data: Changes in hemodynamics and LV geometry from (+) 60 ms right-left delay (RLD) to (−) 60 ms right-left delay (RLD) with and without pulmonary stenosis. Heavy dashed lines represent change from (+) to (−) RLD reflected by the shifting morphology of the ECG. Note the higher RV pressures during pulmonary stenosis. The cardiac output averaged 0.9 L/min with an RLD of (+) 60 ms during PS and 0.7 L/min with an RLD of (−) 60 ms, fractional shortening represented by the percentage change in LV diameter is clearly greater during a (+) RLD as well. During the control state cardiac output remained 1.4 L/min as the RLD was changed from (−) to (+) 60 ms. The change in fractional shortening is also less dramatic during the control state. ECG = electrocardiogram, RVP = right ventricular pressure, BP = blood pressure, LV = left ventricle.
data as the percentage change in length of the anterior-posterior diameter from end-diastolic diameter (EDD) to end-systolic diameter (ESD).

\[ FS = \frac{(EDD - ESD)}{EDD} \]  

where EDD and ESD were defined as the maximum and minimum diameters recorded during end-expiration respectively.

**Echocardiographic Analysis**

Images were recorded to videotape during real-time data acquisition using the Vingmed CFM 800 echocardiography machine. End-diastolic (ED) and end-systolic (ES) short-axis cross-sectional (SACS) images were planimetered by hand. The diameter from the septum to the free wall was designated \( D_1 \) and the diameter that perpendicularly bisected \( D_1 \), from the anterior to posterior wall, was designated \( D_2 \). The eccentricity index (EI) was calculated as the ratio of \( D_1/D_2 \) for ED and ES during both CON and critical PS. Area ejection fraction (EFa) was determined by measuring ED area (EDA) and ES area (ESA) and using the equation:

\[ EFa = \frac{(EDA - ESA)}{EDA} \]

**Statistical Analysis**

For modeling the changes in CO and FS across the various levels of AVD and RLD, mixed modeling via the PROC MIXED procedure in SAS was used by a qualified statistician (ADW). This approach estimates the standard errors by modeling the covariance structure of the repeated measures. These measures are inherently correlated within each subject. Three of the more common covariance structures include “compound symmetry” (cs), for correlations that are constant for any two points in time, “auto-regressive order one” (ar1), for correlations that are smaller for time points further apart, and “unstructured” (un), which has no mathematical pattern within the covariance matrix. Other covariance structures tested included the Toplitz (toep) and the Heterogeneous Compound Symmetry structure (csh). EDA, ESA, EFa, and EI during CON and PS with (+) 80 and (−) 80 ms RLD were compared using a two-tailed paired Student’s t-test.

**Results**

Change in RLD affected CO during critical PS but not during CON. Heart rate was stable across RLDs during PS in each animal (Table I). Optimized RLD correlated with optimized FS, greatest EDD, and a more symmetrical LV chamber.

Figure 3A shows the effect of AVD on CO during CON and critical PS. There were no significant effects of AVD on CO in either CON or PS. Figure 3B is similar to 3A but is designed to reveal trends around the optimal AVD which can be masked by using absolute values, since different animals had different optimal AVDs. Trends in both CON and PS reveal decreases in CO as the AVD deviates in both directions from the optimal settings, but these were not statistically significant.

Figure 4A shows the effect of RLD on CO during CON and critical PS. During CON the highest CO resulted from an RLD = 0 ms. Changes in RLD in either direction from this point resulted in decreases in CO that were not statistically significant. During PS, the highest CO occurred at an RLD of (+)40 ms and became progressively worse as RLD became more negative. Differences across RLD during PS were statistically significant. During PS, optimized settings resulted in a CO = 1.12 L/min ± 0.13 at an RLD of (+)40 ms which was a 21% improvement over simultaneous BiVP (CO = 0.92 ± 0.12), and a 54%

**Table I.**

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Figure 3. (A) Effect of atrioventricular delay (AVD) on cardiac output (CO) in control state (CON) and during critical pulmonary stenosis (PS). Black squares represent CON, white squares represent PS, standard errors are represented by brackets. Differences in CO are not statistically significant in either CON or PS. (B) Similar to Figure 3A, however AVD offset from the optimal setting is represented on the abscissa rather than absolute AVD in order to expose trends masked by animal specific optimal settings. Differences in CO are not statistically significant for either CON or PS.
**Figure 4.** (A) Effect of right-left delay (RLD) on cardiac output (CO) in control state (CON) and during critical pulmonary stenosis (PS). Black squares represent CON, white squares PS. Standard errors are represented by brackets. There is a statistically significant decline in CO as RLD becomes more negative during PS ($P < 0.0001$ mixed modeling repeated measures ANOVA) but no effect during CON. (B) Effect of deviations from the optimal RLD on cardiac output. Similar to Figure 4A, however the RLD with the best cardiac output for each animal is labeled 'optimal' regardless of the absolute value. Then the values at 20 ms increments before and after the optimal value are averaged to produce this figure. This exposes trends around the optimal value which are hidden by Figure 4A since optimal values are animal-specific and averaging the absolute values can mask the trends. Statistically significant differences across RLD exist for both CON, ($P = 0.0035$ mixed modeling repeated measures ANOVA) where the optimal setting is midway between the extremes, and PS ($P = 0.0053$ mixed modeling repeated measures ANOVA), where the optimal setting is 40 ms positive to the midpoint.
improvement over the worst settings ([−]80 ms) (CO = 0.73 ± 0.08, P = 0.0001). Figure 4B is analogous to 3B, as it is designed to reveal trends around the optimal RLD which can be masked in Figure 4A. There was a significant variation in the points in both CON (P = 0.0035) and PS (P = 0.0053). More interestingly, in considering only an increase in RLD from the optimum setting, CO significantly decreased (P = 0.0492).

Figure 5A demonstrates the effect of RLD on LV anterior-posterior diameter measured by somaticrometry at both ED and ES. RLD has no effect on LV anterior-posterior diameter in CON at ED. During ES there are differences in this diameter across the range of RLD during CON, however no clear pattern emerges with respect to RLD. During critical PS, as RLD becomes more positive, EDD becomes slightly larger (P = 0.099) while ESD becomes smaller (P = 0.0001). Figure 5B is similar to 5A but shows the FS of the anterior-posterior diameter. As in Figure 5A, in CON RLD had no effect on FS, while during PS FS was increased with

Figure 5. (A) Effect of right-left delay (RLD) on LV short-axis diameters during control state (CON) and critical pulmonary stenosis (PS) at end-diastole (ED) and end-systole (ES). White icons represent CON, black icons represent PS. Squares represent ED, circles represent ES. At ED there are no significant changes in LV short-axis diameter over the range of RLD during CON, during PS, increases in LV diameter as RLD becomes more positive approach statistical significance (P = 0.09 mixed modeling repeated measures ANOVA). Similarly, at ES, no statistically significant trends emerge during CON, while during PS there are statistically significant differences in LV diameter across the range of RLD (P = 0.02 mixed modeling repeated measures ANOVA). The vertical arrows demonstrate fractional shortening derived from the diameter data. (B) Fractional shortening (FS) is calculated from LV short-axis diameters and is represented on the ordinate while RLD is represented on the abscissa. Black icons represent CON, white icons represent PS. Differences in FS across RLD are statistically significant during PS (P = 0.0001 mixed modeling repeated measures ANOVA) but not during CON. (C) Effect of deviations from the optimal RLD on FS. Black icons represent CON, white icons represent PS. In both CON and PS there is a statistically significant decline in FS as RLD deviates in the negative direction with respect to the optimal delay (P = 0.002 mixed modeling repeated measures ANOVA). For the control state, the optimal RLD is in the middle of the examined range while for the PS state the optimal RLD is 40 ms positive to the middle of the range.
* $p = 0.0001$ change in FS across RLD (repeated measures ANOVA)

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$^* p = 0.002$ change in FS over RLD (repeated measures ANOVA)

$^{**} p = 0.0001$ change in FS over RLD (repeated measures ANOVA)

Figure 5. Continued
a (+) RLD (P < 0.001). Figure 5C demonstrates the effect of deviations from the optimum RLD on FS. Interestingly, as RLD becomes more negative from the optimal setting, FS significantly decreases for both PS (P < 0.001) and CON (P < 0.005) with a more pronounced effect during PS. This can be seen in the representative data shown in Figure 2 where a (+) RLD results in greater FS in both CON and PS.

Figure 6 contains representative data from one animal during PS showing the effect of RLD on LV chamber geometry. Table II shows average changes in EI and EFα as RLD is changed from (+) 80 to (−) 80 ms in both CON and PS. There were no statistically significant differences in EI at either ED or ES for either CON or PS as RLD was changed from positive to negative using paired Student’s t-tests. However, during PS, echocardiograph derived EI with (−) RLD were significantly different versus CON at both ED (0.79 ± 0.07 vs 1.02 ± 0.03, P = 0.011) and ES (0.83 ± 0.05 vs 1.00 ± 0.02, P = 0.017), while (+) RLD differences versus CON were not significant at either ED (0.88 ± 0.06 vs 0.99 ± 0.03) or ES (0.92 ± 0.03 vs 1.01 ± 0.03). During PS in animals #2 and #5 (both of which had an optimal RLD of +60 ms) the EI are markedly more symmetric (closer to 1) during +80 ms RLD; other animals (optimal RLD less than +60 ms) show an attenuated response. Similarly, for EFα the most impressive responses are shown in the same two animals. These changes correlate with the animals in which the optimal RLD is closest to (+) 80 ms. The biggest changes in CO during PS as RLD is varied from (+) to (−) 80 ms occurred in animals.

![Figure 6](image-url)

**Figure 6.** Select echocardiographic images taken from animal #2 (optimal right-left delay (RLD) = +60 ms). All images are taken during pulmonary stenosis (note dilated RV in all four images). Images in column on left are taken at end-diastole (ED), those in column on right are taken at end-systole (ES). In the top row, the images are taken during a positive 80 ms RLD (note positive R wave deflection of superimposed ECG), in the bottom row the images are taken during a negative 80 ms RLD (note negative R wave deflection of superimposed ECG). There was no effect of RLD on LV chamber geometry in the control state. The positive 80 ms RLD (top two images) attenuated distortions in LV chamber geometry demonstrated during the negative 80 ms RLD (bottom two images). Note septal flattening and LV chamber deformity in the bottom two panels.
Table II.

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AVERAGE ± SEM

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<td>0.92 ± 0.03</td>
<td>0.83 ± 0.05**</td>
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— = data unavailable; *p = 0.011 versus CON end-diastole; **p = 0.017 versus CON end-systole.

#4 and #5. Average changes in CO from (+) to (−) 80 ms were significant (P = 0.007).

Discussion

This study explores optimal pacing strategies in acute heart failure due to PS. Our results demonstrate that BiVP with a (+) RLD enhances FS of the LV anterior-posterior diameter and partially normalizes LV eccentricity. It remains unclear how stimulating the RV slightly before the LV improves LV functional geometry. One hypothesis is that optimized pacing reduces RV end-diastolic pressure (EDP) and increases LV EDP restoring a normal trans-septal pressure gradient.

An important flaw in our study design was the prospective decision to obtain echocardiograms at fixed RLDs (+ and −80 ms). This strategy proved problematic because, as shown in Figure 4B, deviations from the optimal RLD of as little as 20 ms result in substantial decreases in CO. In future studies we plan to obtain and analyze echo images at all RLDs studied. Both individual echo images (Fig. 6) and average data (Table II), suggest improvement in symmetry when comparing (+) 80 to (−) 80 ms RLD during PS. Differences in EFs were not significant, but both end-diastole and end-systole EI decreased significantly during PS with a (−) 80 ms RLD compared to controls. In retrospect, the echocardiographic images suggest that the septal-LV free-wall diameter (designated D1 in our study) changes more dramatically when BiVP is optimized during PS than does the D2 diameter, which is the one we measured. Asymmetrical shortening of the minor semiaxes may explain qualitative differences in effects of RLD on CO versus FS during PS (Figs. 4A and 5B). Furthermore, CO is dependent on LV end-diastolic volume (LVEDV) as well as FS. While Figure 4A shows larger differences in CO between control and PS than are apparent in FS in Figure 5B, a concurrent trend toward increased LVEDV is suggested by increasing EDA. LVEDV is estimated to increase from 38.8 to 40.1 mL in control and 20.3 to 23.8 mL in PS, as RLD changes from (−) 80 to (+) 80 ms (Table III). These calculations are based on our prior validation studies. Our sonomicrometry data suggest that optimized timings during BiVP improve LV mechanics by increasing EDD and decreasing ESD. The resolution required to fully define the mechanisms underlying these changes will require more sophisticated technology than used here. Possibilities include MRI, fast CT, multocrystal sonomicrometry, and three-dimensional echocardiography.

Previous studies have demonstrated an effect of AVD on CO both in humans and in experimental animals. Optimized timing orchestrates the sequence of valve closure and ventricular contraction leading to maximized ventricular filling. In our study, although there were trends toward improved CO at AVDs in the middle of the
examined range (Fig. 3B), these changes were not statistically significant. One explanation for this apparent discrepancy is the lack of power in our data. Another possibility is that chemical ablation of the Bundle of His caused a varying degree of injury to the septum affecting ventricular mechanics in unpredictable ways. This will be examined in future studies using segmental wall motion analysis.

An important variable in BiVP is lead location,\textsuperscript{7,8} and multisite pacing has recently shown clinical benefit after open heart surgery.\textsuperscript{9} We did not assess effects of lead location, but acknowledge that RV free-wall lead location, septal pacing, and multisite pacing are appropriate subjects for future studies.

Studies of the consequences of RV pressure and volume loading on LV function using sonomicrometry and echocardiography, demonstrate load-specific effects on systolic FS and EF\textsubscript{a}.\textsuperscript{10} Although ours is the first attempt to examine the relationship between optimized BiVP and pathological loading conditions, the idea that different loading conditions affect LV function in distinct ways suggests that therapies including BiVP should be load-specific. Previous work confirms that RV pressure loading causes a shift in the interventricular septum (IVS) toward the LV and a decrease in its radius of curvature.\textsuperscript{11–14} If optimal BiVP pacing settings increase CO by normalizing chamber geometry, septal mechanics may play an important role and provide the link between optimized RLD in BiVP and enhanced cardiac performance. Septal pacing, a strategy that we did not investigate, should be incorporated in BiVP with variable RLD in future studies.

Ventricular interdependence during RV and LV pressure or volume loading has been well described in both experimental and clinical scenarios.\textsuperscript{15,16} Specifically, previous work has demonstrated the importance of pressure loading on LV pressure-volume relations.\textsuperscript{17–21} It should be noted that our experiments were performed with an open pericardium, which presumably attenuated ventricular interdependence.\textsuperscript{11} Ventricular interdependence may be further reduced when the ventricles do not contract simultaneously. In the case of critical PS, a (+) RLD unloads the RV and appears to allow for shifting of the IVS at LV ED providing for greater LV symmetry throughout the cardiac cycle. This is supported by observations made by Klima and colleagues demonstrating the importance of septal position and contractile function on RV function and on LV-RV interaction.\textsuperscript{17} The ED position of the septum influences septal motion during systole,\textsuperscript{52–24} which the authors suggest may represent a form of septal preload. Our anectodal echocardiographic images (Fig. 6) demonstrate marked deformity of the IVS at ED during critical PS. Decompression of the RV by RV-first BiVP may allow for greater mobility of the IVS during LV systole, thus explaining improvements in LV FS and CO.

A practical issue is whether the evidence presented supports BiVP versus RV pacing alone in RV pressure overload. Figure 4B indicates that the qualitative benefit of BiVP at the optimum RLD was approximately a 10% increase in CO when compared to the earliest RV pacing timing tested. This difference was significant by trend analysis (P < 0.05). In future studies of this issue, RV pacing alone should be compared to optimized BiVP. More recent data from our laboratory demonstrate a statistically significant increase in cardiac output at an RLD of (+) 40 ms versus at (+) 80 ms.\textsuperscript{25}

Previous studies have demonstrated that when RV pressure is increased acutely, RV failure occurs and is associated with ischemia of the RV free wall.\textsuperscript{26,27} These studies and others\textsuperscript{28} suggest that RV function could be improved simply by increasing systemic arterial pressure, presumably by enhancing right coronary driving pressure. We did not measure right coronary flow during our experiments, but this is an important consideration and our results might in part be explained by enhanced RV perfusion. Finally, changing load by another manner, such as caval occlusion, and evaluating the pacing response would help address the cause and effect relationship between pathological ventricular load and optimized pacing.

This experiment confirms preliminary work demonstrating the load dependence of optimized BiVP\textsuperscript{25,20} settings and advances that study by

### Table III.

<table>
<thead>
<tr>
<th>Control</th>
<th>PULMONARY STENOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal</td>
<td>(+) 80 ms</td>
</tr>
<tr>
<td>1</td>
<td>9.48</td>
</tr>
<tr>
<td>2</td>
<td>9.64</td>
</tr>
<tr>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>11.82</td>
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<tr>
<td>5</td>
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<td>6</td>
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<tr>
<td>AVE</td>
<td>11.0</td>
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<tr>
<td>LVEDV</td>
<td>40.1</td>
</tr>
</tbody>
</table>

LVEDV<sub>echo</sub> = 4.4(LVEDA) − 8.3

— = data not available.
correlating optimal RLD with enhanced FS. These data, combined with the selected echocardiographic images, suggest that optimized BiVP works by attenuating distortions in LV geometry imposed on the LV during pathological RV loading conditions. Further study of experimental BiVP is warranted to help define pacing protocols in the perioperative setting.

Clinical implications of the present results merit consideration. Acute pulmonary embolism, acute RV failure after cardiac transplantation in the presence of pulmonary hypertension, primary pulmonary hypertension, and selected forms of congenital heart disease are hemodynamically similar to the conditions of this experiment. The possible value of RV preexcitation in this setting is intriguing. In considering these issues, however, our data do not assess or prove benefits of biventricular pacing compared to normal sinus rhythm in pressure overload of the normal RV.

References