Load dependence of cardiac output in biventricular pacing: Right ventricular pressure overload in pigs

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Background: The effect of biventricular pacing on stroke volume is believed to be dependent on right ventricular/left ventricular delay, but effects in individual patients are unpredictable. This variability may reflect relative right and left ventricular volume and/or pressure overloads. Accordingly, we tested the hypothesis that the relation of cardiac output to right ventricular/left ventricular delay is load dependent in a pig model of pulmonary stenosis.

Methods: After median sternotomy in 6 anesthetized, domestic pigs, complete heart block was induced by ethanol ablation. During epicardial, atrial tracking DDD biventricular pacing, atrioventricular delay was varied between 60 and 180 ms in 30-ms increments. Right ventricular/left ventricular delay was varied at each atrioventricular delay from +80 ms (right ventricle first) to -80 ms (left ventricle first) in 20-ms increments. Aortic flow, right ventricular pressure, peripheral arterial pressure, and electrocardiogram were measured in the control state and during pulmonary stenosis, created by tightening a snare around the pulmonary artery until cardiac output decreased by 50%.

Results: Atrioventricular and right ventricular/left ventricular delay had no effect on cardiac output during the control state, but during pulmonary stenosis there was a statistically significant ($P = .0001$, repeated-measures analysis of variance) right ventricular/left ventricular delay-related trend toward higher cardiac output with right ventricular pacing first. This effect was more pronounced when the optimal atrioventricular delay was determined first, resulting in a 20% increase in cardiac output when the optimal right ventricular/left ventricular delay was compared with simultaneous biventricular pacing.

Conclusions: Optimized biventricular pacing in swine is associated with increased cardiac output during acute pulmonary stenosis, but not during the control state. Further studies are needed to determine whether specific types of right ventricular and left ventricular overload predictably affect the relation between right ventricular/left ventricular delay and cardiac output.

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Hear failure caused by idiopathic dilated cardiomyopathy results in intraventricular conduction delays in up to 30% to 50% of patients^{1,2} leading to asynchronous ventricular contraction, left ventricular (LV) systolic dysfunction,³ and impaired prognosis.⁴ The effect of sequence of ventricular activation on function has interested physiologists since the first experiments with ventricular pacing. Although contemporary permanent endocardial pacing is commonly done

from the apex of the right ventricle, it is now widely known that the location and number of pacemaker leads affects the sequence of ventricular activation and the efficiency of ventricular function. Activation of the endocardium of the right and left ventricles by the His-Purkinje system is nearly instantaneous in the normal heart, whereas single site ventricular pacing propagates in a relatively slow fashion over the ventricular surface. Cardiac resynchronization therapy, also known as biventricular pacing (BiVP), aims to normalize the atrioventricular activation sequence and disturbed ventricular contraction patterns by simultaneous stimulation of both ventricles, or by advanced stimulation of a late activated region.⁵ One of the appeals of this therapy is its capacity to improve myocardial efficiency by increasing mechanical performance, not through alteration of myocyte function but through enhanced ventricular synchrony.

Recent multicenter trials provide objective clinical evidence that cardiac resynchronization therapy is effective. The MIRACLE trial, conducted in patients with dilated cardiomyopathy, a QRS complex of 120 ms or greater, and ejection fraction (EF) less than 35%, demonstrated small but significant improvement in subjective and objective measures of exercise tolerance and cardiac function.⁶ This led to Food and Drug Administration approval of biventricular pacemakers and leads for “permanent” pacing. Data from the INSYNCH III trial indicate that optimization of the right ventricular/left ventricular (RV/LV) pacing delay (RLD) doubles (from 5% to 12%) the improvement in stroke volume (SV) obtained by BiVP versus control.⁷ Experimental data suggest that increased SV can be obtained at no cost in myocardial oxygen consumption, thus increasing mechanical efficiency of the heart.⁸⁻¹⁰ BiVP with adjustable RLD might therefore be a valuable adjunct to the treatment of congestive heart failure during cardiac operations in which both right- and left-sided pressure and volume overload are commonly observed. However, although many patients derive impressive clinical benefit from cardiac resynchronization therapy, results are inconsistent, selection criteria are not fully developed, and effects are unpredictable.

Seeking to develop guidelines for the application of BiVP with an adjustable RLD to the treatment of congestive heart failure, we tested the hypothesis that the optimal RLD and atrioventricular delay (AVD) (defined by maximizing cardiac output) are specific to the type of pathologic ventricular load. Because, at present, there is no Food and Drug Administration approved pacemaker capable of temporary cardiac resynchronization therapy with adjustable RV/LV stimulation sequence, we simulated the effects of such a device using 2 temporary external pacemakers sharing a common right atrial epicardial sensing electrode. In an open chest porcine model we investigated the effect of BiVP with an adjustable RLD and AVD on cardiac output in the

control state and after the induction of RV pressure-overload through acute critical pulmonary stenosis.

Materials and Methods

All animals received humane care in compliance with the “Principles of Laboratory Animal Care” formulated by the National Society for Medical Research, and the “Guide for the Care and Use of Laboratory Animals” prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH Publication 85-23, revised 1985). In addition, the experiment was approved by the Institutional Animal Care and Use Committee of Columbia University.

Seven male domestic pigs weighing 35 to 45 kg were anesthetized with atropine sulfate (1-2 mg intramuscularly), ketamine hydrochloride (20 mg/kg intramuscularly), and xylazine (0.5 mg/kg). They were intubated, mechanically ventilated, and maintained on isoflurane (1.5%-2.5%) mixed with 100% oxygen. A heating pad was used and the electrocardiogram was recorded. The femoral artery was used to measure peripheral arterial pressure. 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 pericardiectomy, animals were systemically heparinized (100 U/kg) and instrumented with an RV micromanometer (Millar Instruments, Inc, Houston, Tex) and a flow probe (Transonic Systems Inc, Ithaca, NY) around the ascending aorta. A snare was placed around the main pulmonary artery. A bipolar right atrial (RA) sensing lead (Medtronic Inc, Houston, Tex) was split such that each proximal electrode was connected to 2 different temporary external pacemakers (Medtronic). Bipolar epicardial pacing leads were then placed on the anterior surface of the right and posterior surface of the left ventricle (Figure 1). The pacemakers were programmed to minimum ventricular sensitivity (ventricular asynchronous) to prevent inhibition of the second pacemaker during biventricular pacing with an interventricular delay.

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 (D.G.R.) finger through a right atrial purse-string suture to guide the needle.¹¹ In 1 of the animals, while we were attempting to establish CHB, the right ventricle promptly dilated and became akinetic, resulting in hemodynamic instability; this animal was excluded from the study. In the remaining 6 animals, after establishment of CHB, during epicardial, atrial tracking DDD BiVP, AVD was varied between 60 and 180 ms in 30-ms increments. For each AVD, RLD was varied from +80 ms (RV first) to -80 ms (LV first) in 20-ms increments at the animals' sinus rate (Table 1). This protocol was repeated while pacing at 100 beats/min. Representative electrocardiographic tracings while the RLD is varied from -80 ms to +80 ms are shown (Figure 2). After data were collected at the atrial sinus rate and 100 beats/min, the snare around the main pulmonary artery was tightened such that the baseline cardiac output was reduced by half. After several minutes to allow normalization of hemodynamics, the pacing

Figure 1. Schematic of biventricular pacing device. RA, Right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle. The proximal electrodes of an RA, bipolar epicardial pacing lead were split to the atrial sensing input of 2 different temporary external pacemakers. Similar leads were then attached to the RV and LV with the proximal electrodes inserted separately into the ventricular outputs of the pacemakers as demonstrated. In this way both devices receive the same atrial sensing signal and pace the RV and LV independently. In this example the effective AVD is 60 ms and the RLD is +40 ms (ie, RV is stimulated first).

protocol was repeated at the 2 specified rates. After completion of the protocol, the pulmonary artery snare was loosened, and after several minutes cardiac output was again recorded to assess the stability of the model. This order was not varied between experiments. Animals were humanely put to death at the conclusion of the experiment. Representative data both during the control state (CON) and during critical pulmonary stenosis (PS) are shown in Figure 3. Average length of the 6 experiments was 2 hours 30 minutes. Average duration of each condition (CON and PS) was roughly 25 minutes.

Data Analysis

The electrocardiogram, RV pressure, peripheral blood pressure, and aortic flow velocity were sampled at 200 Hz and transferred

TABLE 1. Protocol for adjusting RLD and AVD (in milliseconds)

RVD	60	60	60	60	60	80	100	120	140
LVD	140	120	100	80	60	60	60	60	60
RLD	80	60	40	20	0	-20	-40	-60	-80
AVD	60	60	60	60	60	60	60	60	60
RVD	90	90	90	90	90	110	130	150	170
LVD	170	150	130	110	90	90	90	90	90
RLD	90	60	40	20	0	-20	-40	-60	-80
AVD	90	90	90	90	90	90	90	90	90
RVD	120	120	120	120	120	140	160	180	200
LVD	200	180	160	140	120	120	120	120	120
RLD	80	60	40	20	0	-20	-40	-60	-80
AVD	120	120	120	120	120	120	120	120	120
RVD	150	150	150	150	150	170	190	210	230
LVD	230	210	190	170	150	150	150	150	150
RLD	80	60	40	20	0	-20	-40	-60	-80
AVD	150	150	150	150	150	150	150	150	150
RVD	180	180	180	180	180	200	220	240	260
LVD	260	240	220	200	180	180	180	180	180
RLD	80	60	40	20	0	-20	-40	-60	-80
AVD	180	180	180	180	180	180	180	180	180

RVD, Atrioventricular delay for the right ventricle; *LVD*, atrioventricular delay for the left ventricle; *RLD*, RV-LV interventricular delay; *AVD*, effective atrioventricular delay.

through a 16-channel analog to digital converter (MacLab, ADInstruments Inc, Milford, Mass) to a personal computer (IMAC; Apple Computer, Cupertino, Calif). Cardiac output was determined by integrating aortic flow velocity over time during one complete respiratory cycle free of arrhythmias. For each experimental phase, cardiac output was calculated. A statistical modeling procedure (described below) was used to determine the effects of heart rate, AVD, and RLD on cardiac output. To determine the effect of AVD on cardiac output, the RLD was kept at zero and the AVD was changed while the aortic flow velocity was recorded. QRS duration was calculated by determining the time between departure and return to baseline of the electrocardiogram during ventricular contraction.

Statistical Analysis

For modeling the changes in cardiac output across the various levels of AVD and RLD, mixed modeling via the PROC MIXED procedure in SAS (SAS Institute, Inc, Cary, NC) was used. This approach estimates the standard errors by modeling the covariance structure of the repeated measures. These measures are inherently correlated within subject. Three of the more common covariance structures include “compound symmetry” (cs), for correlations that are constant for any 2 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 Toplitiz (toep) and the Heterogeneous Compound Symmetry structure (csh).

Results

The effects of AVD on cardiac output during CON and PS at the animals’ atrial sinus rate are shown in Figure 4, A.

CSP

Figure 2. Representative data demonstrating electrocardiographic changes during changes in RLD from -80 ms to $+80$ ms in 20-ms increments.

There were no statistically significant effects of AVD on cardiac output either during CON or PS. Cardiac output was significantly decreased ($P < .05$) in PS versus CON at each AVD. Figure 4, *B* represents the effect of AVD on cardiac output when the optimal AVD was first determined for each animal, then change in AVD away from the optimal AVD is represented on the abscissa. These differences were not statistically significant for either CON or PS, but the graphs demonstrate physiologic trends in cardiac output around the optimum. Similar trends occurred at each RLD.

The effect of RLD on cardiac output during CON and PS is shown in Figure 5, *A*. Cardiac output for the 5 AVDs were averaged at each RLD to obtain this figure. During CON, at both the animals' atrial sinus rate and during pacing at 100 beats/min, there were no differences in cardiac output as RLD was varied from $+80$ ms to -80 ms. However, at the animals' atrial sinus rate during PS there was a statistically significant ($P < .0001$, repeated-measures analysis of variance [ANOVA]) RLD-related trend toward higher cardiac output with RV pacing first ($+RLD$). Cardiac output averaged 1.05 ± 0.45 L/min (SD) at $+80$ ms and 0.79 ± 0.26 L/min at -80 ms. Figure 5, *B* is similar to Figure 5, *A* but shows the effect of deviations from the optimal RLD on cardiac output for the PS state at the 2 heart rates. The purpose of this is to expose trends around the optimum RLD, which can be obscured when averaging animals with different optimal settings. There was a significant difference in cardiac output as the RLD was varied from the optimum for both rates (atrial sinus rate $P = .009$, while paced at 100 beats/min $P = .0001$, repeated-measures ANOVA).

Figure 6, *A* demonstrates the effect of RLD on cardiac output after the optimal AVD was determined for each animal. In other words, with an RLD of zero the AVD that produced the best cardiac output was determined. Then, using that AVD, the RLD was varied from $+80$ to -80 ms

and those cardiac outputs were averaged to produce this figure. During CON at both heart rates, an RLD of zero produced the best cardiac output with drops in cardiac output developing at the extremes (beyond ± 60 ms). However, during PS at both heart rates, the best cardiac output was at an RLD of $+40$ ms, representing a 20% increase over an RLD of zero during the animals' atrial sinus rate and a 14% increase over an RLD of zero during pacing at 100 beats/min. Differences in cardiac output over changes in RLD were statistically significant during PS at the atrial sinus rate ($P < .001$ repeated-measures ANOVA). Figure 6, *B* similar to Figure 5, *B* demonstrates the effect of deviations from the optimal RLD on cardiac output at the optimal AVD. Differences in cardiac output are significant at both rates ($P = .0001$ repeated-measures ANOVA).

Table 2 demonstrates the effect of pacing site on QRS duration (a measure of asynchrony of activation). In CON, QRS duration rose from a baseline of 76.7 ± 2.1 ms (SEM) to 114.0 ± 3.9 ms during spontaneous ventricular contraction after the establishment of CHB. The QRS duration was 126.7 ± 7.4 ms during RV only pacing, 132.5 ± 5.9 ms during LV only pacing, and 88.3 ± 2.8 ms during BiVP after the establishment of CHB.

Average heart rate before CHB was 72.8 ± 3.5 (SEM). After the establishment of CHB, in CON the atrial sinus rate was 81.2 ± 6.7 , while during critical PS the atrial sinus rate was 86.8 ± 6.0 ($P = .065$, Mann-Whitney test). The atrial sinus rates were significantly lower than the rates while the animals were paced at 100 beats/min ($P < .01$ ANOVA). Heart rates did not change significantly within each animal as the RLD was varied from $+80$ ms to -80 ms in either the CON state or during critical PS.

The average cardiac output in the CON state with an RLD of zero at the beginning of the experiment was 1.50 ± 0.44 (SEM). At the conclusion of the experiment, when the

Figure 3. Representative data demonstrating changes in hemodynamics during change in RLD from -60 ms to $+60$ ms in both the control state and during critical PS. *Thick lines* indicate the moment the RLD was changed from -60 ms to $+60$ ms. *RVP*, Right ventricular pressure; *BP*, blood pressure. PS is demonstrated by increased RVP and decreased cardiac output. In this example, cardiac output was 0.9 L/min during PS with a $+60$ -ms RLD, 0.7 L/min during PS with a -60 -ms RLD, and 1.4 L/min during the control state at both $+60$ -ms and -60 -ms RLD. Also note improvements in systemic arterial blood pressure during PS as the RLD is changed from -60 ms to $+60$ ms.

snare around the main pulmonary artery was loosened, the average cardiac output with an RLD of zero was 1.68 ± 0.38 (SEM) ($P = .66$ Student t test).

Discussion

This study indicates that BiVP with an optimized AVD and RLD significantly enhances cardiac output in the intact porcine heart during critical PS but not during the CON state. Although the settings were animal specific, in each case the cardiac output improved during PS when the RV was stimulated first. This trend was preserved when animals were paced at 100 beats/min although it was less pronounced. These results suggest that the relationship between cardiac output and optimized BiVP settings is load dependent. Should this relationship be predictable, objective criteria might be developed to guide the use of cardiac resynchronization therapy in different clinical scenarios.

The present experiment is the first, to our knowledge, to investigate the relationship between optimal BiVP settings

and type of cardiac pathophysiology. We used a simple model to simulate RV pressure overload, the stability of which is confirmed by a return to baseline cardiac output after release of the pulmonary artery snare. Our model of CHB resulting in ventricular asynchrony and our use of BiVP appear to be valid. Using the QRS duration as a measure of the synchrony of activation, we were able to successfully resynchronize the ventricles after the establishment of CHB through BiVP (Table 2).

In this study we focused on the effect of heart rate, AVD, and RLD on cardiac output. Physiologically we know that pacing site may be as or more important to optimizing ventricular function¹²⁻¹⁴ and this variable should be incorporated in future studies. To our surprise, cardiac output consistently dropped when animals were paced at 100 beats/min compared with their atrial sinus rates. Heart rate can be a critical determinant of cardiac output in pathologic circumstances in which the stroke volume is fixed and cannot

Figure 4. A, Effect of AVD on cardiac output with and without critical PS. These data are taken during simultaneous biventricular pacing (RLD = 0). *Black squares* represent controls and *white squares* represent PS. There is no treatment effect overall ($P = .696$), other than what existed at baseline (AVD = 60), that is, no interaction effect; the slopes of the 2 lines are similar. For each AVD the cardiac output during PS was significantly reduced ($P < .01$ Student t test) versus control. B, Effect of deviations from the optimal AVD on cardiac output. The AVD with the highest cardiac output was determined for each animal in each state and that AVD is labeled "optimum" on the abscissa. Cardiac outputs are averaged at AVD intervals of 30 ms before and after the optimum. Differences were not statistically significant.

respond to increases in preload. However, in our model cardiac output was more closely related to venous return than heart rate, suggesting that stroke volumes dropped substantially, presumably due to reduced ventricular filling. The relationship between AVD and cardiac output is believed to act primarily through optimization of ventricular filling.¹⁵ Figures 4, A and B support this mechanism by demonstrating a curvilinear relationship between AVD and cardiac output. However, we did not formally investigate this relationship with independent measures of preload; this should be a component of future studies.

This study showed a consistent trend towards enhanced cardiac output with (+) RLD during BiVP (Figure 5, A). This trend is more pronounced when the optimal AVD is determined first and the cardiac outputs are recorded as RLD is varied at that AVD (Figure 6, A). This suggests that the most efficient method of determining the optimal pacing settings in the clinical setting is to record cardiac outputs while the AVD is adjusted with an RLD of zero to determine the optimal AVD. Then at that AVD vary the RLD from +80 ms to -80 ms until cardiac output is optimized. Should our results be reproducible we would be able to

Figure 5. A, Effect of RLD on cardiac output in the control state and during critical PS at animals' atrial sinus rate and while being paced at 100 beats/min. *Black icons* represent the control state; *white icons*, PS; *squares*, data collected during animals' atrial sinus rate; *circles*, during pacing at 100 beats/min. The RLD in milliseconds is represented on the abscissa and average cardiac output in L/min for all 5 AVDs on the ordinate. While animals are paced at their atrial sinus rate there is a statistically significant RLD-related change in cardiac output for PS ($P = .0001$, repeated-measures ANOVA) but not for the control state ($P = .91$). Standard errors are represented by *brackets*. Differences in cardiac output while paced at 100 beats/min were not statistically significant in either state. **B,** Effect of deviations from the optimal RLD on cardiac output during critical PS at the atrial sinus rate and while paced at 100 beats/min. *White squares* represent critical PS at atrial sinus rate; *white circles* represent critical PS while paced at 100 beats/min. Standard errors are represented by *brackets*. At both rates there are statistically significant differences in cardiac output as RLD is varied in 20-ms increments from the optimum ($P < .0009$ for atrial sinus rate, $P < .0001$ for paced at 100 beats/min, repeated-measures ANOVA).

A

B

Figure 6. A, For each animal the AVD with an RLD of zero that yielded the highest cardiac output was determined. The cardiac outputs from +80- to -80-ms RLD at this AVD were averaged for each group during the control and PS states at the animals' sinus rate and during pacing at 100 beats/min. During PS at the animals' atrial sinus rate there was a statistically significant effect of RLD on cardiac output ($P = .0001$, repeated-measures ANOVA). B, Effect of deviations from the optimal RLD during critical PS on cardiac output after the optimal AVD has been established. *White squares* represent critical pulmonary stenosis at atrial sinus rate; *white circles* represent critical PS while paced at 100 beats/min. Standard errors are represented by *brackets*. At both rates there are statistically significant differences ($P < .0001$, repeated-measures ANOVA) in cardiac output as RLD is varied in 20-ms increments from the optimum.

make recommendations for the optimal settings based on patients' specific pathology making the process more efficient.

During critical PS at the animals' atrial sinus rate, when an RLD of zero (simultaneous BiVP) is compared with the best RLD (+40 ms) the cardiac output improves from 1.30 ± 0.25 L/min to 1.57 ± 0.27 L/min (SEM), which represents a 21% increase (Figure 6, A). When the best RLD is compared with the worst RLD (−60 ms), the improvement in cardiac output is 85% (0.85 ± 0.22 L/min vs 1.57 ± 0.27 L/min). When pacing at 100 beats/min the improvements in cardiac output when the best RLD is compared with an RLD of zero and the worst RLD are 14% and 38%, respectively. These data suggest that compared with simultaneous BiVP, an additional improvement in cardiac output of approximately 20% is possible by optimizing the AVD and RLD, and that the optimal settings may be load dependent. The increase in cardiac output, presumably without the expense in terms of increased myocardial oxygen demand and diminished peripheral perfusion seen with inotropes and pressors commonly used to achieve this effect, could be a major adjunct to clinicians' options when trying to enhance cardiac output in the setting of heart failure.

Advantages of BiVP with optimized RLD over single chamber pacing have been addressed in other studies (MIRACLE trial) and can be inferred from our data as well. As shown in Figure 6, A the optimal RLD during BiVP with PS at the animals' best AVD was +40 ms with cardiac output dropping substantially when the RLD was extended to +60 and +80 ms. If RV only pacing had resulted in better cardiac outputs, then we would have expected to see an increase in cardiac output as the RLD increased with a plateau effect developing as the programmed RLD approached the interventricular conduction delay seen with RV only pacing. The fact that the optimal RLD was not at the most positive setting, and that the most positive setting produced diminished cardiac outputs suggests a benefit to BiVP with optimized RLD over single chamber pacing.

The mechanism of the observed effects of RLD was not formally investigated. We speculate that the induction of critical PS made cardiac output relatively more dependent on RV function than under normal physiologic circumstances. If the RV free wall is failing due to pressure overload, then preexcitation of the RV might increase RV stroke volume. In open-chest anesthetized dogs, ventricular pacing has been shown to produce reciprocal contraction patterns in opposing sites of the left ventricle.^{16,17} Earlier activated regions shorten first and more vigorously because of their relatively low afterload. This causes regions in the opposite LV wall to be prestretched before their activation. By virtue of a local Frank-Starling mechanism, the later contractions are stronger and have a greater shortening during the ejection phase. Therefore, regional differences in

TABLE 2. Relationship between pacing site and QRS duration (in milliseconds)

Animal	Sinus rhythm (before CHB)	Sinus rhythm (after CHB)	RVP	LVP	BiVP
1	75	105	115	150	80
2	75	110	130	135	85
3	85	110	115	130	90
4	80	115	150	145	85
5	70	—	105	110	90
6	75	130	145	125	100
ave	76.7	114.0	126.7	132.5	88.3
SEM	2.1	3.9	7.4	5.9	2.8

RVP, Right ventricular pacing; LVP, left ventricular pacing; BiVP, biventricular pacing with simultaneous RV, LV stimulation; CHB, complete heart block; — = data unavailable (animal became severely hypotensive before ventricles contracted).

contraction pattern during ventricular pacing may be regarded as differences in effective local preload.¹⁷ These observations suggest that BiVP with optimized AVD and RLD might yield hemodynamic benefits over single chamber pacing by maintaining ventricular synchrony and normal regional function. In its focus on acute RV failure, this experiment is not directly transferable to recent clinical studies. Most clinical trials have dealt with dilated cardiomyopathy with chronic failure, low ejection fraction, and an interventricular conduction delay. In that setting, delayed activation of the lateral left ventricle is the primary physiologic defect, and clinical BiVP has focused on pacing this region with an electrode in lateral branches of the coronary sinus.^{6,10,14,18} Surgical studies also have shown that lateral wall pacing through the epicardial approach is effective in these patients; in some clinical studies pacing of the lateral left ventricle alone has proven effective. Thus, current clinical investigation focuses on the utility of LV pacing and localizing the pacing electrode to the point of latest electrical activation. However, this approach is not uniformly successful and the effects of BiVP are not always predictable.⁶

The present study suggests that the recent focus on LV pacing for heart failure may be inappropriate in some patients. In particular, patients with RV pressure overload may benefit from initial pacing of the right ventricle. Finally, because the present study was done in pigs with intrinsically normal myocardium and only acute heart failure, it is not certain that our data are directly transferable to the clinical setting.

Very little is known about benefits of BiVP in the perioperative setting, and little objective data are available. Similarly, the efficacy of BiVP in atrial fibrillation or right bundle branch block is not well understood. Consequently, we propose a clinical trial be undertaken to further under-

standing of the effect of BiVP in these settings. We believe that these experiments will lead to clinical pacing techniques that will be useful and possibly life saving in humans after cardiac operations.

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References

1. Farwell D, Patel NR, Hall A, et al. How many people with heart failure are appropriate for biventricular resynchronization? *Eur Heart J*. 2000; 21(15):1246-50.
2. Santini M, Ricci R. Biventricular pacing in patients with heart failure and intraventricular conduction delay: State of the art and perspectives: the European view. *Eur Heart J*. 2002;23(9):682-6.
3. Xiao HB, Brecker SD, Gibson DG. Effects of abnormal activation on the time course of the left ventricular pressure pulse in dilated cardiomyopathy. *Br Heart J*. 1992;68:403-7.
4. Xiao HB, Roy C, Fujimoto S, et al. Natural history of abnormal conduction and its relation to prognosis in patients with dilated cardiomyopathy. *Int J Cardiol*. 1996;53:163-70.
5. Breithardt O-A, Stellbrink C, Franke A, et al. Acute effects of cardiac resynchronization therapy on left ventricular Doppler indices in patients with congestive heart failure. *Am Heart J*. 2002;143:34-44.
6. Abraham WT. Rationale and design of a randomized clinical trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with advanced heart failure. The multicenter INSYNCR randomized clinical evaluation (miracle). *J Card Fail*. 2000;6:369-80.
7. Delurgio DB, Kieck GK, Greenberg J, Leon AR, Mera FV, Ransom SA. Sequential bi-ventricular pacing increases acute stroke volume compared to isolated left ventricular pacing. *Pacing Clin Electrophysiol*. 2002;25(4 Pt 2):528.
8. Barold SS. What is cardiac resynchronization therapy? *Am J Med*. 2001;111(3):224-32.
9. Ukkonen H, Beanlands RSB, Burwash IG, et al. Effect of cardiac resynchronization on myocardial efficiency and regional oxidative metabolism. *Circulation*. 2003;107:28-31.
10. Nelson GS, Berger RD, Fetters BJ, et al. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. *Circulation*. 2000;102(25):3053-9.
11. Weir EK, McMurtry IF, Grover RF. Experimental models of complete heart block. *Basic Res Cardiol*. 1975;70:446-55.
12. Raichlen JS, Campbell FW, Edie RN, Josephson ME, Harken AH. The effect of the site of placement of temporary epicardial pacemakers on ventricular fibrillation in patients undergoing cardiac surgery. *Circulation*. 1984;70(3 Pt 2):1118-23.
13. Hettrick DA, Euler DE, Pagel PS, et al. Atrial pacing lead location alters the effects of atrioventricular delay on atrial and ventricular hemodynamics. *Pacing Clin Electrophysiol*. 2002;25(6):888-96.
14. Ansalone G, Giannantoni P, Ricci R, Trambaiolo P, Fedele F, Santini M. Doppler myocardial imaging to evaluate the effectiveness of pacing sites in patients receiving biventricular pacing. *J Am Coll Cardiol*. 2002;39(3):489-99.
15. Wish M, Fletcher RD, Gottdiener JS, Cohen AI. Importance of left atrial timing in the programming of dual-chamber pacemakers. *Am J Cardiol*. 1987;60(7):566-71.
16. Badke FR, Boinay P, Covell JW. Effects of ventricular pacing on regional left ventricular performance in the dog. *Am J Physiol*. 1908; 238:H858-67.
17. Prinzen FW, Hunter WC, Wyman BT, McVeigh ER. Mapping of regional myocardial strain and work during ventricular pacing: experimental study using magnetic resonance imaging tagging. *J Am Coll Cardiol*. 1999;33:1735-42.
18. Daubert J, Linde C, Cazeau S, Sutton R, Kappenberger L, Bailleul C. Protocol design of the MUSTIC (multi-site stimulation in cardiomyopathy) study (Abstract). *Arch Mal Coeur Vaisseurs*. 1998;91:154.