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Biventricular pacing improves left ventricular function by 2-D strain in right ventricular failure

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Abstract

Background: We used speckle-tracking echocardiography to test the hypothesis that regional left ventricular (LV) strain would improve during optimized biventricular pacing (BiVP) in acute right ventricular (RV) pressure overload (PO).

Materials and methods: Complete heart block and RVPO were induced in five open-chest fully anesthetized pigs. BiVP was optimized by adjusting atrioventricular and interventricular delays to maximize cardiac output derived from an aortic flow probe. LV short axis views were obtained during atrio-RV pacing (RVP), atrio-LV pacing (LVP), and BiVP. Intraventricular synchrony was assessed by comparing speckle-tracking echocardiography-derived time to peak (TTP) strain in the anterior septal (AS) and posterior wall segments. Segmental function was assessed using radial strain.

Results: Cardiac output was higher with optimized (RV first) BiVP than with L VP (0.96 ± 0.26 L/min *versus* 0.89 ± 0.27 L/min; $P = 0.05$). AS TTP strain (502 ± 19 ms) during LVP was prolonged *versus* BiVP (392 ± 58 ms) and *versus* RVP (390 ± 53 ms) ($P = 0.0018$). AS TTP strain during LVP was prolonged *versus* posterior (502 ± 19 ms *versus* 396 ± 72 ms, $P = 0.0011$). No significant difference in TTP strain in these segments was seen with BiVP or RVP. Posterior strain ($20\% \pm 5\%$) increased 66% *versus* AS strain ($12\% \pm 6\%$) during BiVP ($P = 0.0029$). A similar increase occurred during RVP (posterior $20\% \pm 3\%$ *versus* AS $12\% \pm 7\%$, $P = 0.0002$). Posterior strain did not increase during LVP.

Conclusions: BiVP and RVP restore intraventricular LV synchrony and increase regional function *versus* LVP during RVPO. RV pre-excitation unloads the RV and reduces the duration of AS contraction, facilitating synchrony of all LV segments and increasing free wall LV contraction.

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Keywords

Speckle-tracking echocardiography; Mechanical dyssynchrony; Acute right ventricular failure

1. Introduction

Acute right ventricular (RV) failure is a well-recognized problem after acute pulmonary embolism, after cardiac transplantation, during pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension, and during surgical correction of congenital heart disease. Registry data from the International Society of Heart and Lung Transplantation show that, despite advances in perioperative management, RV dysfunction accounts for 50% of all cardiac complications and 19% of all early deaths in patients after heart transplantation [1]. Current therapies for the failing RV are limited to preload optimization, vasopressors and vasodilators to adjust afterload, and inotropic support to improve contractility [2]. Mechanical circulatory assistance is available for end-stage RV failure.

Clinical studies have demonstrated that pathologic increases in pulmonary pressures not only affect the RV, but also worsen left ventricular (LV) synchrony and function and alter function of the interventricular septum. Dohi *et al.* [3] used speckle-tracking echocardiography (STE) to demonstrate LV regional dyssynchrony with paradoxical motion of the interventricular septum in patients with chronic RV pressure overload (RVPO). Takamura *et al.* [4] showed that acute pulmonary embolism reduces LV strain in patients. They concluded that coordination of radial LV wall motion plays a key role in the short-term regulation of cardiac output (CO) in patients with acute pulmonary embolism.

These observations suggest that resynchronization therapy based on biventricular pacing (BiVP) might be of value in RVPO. However, there is little experience with cardiac pacing in acute RV failure [5]. Preliminary studies report improved hemodynamics with temporary atrial-RV pacing in patients with RV dysfunction and after surgery for congenital heart defects [6,7]. Our laboratory demonstrated in a pig model of critical pulmonary stenosis that sequential BiVP with RV pre-excitation can improve CO by more than 20% [8]. Potential mechanisms include increased RV contractility, improved RV and LV synchrony [9], and enhanced LV geometry and fractional shortening [10]. We have not, however, explored the effects of pacing on LV synchrony and radial strain.

STE is a novel strain imaging technique that quantifies regional LV deformation and synchrony [11]. Radial strain has been useful in assessing the response to BiVP and has been recognized as an accurate and noninvasive measure of cardiac function and mechanical synchrony [12,13]. In the current study, we apply STE to define the effects of BiVP in a RVPO model, seeking mechanisms that may be of value in clinical studies.

2. Materials and methods

2.1. Experimental protocol

All animal 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. Five male pigs (40–50 kg) were anesthetized intramuscularly with atropine (0.02 mg/kg), ketamine (20 mg/kg), and xylazine (0.5 mg/kg) and subjected to oral endotracheal intubation. They were mechanically ventilated with a rate- and volume-regulated anesthesia ventilator (Fraser Harlake, Orchard Park, NY) on a mixture of 100% oxygen and titrated (1.75%–2.5%) isoflurane to maintain 100% oxygenation. Arterial blood gases and serum electrolytes were monitored with a handheld i-STAT (Abbott Laboratories, Abbott Park, IL). Sodium bicarbonate was administered to maintain a physiologic pH of 7.4–7.6. Lidocaine was administered as an initial intravenous bolus (3 mg/kg) and continuously at 50 µg/kg/min for arrhythmia prophylaxis. To maintain blood volume, 0.9% saline solution was administered intravenously at 10 mL/kg/h for 1 h then at 5 mL/kg/h for the duration of the study. Body temperature, monitored by rectal thermometer, was maintained at 41°C with a temperature therapy pad (Gaymar Industries, Orchard Park, NY). Anticoagulation was achieved with intravenous boluses of heparin sodium (100 U/kg/h). Standard limb leads were placed for ECG monitoring. Peripheral arterial pressure was measured from the femoral artery. The chest was opened by median sternotomy using electrocautery and a sternal saw. The pericardium was incised longitudinally, and traction sutures were placed about the free edges of the pericardium to expose and support the heart. Solid-state pressure transducer catheters (5-Fr; Millar Instruments, Houston, TX) were inserted into the RV and LV via stab wounds in the apex to measure instantaneous pressures. An ultrasonic flow probe (24 mm diameter; Transonic Systems, Ithaca, NY) was placed around the ascending aorta to measure aortic flow velocity.

Bipolar temporary epicardial pacing leads (Medtronic, Houston, TX) were clipped to the right atrial appendage and sewn into the myocardium of the RV outflow tract and the posterior lateral aspect of the LV. The pacing leads were connected to a custom temporary InSync III (Medtronic) pacing unit. Sensing and pacing function of the leads were tested and confirmed. Complete heart block was established by atrioventricular node ablation with injection of 0.2-mL aliquots of 100% ethanol into the region of the bundle of His to allow for complete control of the sequence of activation [14]. Immediately after complete heart block, dual-chamber mode simultaneous BiVP at a heart rate of 90 beats/min with interventricular delay (VVD) of 0 ms was initiated. Atrioventricular sequential pacing was then maintained throughout the experiment with dual-chamber mode pacing or BiVP.

2.2. Pulmonary hypertension and BiVP

After heart block was initiated, acute RVPO was induced by tightening an umbilical tape snare placed around pulmonary artery until peak RV pressure doubled. Systemic arterial hypotension was avoided by volume infusion and phenylephrine. Allowing 5 min for hemodynamics to stabilize, the atrioventricular pacing delay (AVD) was varied between 90 and 270 ms in 30-ms increments for 10-s test intervals. At the AVD that produced the

maximum CO, VVD was varied between +80 and –80 ms in 20-ms increments for 10-s test intervals (positive VVD indicates RV-first pacing). Optimum BiVP was defined as the AVD and VVD that produced optimum CO. At the end of AVD and VVD optimization, a final comparison was preformed with 30-s intervals of atrio-RV pacing (RVP), atrio-LV pacing (LVP), and BiVP. Pacing was maintained at 90 beats/min throughout. Total pacing optimization time lasted 7 min 50 s. The animals were humanely sacrificed at the conclusion of the experiment.

2.3. Hemodynamic data recording and analysis

The ECG, peripheral arterial pressure, RV and LV pressure, and aortic flow velocity signals were sampled at 200 Hz by a 16-channel analog-to-digital converter (A D Instruments, Inc, Milford, MA) and recorded on a personal computer (Apple Computer, Cupertino, CA). Data were recorded using Chart Software (AD Instruments, Inc) and exported to Matlab software (Math Works, Inc, Natick, MA). CO was then measured by integrating aortic flow velocity tracings over one respiratory cycle employing custom-designed routines in Matlab.

2.4. Echocardiography

2-D echocardiograms of the mid-short axis (at the level of the papillary muscle) were obtained during the final comparison of RVP, LVP, and BiVP immediately after each 30-s pacing interval. Images were obtained with a hand-held transducer (GE-Vingmed Ultrasound AS, Horten, Norway) applied gently to the epicardium of the exposed heart by the same experienced echocardiographer (S.C.) in all animals. Images were analyzed offline using commercially available speckle-tracking software (EchoPac; GE-Vingmed Ultrasound AS). Images were of high quality with adequate views of all myocardial segments. Frame rates were set to a range between 60 and 90 Hz, allowing for adequate temporal resolution and frame-by-frame tracking of stable patterns of natural acoustic markers. The region of interest (ROI) was carefully drawn by manual point-and-click method along the endocardial border at end systole. This generated an ROI with an automatic width adjusted to fit the endocardial and epicardial borders. The ROI was inspected over a single beat and was adjusted if any of the segments did not properly track well during any portion of the cardiac cycle. Results were averaged over three consecutive beats. All 90 segments available for analysis were processed and reported.

The STE software automatically divided the LV into six equal segments: septal, anterior septal, anterior, lateral, posterior, and inferior segments. Peak radial strain was measured in each segment and is defined as the peak deformation during the cardiac cycle relative to the initial length at end diastole. It is expressed as a percent change, with a more positive value indicating better function. Intraventricular synchrony was defined as the differences in time to peak (TTP) strain in msec between the anterior septal and the posterior wall segments, with greater differences representing a higher degree of LV intraventricular dyssynchrony.

2.5. Statistical analysis

Descriptive statistics were calculated and differences were compared by ANOVA. For each of the data points, two independent observers were masked to the pacing setting and analyzed the data using the same echocardiographic platform and images. Only the original

observer's data are reported. Interobserver variability was assessed for both the radial strain and TTP radial strain analyses.

3. Results

RVPO approximately doubled average RV peak systolic pressures from baseline, with a tendency toward septal wall flattening. Table 1 presents optimum AVDs and VVDs during RVPO. Optimum AVD ranged from 120 to 180 ms. Optimum VVD was +40 to +80 ms. CO increased by 8.6% with BiVP compared to L VP (0.96 ± 0.26 L/min *versus* 0.89 ± 0.27 L/min; $P = 0.05$ by ANOVA). CO during RVP (0.93 ± 0.27 L/min) was higher than LVP but lower than BiVP, a difference that was not statistically significant. Table 2 presents average mean arterial pressures, end diastolic filling pressures, and maximal systolic pressure generation during systole for the RV in five pigs in the three pacing modes. End diastolic filling pressures and maximal systolic pressure generation for the LV were available in four pigs.

STE was analyzed in all 90 segments in all animals. Representative radial strain analysis is shown in Fig. 1. During BiVP, strain imaging showed coordinated radial segmental strain throughout a single cardiac cycle (Fig. 1A). All six segments reached peak strain simultaneously before aortic valve closure. Similarly, during RVP, all six segments were also well coordinated, with maximal peak strains before aortic valve closure (Fig. 1B). During LVP, however, there was a significant anterior septal wall delay in TTP radial strain well beyond aortic valve closure time, representing post-systolic, inefficient contraction (Fig. 1C). In addition, there was an associated reduction in peak strains predominantly in the posterior and lateral wall segments.

Fig. 2 shows segmental LV TTP strains from the peak of the QRS across the three different pacing modes. Anterior septal TTP strain was significantly prolonged during LVP *versus* BiVP and RVP (502 ± 19 ms *versus* 392 ± 58 ms and 390 ± 53 ms, respectively; $P = 0.0018$). LVP led to LV dyssynchrony, as measured by an anterior septal to posterior wall delay of 106 ms (anterior septal: 502 ± 19 ms and posterior: 396 ± 72 ms; $P = 0.0011$). This dyssynchrony was eliminated during BiVP and RVP, with no anterior septal to posterior wall delay. Regional strain analysis also showed prolonged contraction of the anterior wall during LVP compared to the other two modes.

Fig. 3 illustrates segmental LV peak strains across the three pacing modes. Strain was 66% higher in the posterior wall segment than the anterior septal during BiVP (posterior: $20\% \pm 5\%$ and anterior septal: $12\% \pm 6\%$; $P = 0.0029$) and RVP (posterior: $20\% \pm 3\%$ and anterior septal: $12\% \pm 7\%$; $P = 0.0002$). Regional differences in function were not observed during LVP.

The interexaminer reliability coefficient (IRC) was 0.80 for radial strain and 0.52 for TTP radial strain. The low IRC for TTP radial strain was mainly due to discrepant readings of TTP radial strain in two cardiac cycles. This discrepancy was most likely caused by recording errors from one of the observers. When these two cardiac cycles were excluded, the IRC increased to 0.64.

4. Discussion

Our results demonstrate that pre-excitation of the “failing” RV benefits the “nonfailing” LV through improved LV intraventricular synchrony and increased free wall radial strain. These findings enhance our understanding of optimal pacemaker programming during acute RV failure due to RVPO.

A 106-msec delay between anterior septal and posterior wall contraction during LVP demonstrates that inappropriate myocardial activation can cause dyssynchronous contraction. Dyssynchronous contraction wastes mechanical energy during systole, with peak contraction of early activated segments during pre-ejection phases and late activated segments peaking against a closed aortic valve. Our data indicate that RV pre-excitation in RVPO improves LV synchrony and that the benefits are seen with the proper timing of septal contraction. Prolonged RV contraction due to high RV afterload leads to a significant left-to-right delay in time to peak shortening, with the lengthening of RV shortening compared to that of the LV [15]. Pacing the RV first may compensate for the delayed contraction and lead to greater synchrony, improving maximal work during the ejection phase of systole and resulting in greater CO.

RV pre-excitation enhances not only synchronous contraction of the LV but also functional benefits measured by radial strain in the LV free wall. Physiologically, pre-exciting a dilated, pressure-overloaded RV should restore normal left to right transseptal pressure gradient and should improve global LV filling properties [16]. However, we observed systolic improvement only along the posterior (free wall) of the LV. One possible explanation could be the effects of differences in curvature on LV-free wall force generation [17]. Alternatively, these differences could reflect the location of the pacing electrode in the posterior wall. Others have reported the unequal effects of BiVP on the amplitude of radial deformation in various LV segments using STE [18,19] but, to our knowledge, none in the setting of acute RVPO.

Whether BiVP (with RV pre-excitation) supports CO more effectively than RVP alone in acute RVPO is uncertain and is not supported by the present data. Both groups had increased CO with RVP compared to LVP. However, BiVP was superior to RVP in three of five animals, while RVP alone was superior in the remaining two. This difference merits further study. Contributing factors may include efficiency of transmission of LV pressure across the interventricular septum, systolic and diastolic transseptal pressure gradients and related septal distortion, and subendocardial ischemia of the RV or LV. The severity of pulmonary stenosis may also be contributory. In previous studies from our laboratory, optimized BiVP improved CO as much as 20% in acute RVPO [10]. In those studies, we snared the pulmonary artery until CO decreased by 50%. That practice was discarded in favor of snaring until RV systolic pressures doubled, in order to improve hemodynamic stability. Another important innovation was implementing pacing changes in randomized sequence, rather than the linear sequence used earlier. Because the effects of BiVP are dependent on the severity of cardiac dysfunction [20], variable hemodynamic stability of this preparation may be causing the observed heterogenous response of CO to BiVP.

In previous studies, we showed that CO was optimized with RV-first BiVP, which increased RV dP/dt, decreased the left-to-right end diastolic pressure gradient, and improved LV-RV pressure synchronization [9]. In addition, we demonstrated improved LV geometry and LV fractional shortening by standard 2-D echo in RVPO [10]. The present study supports and extends these findings by suggesting that pacing during RVPO not only impacts interventricular dyssynchrony and RV pressure, but also affects the LV by improving intraventricular LV synchrony and mechanics via the septum and free wall. These studies suggest that RV pre-excitation enhances LV function in RVPO by multiple mechanisms, including enhanced RV contractility, improved interventricular synchrony, and improved LV intraventricular synchrony.

The impact of RV pre-excitation on enhanced LV mechanics and function in RVPO has been studied in other settings. Handoko *et al.* [21], using an isolated rat heart model, similarly showed that RV resynchronization during pulmonary hypertension could synchronize pressure generation across the septum, improve RV systolic function, and reduce adverse diastolic interaction.

Using a computer simulation of the LV, Lumens *et al.* [22] found that RV pre-excitation during severe pulmonary hypertension homogenizes workload over the ventricular walls and improves global function. Dubin *et al.* [6] and Janousek *et al.* [23] attempted to resynchronize the ventricles of patients with congenital heart disease and right bundle branch block (RBBB), with success indicating that cardiac resynchronization therapy could be a promising adjunct to the treatment or prevention of RV failure. In addition, Byrne *et al.* [24] compared the effects of BiVP on a canine model of pure left bundle branch block (LBBB) *versus* pure RBBB using tagged MRI. He concluded that BiVP in RBBB does not improve global mechanical function to the degree that it does in animals with LBBB. He also found that single-site RVP produced similar results to BiVP and that LV-only pacing worsened hearts with RBBB findings.

Radial strain dyssynchrony measured by STE has been well validated as a clinically useful marker for both acute and chronic responses to BiVP for patients with electrical conduction abnormality and LV systolic heart failure in both experimental and human studies. We demonstrate a new use for STE in elucidating the mechanism in which BiVP improves synchrony and regional LV function in a RVPO model.

4.1. Study limitations

This study analyzes effects of BiVP optimization in isolated RVPO in open-chested pigs. Clinically, RV failure due to RVPO is predominantly the result of pulmonary hypertension secondary to LV failure. However, many other right-sided causes of RVPO exist, including acute pulmonary embolism, chronic thromboembolic pulmonary hypertension, primary pulmonary hypertension, and others. The pathophysiology of RV failure in this setting is poorly understood, which is the objective of this paper.

Heart block was used in this setting to obtain complete control in sequence of activation and to pace a full range of AVD from 90 ms to 270 ms. This may imply that control of AVD and VVD is not sufficient to optimize temporary BiVP in acute RVPO unless heart block or

RBBB or LBBB is present. Since RVPO can delay timing of peak RVP [9], the answer to this question is unknown and requires further study. In acute LV failure after cardiopulmonary bypass, however, heart block has not been required to optimize temporary BiVP [25].

Our study sample was small, making our results susceptible to outliers and variability in data analysis. “Double peaks” are a potential problem in STE analysis that can cause the TTP strain and peak strain curves to be ambiguous in distinguishing possible maxima [13]. Techniques we use to offset this problem include masking the investigators to the pacemaker timing at any given setting. Furthermore, data are analyzed in duplicate by two masked observers. The relatively low values for IRC for TTP strain are related to interpretation of data with double peaks and suggest that oversight is necessary for analysis of data with double peaks.

A related limitation of this study is the use of techniques primarily intended for analysis of LV function in a study focusing primarily on RV dysfunction. This choice reflects in part limitations of available techniques for analyzing RV dysfunction, related to the asymmetrical shape of the RV and shape changes with failure. The RV and the LV are closely related, however, where RV dysfunction may impair LV function. Thus, close analysis of LV function in RVPO is of value. Alternative techniques focusing on RV-LV interactions, rather than primary LV function, include measurement of septal curvature, RV/LV transverse diameters, and septal bowing. These techniques were not used in the present study and will be examined in future investigations of this model. Additionally, we applied the echo transducer directly to the epicardial surface of the heart, which is not feasible in most clinical settings. The possibility that artifacts may occur in epicardial STE analysis has not been systematically studied. However, transesophageal and transthoracic echo have been shown equivalent for strain and strain rate analysis with STE [26].

Our study looks at echocardiographic data during three discrete pacing modes: optimized BiVP, RVP, and LVP. Because the animals were in complete heart block, a no-pacing group during RVPO could not be used to serve as a control group. Baseline data prior to heart block and RVPO should be obtained in future studies to serve as control data. In addition, collecting echocardiography data across a broader range of VVD-AVD combinations would provide a more precise understanding of the effects of sequential pacing on LV strain and synchrony.

5. Conclusion

Both BiVP (RV-first pacing) and RVP restore intraventricular synchrony and increase regional LV function compared to L VP during acute RVPO. RV pre-excitation unloads the RV, reducing the duration of anterior septal wall contraction and homogenizing LV wall timings. Functional benefit is found primarily in the opposing LV free wall. STE is able to assess regional timing and function during RVPO, defining acute responses to BiVP. The present data could support future clinical trials of BiVP or RVP in patients with RV failure due to RVPO.

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Fig. 1 -
Representative radial strain analysis. (A) Representative example of optimized BiVP with right ventricle paced first. With optimized BiVP, all six segments reached peak strain simultaneously before aortic valve closure. (B) Representative example of atrio-right ventricular pacing only. Similar to BiVP, all six segments reached peak strain simultaneously. (C) Representative example of atrio-left ventricular pacing only in a different pig. There was a significant anterior septal wall delay in time to peak radial strain after aortic valve closure, indicating postsystolic contraction.

Fig. 2 - Segmental left ventricular time to peak radial strain for each of the three different pacing modes. There is a significant anterior septal segment delay with LVP compared to BiVP and RVP. There is also a significant delay between anterior septal and posterior wall segments with LVP.

Fig. 3 -
Segmental left ventricular peak radial strains for each of the three pacing modes. With BiVP and RVP, radial strain is 66% higher in the posterior wall segment than the anterior septal. These regional differences in function were not observed during LVP.

Table 1 -

Optimized biventricular settings and average cardiac output.

Biventricular pacing optimization data—optimal settings							
Pig	HR (beats/min)	AVD (msec)	VVD (msec)	Bivopt	CO (L/min)	LVP	% Change BiVP versus LVP (worse)
1	90	150	+80	0.72	0.68	0.70	2.9%
2	90	150	+40	0.77	0.80	0.70	10.0%
3	90	150	+40	1.36	1.37	1.32	3.0%
4	90	180	+60	0.89	0.82	0.73	21.9%
5	90	120	+40	1.06	1.00	1.01	5.0%
Mean (SD)	90 (0)	150 (21.2)	+52 (17.9)	0.96 (0.26)	0.93 (0.27)	0.89 (0.27)	8.6% (0.80)

Optimum AVD and VVD for each pig are listed with corresponding cardiac output for BiVP with optimum AVD and VVD, RV paced first (RVP) and LV paced first (LVP). Percent change between BiVP and LVP is also listed. Mean values and standard deviation across five pigs are shown across the bottom.

Table 2 -

Effects of BiVP optimization.

Variable	BiVP	RVP	LVP
CO, L/min	0.96 (0.26)	0.93 (0.27)	0.89 (0.27)
MAP, mm Hg	45 (15)	44 (13)	42 (12)
EDP, mm Hg			
RV	4.2 (4.9)	4.0 (5.1)	4.2 (4.6)
LV	1.5 (3.4)	1.3 (3.1)	0.9 (2.7)
dP/dt _{max} , mm Hg/s			
RV	342 (118)	351 (123)	322 (120)
LV	553 (186)	556 (158)	570 (180)

dP/dt_{max} = maximum rate of increase of ventricular pressure; EDP = end diastolic pressure; MAP = mean arterial pressure.

Values are means (SD) for CO, MAP, EDP, and dP/dt_{max}. Means are of five pigs, except for LV EDP and dP/dt_{max}, which are for four pigs.