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Effects of biventricular pacing on left heart twist and strain in a porcine model of right heart failure

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Abstract

Background—Biventricular pacing (BiVP) improves cardiac output (CO) in selected cardiac surgery patients, but response remains variable, necessitating a better understanding of the mechanism. Accordingly, we used speckle tracking echocardiography (STE) to analyze BiVP during acute right ventricular pressure overload (RVPO).

Materials and methods—In nine pigs, the inferior vena cava (IVC) was snared to decrease CO and establish a control model. Heart block was induced, the pulmonary artery snared, and BiVP initiated. Echocardiograms of the left ventricular midpapillary level were taken at varying atrioventricular delay (AVD) and interventricular delay (VVD) for STE analysis of regional circumferential strain (CS) and radial strain (RS). Echocardiograms were taken of the left ventricular base, midpapillary, and apex during baseline, IVC occlusion, and each BiVP setting for STE analysis of twist, apical and basal rotations, CS, RS, and synchrony. Indices were correlated against CO with mixed linear models.

Results—During IVC occlusion, CO correlated with twist, apical rotation, RS, RS synchrony, and CS ($P < 0.05$). During RVPO with BiVP, CO only correlated with RS synchrony and CS ($P < 0.05$). During AVD and VVD variations, CO was associated with free wall RS ($P < 0.008$). CO correlated with septal wall CS during AVD variation and free wall CS during VVD variation ($P < 0.008$).

Conclusions—In an open chest model, twist, RS, RS synchrony, and CS analyzed by STE may be noninvasive surrogates for changes in CO. During RVPO, changes in RS synchrony and CS with varying regional strain contributions may be the primary mechanism in which BiVP improves CO. Lack of correlation of remaining indices may reflect postsystolic function.

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Keywords

Speckle tracking echocardiography; Right ventricular pressure overload; Biventricular pacing

1. Introduction

Cardiac resynchronization therapy (CRT), or permanent biventricular pacing (BiVP), is now a standard of care for patients with systolic dysfunction and prolonged QRS duration [1,2]. Several studies have found that temporary BiVP improves postoperative cardiac function in patients with similar criteria undergoing surgery on cardiopulmonary bypass [3,4]. Few studies, however, have focused on the effects of BiVP on right ventricular (RV) failure.

Similar to left ventricular (LV) dysfunction, RV dysfunction can be caused by prolonged pressure or volume overload, ischemia, intrinsic myocardial disease, or pericardial constraint. The most common cause of RV failure is pressure overload due to LV failure with secondary pulmonary hypertension [5]. Preliminary clinical studies have found that BiVP in the setting of RV failure improves RV function and systemic hemodynamics [6,7]. Janousek *et al.* [8] found that CRT may prevent RV failure in patients with a systemic RV. Animal studies investigating the mechanism of response to BiVP during RV failure have shown that optimized BiVP produces best cardiac output (CO), increases RV contractility, and enhances LV geometry and fractional shortening [9,10]. In the setting of both LV and RV failures, systolic function of the failing ventricle improved as synchrony of RV and LV contractions was maximized with BiVP [10–12]. None of these studies, however, have elucidated the effects of optimized BiVP on intraventricular synchrony, strain, and twist.

Speckle tracking echocardiography (STE) is a technique that provides quantitative spatial and temporal information [13] by tracking the speckles in each ultrasonic image frame-by-frame. STE can analyze myocardial strain, synchrony, and rotation and has been validated against tagged magnetic resonance imaging, the noninvasive gold standard for measurement of systolic deformation [14,15]. Because failure in the RV directly affects the function of the LV, we applied STE analysis to the LV to determine the mechanism of hemodynamic response to temporary BiVP during right ventricular pressure overload (RVPO). We focused on the relationship between twist, radial strain (RS), circumferential strain (CS) and RS and CS synchrony and hemodynamic response to BiVP. To establish a control model, a similar correlation was measured with different loading conditions through inferior vena cava (IVC) occlusion in the healthy porcine heart after sternotomy and pericardiotomy.

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. Nine male pigs (30–35 kg) were properly anesthetized and intubated according to previously described procedures [9]. Standard limb leads were placed for electrocardiogram monitoring. Peripheral arterial

pressure was measured from the femoral artery. The chest was opened by median sternotomy and the pericardium was incised longitudinally. Solid-state pressure transducer catheters (5-Fr; Millar Instruments, Houston, TX) were inserted into the RV and LV via an incision 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 CO.

2.2. Echocardiography

Images were obtained with a hand-held transducer (Vivid 7; GE-Vingmed Ultrasound AS, Horten, Norway). Using scanning gel, the transducer was applied gently to the epicardium of the exposed heart by the same experienced echocardiographer in all animals. Two-dimensional short axis echocardiograms were taken at the basal level defined as the tips of mitral valve leaflets, midpapillary level, and apical level defined as the level proximal to complete end-systolic lumen obliteration. End-systole was defined as the time coincident with aortic valve closure as measured by Doppler and confirmed with the end of the flow profile measured by aortic flow probe.

2.3. IVC occlusion

Following sternotomy and pericardiotomy in nine animals, echocardiograms were taken at the basal, midpapillary, and apical levels of the LV. An umbilical tape snare was then placed around the IVC and tightened until baseline CO was reduced by 10% and 30%. Occlusion was held for 2 min to ensure hemodynamic stability. Five pigs tolerated 10% occlusion and four pigs tolerated 30% occlusion. Pigs with lower baseline CO were less tolerant of IVC occlusion, causing a higher than expected average CO in the IVC occlusion groups. Echocardiograms at the basal, midpapillary, and apical levels were taken after each occlusion. Only echocardiograms taken during a stable hemodynamic state were used.

2.4. Heart block

Bipolar temporary epicardial pacing leads (Medtronic, Houston, TX) were sewn to the right atrial appendage, the epicardium 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. Immediately after complete heart block, BiVP was initiated at a heart rate of 90 beats/min or 10 beats above intrinsic heart rate with atrioventricular delay (AVD) of 150 ms interventricular delay (VVD) of 0 ms.

2.5. Pulmonary hypertension

After heart block was initiated, acute RVPO was induced by tightening an umbilical tape snare placed around the pulmonary artery until peak RV pressure doubled. Systemic arterial hypotension was avoided by volume infusion and phenylephrine. Six pigs remained hemodynamically stable to allow BiVP optimization.

2.6. BiVP optimization

AVDs were randomly varied between 90 and 270 ms in 30-ms increments for 10-s test intervals and repeated to account for hemodynamic changes (settings = 14). 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) and repeated (settings = 18). Echocardiograms at the midpapillary level were obtained at each AVD and VVD setting for regional STE strain analysis. Optimum BiVP was defined as the AVD and VVD that produced greatest CO.

At the end of AVD and VVD optimization, a final comparison was performed with 10-s test intervals of best BiVP setting (AVD/VVD combination that produced maximum CO), worst BiVP (AVD/VVD combination that produced the worst CO), AVD 150/VVD -80, AVD 150/VVD 0, and AVD 150/VVD +80. Echocardiograms were taken at the basal, midpapillary, and apical levels after each test interval and analyzed for twist, apical and basal rotations, CS, RS, and synchrony. The animals were humanely killed at the conclusion of the experiment.

2.7. Speckle tracking echocardiography

All echocardiograms were processed off-line using commercially available STE software (EchoPac; GE-Vingmed Ultrasound AS) with previously described methods [16]. 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. Basal and apical rotations were calculated as the average rotation of all six segments at end-systole. Twist was calculated as the difference between end-systolic apical and basal rotations. End-systolic RS and CS were calculated as the average strain of six segments at the midpapillary level at end-systole. RS and CS synchrony were calculated as the difference in time to peak strain between free wall and septal segments. Results were averaged over three consecutive beats.

2.8. Postsystolic strain index/postsystolic rotation index

Postsystolic strain index (PSI) was calculated as (postsystolic strain - end-systolic strain)/peak systolic strain. If there was no postsystolic strain, the strain at the beginning of diastole was used, yielding a PSI of zero. Postsystolic rotation index (PSRI) was calculated similarly with rotation instead of strain to quantify the degree of delayed rotation.

2.9. Statistical analysis

During IVC occlusion and final comparison, basal and apical rotations, twist, RS, CS, RS synchrony, and CS synchrony were correlated with CO using linear mixed effects models. PSI/PSRI during control and after RVPO were compared using linear mixed effects model. RS and CS in each of the six midpapillary segments were correlated with CO during each AVD and VVD setting with mixed linear models. Random subject effects were included in all the models to account for within-subject correlations. To adjust for multiple comparisons during AVD/VVD variation, a *P* value of 0.0083 was considered significant. All analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

3. Results

3.1. IVC occlusion

Representative RS (Fig. 1A) and apical and basal rotation (Fig. 2A and B) waveforms at baseline after sternotomy and pericardiotomy are shown. Average hemodynamics (Table 1) and values for each STE index (Table 2) are also listed. Five pigs tolerated 10% IVC occlusion and four pigs tolerated 30% IVC occlusion. In general, pigs with a higher baseline CO better tolerated IVC occlusion, increasing cumulative average hemodynamics during occlusion. Increases in twist and apical rotation correlated with an increase in CO ($P < 0.001$ and $P < 0.029$, respectively) but basal rotation did not. Both improved RS and CS correlated with improved CO ($P = 0.003$ and $P = 0.001$, respectively). Increased RS synchrony also correlated with improved CO ($P = 0.040$) but CS synchrony did not. Improved RS and CS were associated with mean arterial pressure ($P = 0.036$ and $P = 0.033$, respectively). No indices were significantly associated with LV dp/dt.

3.2. Right ventricular pressure overload

Figure 1B shows representative RS waveform with optimized BiVP during RVPO settings. Note the delay in radial strain with BiVP during RVPO. A similar delay is seen in basal rotation after RVPO (Fig. 2C). Average hemodynamics (Table 3) and values for each STE index (Table 2) are listed for each BiVP setting during RVPO. After RVPO, improvement in RS synchrony and CS significantly correlated with increased CO ($P = 0.048$ and $P = 0.002$, respectively). No other indices were found to be statistically significantly correlated with improvement in CO. No indices were significantly associated with mean arterial pressure or LV dp/dt(max).

3.3. PSI/PSRI

Average PSI/PSRI during IVC occlusion and RVPO with BiVP are listed in Table 4. CS PSI and basal PSRI significantly increased after RVPO ($P = 0.005$ and $P = 0.015$, respectively).

3.4. AVD/VVD regional analysis

During AVD variation, RS in the anterior segment and CS in the septal segment were significantly associated with CO. During VVD variation, improvement in posterior, inferior, and lateral RS were significantly associated with increases in CO ($P < 0.001$, $P < 0.001$, and $P = 0.003$, respectively). Improvement in CS posterior segment was associated with increases in CO ($P < 0.001$), whereas a decrease, or paradoxical stretching, in anterior CS correlated with improvement in CO ($P = 0.006$).

4. Discussion

The aim of this study was to elucidate the mechanism by which BiVP improves hemodynamics during RVPO. We found that in the control state, RS, RS synchrony, CS, twist, and apical rotation significantly correlated with changes in CO, a finding that is expected since the contribution of strain, synchrony, and twist to cardiac function has been well documented [17–20]. When RVPO was induced and BiVP initiated, however, only RS synchrony and CS continued to correlate with CO. The loss of correlation between RS,

twist, apical rotation, and CO may be due to delays in peak function after RVPO such that variations caused by BiVP did not yield a measurable change in hemodynamics.

4.1. IVC occlusion

During the control state, RS, RS synchrony, CS, twist, and apical rotation correlated significantly with CO. Of the indices analyzed, twist correlated most closely with CO. It has previously been reported that torsional deformation permits the generation of an ejection fraction of 60% when simple longitudinal or circumferential shortening would not allow an ejection fraction >30% [18,21], explaining its closer relationship with hemodynamic changes.

Increases in apical rotation correlated with improvement in CO but basal rotation did not, which is supported by previous findings that the apex is the primary contributor to twist [22]. The amount of apical postsystolic rotation, and consequently twist, may be a consequence of sternotomy and pericardiotomy but was not able to be confirmed due to the difficulty in obtaining quality transthoracic echocardiograms in a closed porcine chest.

4.2. BiVP during RVPO

After initiation of RVPO and BiVP, RS synchrony and CS continued to correlate with CO but twist, apical rotation, and RS were no longer significantly associated with improvement in CO. Studies have been equivocal on whether CRT acutely improves global ventricular function. Some studies suggest that immediate improvement in torsion is associated with long-term LV reverse remodeling [23]. Other studies, however, contend that there is no acute improvement in torsion despite hemodynamic benefit from BiVP [24,25]. One possible explanation for the lack of improvement in twist or rotation in our study may be delayed peak rotation and, consequently, delayed untwisting with BiVP after RVPO. Basal PSRI significantly increased compared with control, whereas apical rotation did not significantly change. With delayed peak rotation, maximum torsion occurred against a closed aortic valve and did not contribute to hemodynamic changes. Song *et al.* [26] also found decreases in twist, primarily in the base, in patients with pulmonary hypertension. RVPO may thus cause a decrease in effective LV twist, and in our model, twist did not correlate with hemodynamics changes during RVPO and BiVP.

CS PSI also significantly increased during RVPO but RS PSI did not. Postsystolic strain has been reported in several studies of ischemia [27,28]. The presence of greater post-systolic strain and rotation during RVPO may reflect global ischemia secondary to periods of low CO. Despite increases in CS PSI after RVPO, improvement in CS continued to correlate with increases in CO. Thus, it may not necessarily be the change in PSI/PSRI that determines contribution to hemodynamics. Instead, it may be the absolute value above which the index no longer significantly contributes to CO. The amount of postsystolic activity above which strain and rotation no longer significantly contribute to CO during RVPO necessitates further investigation. In this study of BiVP during RVPO, RS synchrony and CS may primarily affect changes in hemodynamics.

4.3. Regional changes during AVD/VVD variation

In addition to investigating global strain contribution to CO with BiVP during RVPO, we aimed to analyze regional strain contribution and found different regional RS and CS contributions. During both AVD and VVD variations, free wall RS significantly correlated with increases in CO. This supports our previous study analyzing the effects of BiVP during RVPO [16] and acute LV volume overload [12] that found greater RS changes in the free wall than in the septum. Our findings are in contrast, however, with other studies that found that CRT improved septal RS and decreased lateral RS [29,30]. This difference may be due to the use of epicardial RV pacing leads in our model instead of intracardiac leads used in patients receiving CRT.

Regional CS had varying patterns during AVD variation than VVD variation. During AVD variation, improvement in septal CS correlated the most with increasing CO. During VVD variation, however, improvement was predominately in the posterior segment with paradoxical strain, or stretching, of the anterior segment. This difference may be explained by the changes in ventricular function during AVD and VVD variations. AVD variation determines the optimal timing of the atrial kick with ventricular filling to maximize preload [31], whereas VVD variation predominantly affects interventricular synchrony [23]. Hayabuchi *et al.* [32] showed that CS is greater in the septum in a pediatric population with RVPO than in controls. Paradoxical CS stretching was reported in a patient with acute myocarditis [33] and during intermittent ligation of the left anterior descending artery in open chest pigs [34]. Thus, the paradoxical CS stretching observed in this model may be another indication of the ischemic damage from periods of low CO.

4.4. Study limitations

We were not able to separate effects of pacing from effects of RVPO on strain and rotation. Induction of heart block caused changes in hemodynamics so that we were unable to compare a no-pacing group against the BiVP group. Limited sample size did not provide enough power to determine predictors of hemodynamic improvement with varying BiVP settings or the degree of postsystolic function above which changes did not result in hemodynamic response. In addition, we were not able to elucidate the relationship between the level of RV failure and benefit of BiVP. These would be the aims for future studies.

5. Conclusions

In an open chest, open-pericardium porcine model, twist, RS, RS synchrony, and CS analyzed by STE may be noninvasive surrogates to monitor changes in CO. After RVPO was induced and BiVP initiated, only RS synchrony and global CS remain significantly correlated with changes in CO. Changes in RS synchrony and CS may be the primary mechanism in which BiVP improves CO during RVPO. The lack of correlation between CO and twist, apical rotation, and RS during BiVP may reflect variations in postsystolic function. Analysis during AVD and VVD variations revealed varying regional RS and CS contribution to CO.

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Fig. 1. Representative radial strain waveforms during baseline (A) and during RVPO with optimized BiVP settings (B). Note the delay in radial strain with BiVP during RVPO.

Fig. 2.
Representative basal (A) and apical (B) rotation waveforms during baseline. Representative basal (C) and apical (D) rotations with optimized BiVP settings during RVPO. Note the delay in basal rotation with BiVP during RVPO.

Table 1

Average hemodynamics during IVC occlusion.

Hemodynamic index	Baseline (<i>n</i> = 9)	10% IVC occlusion (<i>n</i> = 5)	30% IVC occlusion (<i>n</i> = 4)
CO (L/min)	1.5 (0.7)	3.0 (2.7)	1.4 (0.4)
MAP (mmHg)	70 (11)	66 (7)	51 (8)
Peak LVP (mmHg)	65.1 (21.1)	100.1 (79.4)	53.6 (12.4)
Peak RVP (mmHg)	21.9 (22.5)	44.4 (65.0)	12.2 (3.2)

LVP = left ventricular pressure; MAP = mean arterial pressure; RVP = right ventricular pressure.

Average hemodynamic values during baseline, 10% IVC occlusion, and 30% IVC occlusion are listed with standard deviation in parenthesis. Five pigs tolerated 10% IVC occlusion and four pigs tolerated 30% IVC occlusion. In general, pigs with a higher baseline CO better tolerated IVC occlusion, increasing average hemodynamics during occlusion.

Table 2

Average values for each STE index.

STE index	Control, <i>N</i> = 9		RVPO, <i>N</i> = 6	
	Average (STD)	Coefficient (<i>P</i> value)	Average (STD)	Coefficient (<i>P</i> value)
Twist (°)	5.81 (2.50)	3.30 (<0.001)	4.08 (3.51)	—
Basal rotation (°)	−3.34 (1.59)	—	−1.80 (2.05)	—
Apical rotation (°)	2.47 (2.04)	2.25 (0.029)	2.29 (2.18)	—
RS (%)	26.78 (13.83)	17.45 (0.003)	10.63 (7.75)	—
CS (%)	−10.49 (2.43)	−2.70 (0.001)	−7.61 (2.65)	−4.10 (0.002)
RS synchrony (STD)	96.21 (59.51)	−61.25 (0.040)	98.76 (120.46)	−148.9 (0.048)
CS synchrony (STD)	21.57 (18.43)	—	121.33 (75.29)	—

Average values for each STE index are listed with standard deviation in parenthesis. *P* values and coefficients for each index with a significant association with CO are also listed.

Table 3

Average hemodynamics during BiVP in RVPO.

Hemodynamic index	Best BiVP	Worst BiVP	AVD 150/VVD -80	AVD 150/VVD 0	AVD 150/VVD +80
CO (L/min)	1.55 (0.33)	1.01 (0.26)	1.49 (0.39)	1.58 (0.29)	1.42 (0.41)
MAP (mmHg)	80.76 (29.79)	46.31 (19.62)	69.81 (23.21)	78.51 (27.90)	72.62 (24.22)
LV dp/dt(max) (mmHg/s)	947.72 (346.05)	671.16 (205.29)	958.91 (273.14)	982.26 (304.45)	839.56 (222.69)
Peak LVP (mmHg)	94.83 (30.37)	60.53 (15.89)	86.80 (22.05)	92.04 (29.29)	84.28 (18.75)
Peak RVP (mmHg)	33.94 (6.69)	24.99 (6.40)	34.70 (7.42)	35.84 (6.37)	33.06 (7.61)

LVP = left ventricular pressure; MAP = mean arterial pressure; RVP = right ventricular pressure.

Average hemodynamic values for each BiVP setting are listed with standard deviation in parenthesis.

Table 4

PSI and PSRIs.

Post-systolic function index	STE index	Control	RVPO	P value
PSI	RS	0.09 (0.13)	0.27 (0.50)	0.210
	CS	0.01 (0.01)	0.11 (0.15)	0.005
PSRI	Base	0.06 (0.11)	0.39 (0.57)	0.015
	Apex	0.54 (0.42)	0.34 (0.56)	0.219
	Twist	0.31 (0.2)	0.35 (0.36)	0.200

Average values listed with standard deviation in parenthesis.