Effects of sequential biventricular pacing during acute right ventricular pressure overload

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Quinn, T. Alexander, George Berberian, Santos E. Cabrera, Lauren J. Maskin, Alan D. Weinberg, Jeffrey W. Holmes, and Henry M. Spotnitz. Effects of sequential biventricular pacing during acute right ventricular pressure overload. Am J Physiol Heart Circ Physiol 291: H2380–H2387, 2006. First published June 2, 2006; doi:10.1152/ajpheart.00446.2006.—Temporary sequential biventricular pacing (BiVP) is a promising treatment for postoperative cardiac dysfunction, but the mechanism for improvement in right ventricular (RV) dysfunction is not understood. In the present study, cardiac output (CO) was optimized by sequential BiVP in six anesthetized, open-chest pigs during control and acute RV pressure overload (RVPO). Ventricular contractility was assessed by the maximum rate of increase of ventricular pressure (dp/dtmax). Mechanical interventricular synchrony was measured by the area of the normalized RV-left ventricular (LV) pressure diagram (App). Positive App indicates RV pressure preceding LV pressure, whereas zero indicates complete synchrony. In the control state, CO was maximized with nearly simultaneous stimulation of the RV and LV, which increased RV (P = 0.006) and LV dp/dtmax (P = 0.002). During RVPO, CO was maximized with RV-first pacing, which increased RV dp/dtmax (P = 0.007), but did not affect LV dp/dtmax, and decreased the left-to-right, end-diastolic pressure gradient (P = 0.023). Percent increase of RV dp/dtmax was greater than LV dp/dtmax (P = 0.014). There were no increases in end-diastolic pressure to account for increases in dp/dtmax. In control and RVPO, RV dp/dtmax was linearly related to App (r = 0.779, P < 0.001). The relation of CO to App was curvilinear, with a peak in CO with positive App in the control state (P = 0.004) and with App approaching zero during RVPO (P = 0.001). These observations imply that, in our model, BiVP optimization improves CO by augmenting RV contractility. This is mediated by changes in mechanical interventricular synchrony. Afterload increases during RVPO exaggerate this effect, making CO critically dependent on simultaneous pressure generation in the RV and LV, with support of RV contractility by transmission of LV pressure across the interventricular septum.

BIVENTRICULAR PACING (BiVP), or cardiac resynchronization therapy, is an important evolving therapeutic modality for congestive heart failure, reversing intraventricular conduction delay and left ventricular (LV) dysfunction intrinsic to dilated cardiomyopathy (2). In addition to long-term benefits for cardiac function and geometry in patients with various forms of chronic heart failure, BiVP is associated with acute improvements in ventricular systolic and diastolic function, inter- and intraventricular synchrony, and cardiac output (CO), with no cost to energy consumption (2). These acute benefits of BiVP suggest its possible value as an adjunct to the treatment of LV or right ventricular (RV) dysfunction after cardiac surgery. Although its use for perioperative management has not been carefully evaluated, initial studies have shown the utility of temporary BiVP after surgery for acquired (19, 56) and congenital (27, 40, 47) heart disease.

Studies investigating sequential BiVP by alteration of the interventricular pacing delay (VVD) have shown further acute improvements by optimized BiVP timing compared with simultaneous BiVP (5, 6, 9, 28, 30, 36, 39, 51, 53, 58, 59). We have shown the beneficial effects of optimizing VVD during acute RV pressure (45), RV volume (46), and LV volume (3) overload in open-chest pigs. With optimization, CO increased with RV-first pacing during RV pressure overload (RVPO) and LV volume overload and with LV-first pacing during RV volume overload. This may be important in treatment of perioperative cardiac dysfunction, in which acutely altered ventricular loading is commonly observed; however, the mechanism is not understood.

In this study, we consider a model of acute RVPO previously reported by our laboratory (45). Little work has been done using pacing to treat RV dysfunction. Preliminary studies have demonstrated improvement in CO with improvement in RV contractility and mechanical interventricular synchrony (11, 15, 22, 23). The same mechanisms may explain improvements in CO with optimized BiVP in acute RVPO. We therefore tested the hypothesis that optimization of VVD with temporary BiVP during acute RVPO would improve CO by improving RV contractility and/or mechanical interventricular synchrony.

METHODS

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.

Animal preparation. Six 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. Arterial blood gases and serum electrolytes were monitored by a handheld i-STAT (Abbott Laboratories, Abbott Park, IL) to optimize ventilation. Lidocaine was administered as an initial intravenous bolus (3 mg/kg) and continuously at 50 µg·kg⁻¹·min⁻¹ for arrhythmia prophylaxis. To maintain blood volume, 0.9% saline solution was administered intra-
venously at 10 ml·kg⁻¹·h⁻¹ for 1 h and then at 5 ml·kg⁻¹·h⁻¹ for the duration of the study. Body temperature, which was monitored by a 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⁻¹·h⁻¹).

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. An umbilical tape snare was placed around the main pulmonary artery. Bipolar temporary epicardial pacing leads (Medtronic, Houston, TX) were clamped to the right atrial appendage and sewn into the myocardium of the RV outflow tract and the inferomedial aspect of the LV.

Experimental protocol. The pacing leads were connected to a custom temporary InSync III (Medtronic) pacing unit. Proper sensing and pacing function of the leads were tested and confirmed. Complete heart block was established by atrioventricular (AV) node ablation and pacing function of the leads were tested and confirmed. Complete electrical activation of the RV and LV, heart block resulted in independent pacing-induced activation of the ventricles. Thus we chose to define a separate end-diastolic (ED) point for each ventricle based on mechanical events. The RV and LV ED point of each cardiac cycle was defined as the point before the rapid upstroke of pressure in that ventricle, determined as the point before the rate of pressure increase (dP/dt) exceeded 10% of maximal dP/dt (dP/dtmax). ED pressure (EDP) for each ventricle was taken at the respective ED point. The transesophageal EDP gradient was calculated as LV pressure – RV pressure at the LV ED point, before the activation of the LV, to examine its influence on LV filling and contraction.

Hemodynamics. Time to peak ventricular pressure was measured from the ED point in each ventricle. CO was calculated by integration of the aortic flow tracing over each cardiac cycle. Ventricular contractility was assessed by dP/dtmax. Mechanical interventricular synchrony was quantified as the area of the normalized RV-LV pressure diagram ($A_{pp}$, Fig. 1) (60, 62). $A_{pp}$ expresses synchrony based on the pressure waveforms during the complete cardiac cycle, with a loop area of 0 indicating complete synchrony and a maximum area of 1 indicating complete asynchrony. For our purposes, a counterclockwise loop was given positive values, indicating RV pressure preceding LV pressure; zero indicates complete synchrony.

[Fig. 1. Representative examples of raw (A) and normalized (B) right ventricular (RV) and left ventricular (LV) pressure (RVP and LVP, respectively) curves and resulting normalized RV-LV pressure diagrams (C) for optimum interventricular pacing delay (VVD) during control and RV pressure overload (RVPO). VVD is simultaneous (0 ms) in control and RV-first pacing (60 ms) in RVPO. $A_{pp}$, normalized RV-LV pressure diagram area. Arrows denote direction of the loop, with counterclockwise resulting in positive values, indicating RV pressure preceding LV pressure; zero indicates complete synchrony.]
maximum CO and the worst VVD as the setting that produced the lowest CO in each pig. Values at the optimum and worst VVD settings were compared to account for changes in CO. These values (see Table 3) differ from the average values at the optimum and worst VVD settings on the plots, because the optimum and worst VVD settings differed between pigs.

Statistical analysis. Values are means (SD) unless otherwise stated. A two-tailed paired Student’s *t*-test was used for comparison of 1) hemodynamic data in control and RVPO, 2) hemodynamic data at the optimum and worst VVD settings, and 3) percent change of RV and LV dP/dtmax with optimization. A mixed-model procedure for repeated-measurements analysis (PROC MIXED) (31, 32) was used for 1) modeling the changes in hemodynamic variables across the levels of VVD, 2) comparing hemodynamic variables between control and RVPO across the levels of VVD (with repeated measures on 2 factors), and 3) measuring the correlation between RV dP/dtmax and APP. Because repeated measurements within subjects may be correlated, this procedure allows more flexibility to model this “correlation structure,” commonly referred to as a covariance pattern. This allows for improved estimates of the standard errors of measurement, and, therefore, more powerful tests. *P < 0.05 was considered significant for all tests. Statistical analyses were performed using the SAS System software (SAS Institute, Cary, NC).

RESULTS

Representative examples of interventricular synchrony analysis are illustrated in Fig. 1. Differences in the time course of pressure generation become apparent when the data are normalized and presented as a fraction of the total generated pressure (Fig. 1B). With optimum VVD, peak RV pressure precedes peak LV pressure in the control state but follows peak LV pressure during RVPO. This reflects prolongation of the time to peak RV pressure during RVPO. Thus APP is positive in the control state and negative during RVPO (Fig. 1C).

Optimization of AVD and VVD. Table 1 presents the optimum and optimum and worst VVD during control and RVPO in each pig. The optimum AVD was 150 or 180 ms in all pigs. In the control state, the optimum VVD ranged from 20 to 40 ms and the worst VVD from 80 to 60 ms. Table 2 presents the average values at the optimum and worst VVD settings on the plots, because the optimum and worst VVD settings differed between pigs. 

Table 1. Optimization of AVD and VVD

<table>
<thead>
<tr>
<th>Control</th>
<th>RVPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimum AVD, ms</td>
<td>Optimum VVD, ms</td>
</tr>
<tr>
<td>150</td>
<td>0</td>
</tr>
<tr>
<td>150</td>
<td>−20</td>
</tr>
<tr>
<td>150</td>
<td>20</td>
</tr>
<tr>
<td>150</td>
<td>40</td>
</tr>
<tr>
<td>150</td>
<td>0</td>
</tr>
<tr>
<td>150</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are means (SD) unless otherwise stated. AVD, atrioventricular delay; RVPO, right ventricular (RV) pressure overload; VVD, interventricular pacing delay. Positive VVD indicates RV-first pacing.

Table 2. Effects of acute RVPO

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>RVPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO, l/min</td>
<td>2.6 (0.9)</td>
<td>2.6 (0.5)</td>
</tr>
<tr>
<td>EDP, mmHg</td>
<td>3.9 (1.6)</td>
<td>5.4 (1.1)*</td>
</tr>
<tr>
<td>RV</td>
<td>8.4 (1.3)</td>
<td>6.7 (3.1)</td>
</tr>
<tr>
<td>LV</td>
<td>4.5 (0.8)</td>
<td>0.5 (1.7)*</td>
</tr>
<tr>
<td>Gradient</td>
<td>2.0 (0.5)</td>
<td>0.5 (0.5)</td>
</tr>
<tr>
<td>dP/dtmax, mmHg/s</td>
<td>169 (38)</td>
<td>240 (63)*</td>
</tr>
<tr>
<td>RV</td>
<td>652 (121)</td>
<td>485 (52)*</td>
</tr>
<tr>
<td>LV</td>
<td>485 (52)</td>
<td>276 (15)*</td>
</tr>
<tr>
<td>tRVP, ms</td>
<td>180 (15)</td>
<td>249 (11)</td>
</tr>
<tr>
<td>tLVP, ms</td>
<td>238 (17)</td>
<td>276 (15)*</td>
</tr>
<tr>
<td>APP</td>
<td>0.23 (0.10)</td>
<td>−0.10 (0.16)*</td>
</tr>
</tbody>
</table>

Values are means (SD) for 6 animals. APP, area of normalized RV-LV pressure diagram; CO, cardiac output; EDP, end-diastolic pressure; dP/dtmax, maximum rate of increase of ventricular pressure; tRVP and tLVP, time to peak RV and LV pressure, respectively. Positive APP indicates RV pressure preceding LV pressure. *P < 0.05 vs. control.
During RVPO, the optimum VVD ranged from 20 to 60 ms and the worst VVD from −80 to −20 ms.

Effects of acute RVPO. Table 2 presents the effects of inducing RVPO during simultaneous BiVP (VVD = 0 ms) at the optimum AVD. Induction of RVPO increased RV EDP, RV dP/dt max, and the time to peak RV pressure but decreased the EDP gradient and LV dP/dt max and reversed A PP from positive to negative.

Effects of varying VVD. Figure 2A summarizes the effect of VVD on average CO. In the control state, there was a peak in CO with nearly simultaneous stimulation of the RV and LV (VVD = 0–20 ms, \( P = 0.001 \)). During RVPO, CO peaked with RV-first pacing (VVD = 20–40 ms, \( P = 0.001 \)). Figure 2B shows the effect of VVD on the average EDP gradient. In control and RVPO, the EDP gradient decreased with RV-first pacing and increased with LV-first pacing (\( P = 0.001 \)). This reflects that, by our definition, when the RV is paced first, the RV is already generating pressure at LV ED, and when the LV is paced first, the RV is still in the filling phase at LV ED. During RVPO, the EDP gradient-VVD relation shifted downward (\( P = 0.002 \)) because of the increase in RV EDP. There was no effect of VVD on RV or LV EDP (not shown).

Figure 3, A and B, demonstrates the result of altering VVD on LV dp/dt max. In the control state, there was a small peak in LV dp/dt max with nearly simultaneous stimulation of the RV and LV (VVD = 0–20 ms, \( P = 0.016 \)), most likely reflecting effects of changes in regional LV synchrony (2). During RVPO, LV dp/dt max changed little with LV-first pacing but decreased slightly with RV-first pacing (\( P = 0.016 \)). The absolute LV dp/dt max-VVD relation was shifted downward during RVPO (Fig. 3C; \( P = 0.025 \)), but the decrease in LV EDP was not statistically significant.

Figure 4A illustrates the effect of VVD on interventricular synchrony measured by average A PP. In control and RVPO, A PP increased with RV-first pacing and decreased with LV-first pacing (\( P < 0.001 \)). During RVPO, the A PP-VVD curve shifted downward (\( P < 0.001 \)) because of the increase in the time to peak RV pressure. Figure 4B demonstrates the relation between average RV dp/dt max and average A PP. In control and RVPO, RV dp/dt max was linearly related to A PP (\( r = 0.779, P < 0.001 \)). During RVPO, the RV dp/dt max-A PP relation shifted rightward (\( P < 0.001 \)), reflecting the downward shift in the A PP-VVD curve. Figure 4C illustrates the relation between average CO and average A PP. CO increased with increasing A PP to a maximum and then decreased. In control, CO peaked with positive A PP, however, during RVPO, CO peaked with A PP approaching zero as the relation was shifted to the right.

Effects of BiVP optimization. Table 3 presents the average effects of VVD optimization. In the control state and RVPO, optimization increased CO, RV dp/dt max, and A PP. However, LV dp/dt max increased only in the control state, and the EDP
gradient decreased only during RVPO. In control and RVPO, the percent change of RV $dP/dt_{max}$ was greater than the percent change of LV $dP/dt_{max}$.

**DISCUSSION**

The present results demonstrate that VVD optimization during BiVP increased CO and RV $dP/dt_{max}$. RV $dP/dt_{max}$ was linearly related to $A_{PP}$, a measure of mechanical interventricular synchrony. The relation of CO to $A_{PP}$ was curvilinear, with a peak in CO that occurred with positive $A_{PP}$ in the control state and with $A_{PP}$ approaching zero during RVPO. These observations imply that CO is dependent on RV contractility and interventricular synchrony. Increased afterload during RVPO exaggerates this effect, inasmuch as CO becomes critically dependent on simultaneous pressure generation in the RV and LV, with support of RV contractility by transmission of LV pressure across the interventricular septum.

**Ventricular contractility and interventricular synchrony.** In this experiment, the effect of VVD was greater on RV $dP/dt_{max}$ than on LV $dP/dt_{max}$ (Table 3). In control and RVPO, RV $dP/dt_{max}$ increased with RV-first pacing (VVD/H11022 0 ms) and decreased with LV-first pacing (Fig. 3, A and B). Although $dP/dt_{max}$ is known to be preload dependent (35), there were no changes in RV EDP with VVD, so the effect of VVD optimization did not appear to be mediated by EDP. In studies by Damiano et al., similar effects of VVD on RV $dP/dt_{max}$ (13) and CO (12) were observed in an electrically isolated RV preparation. The mechanism of their observations, however, was not completely defined.

We hypothesize that benefits of VVD in our experiment are mediated by the contribution of LV contraction to RV contractility. The LV can contribute directly to RV contractility via mechanical coupling of the ventricles, inasmuch as continuity of the RV free wall with the LV myocardium permits the transmission of forces generated by LV contraction (7). This is supported by studies showing that 1) surgical replacement of the RV free wall with a prosthetic patch has little effect on RV $dP/dr$ (50, 52), 2) alteration of LV free wall function directly affects RV developed pressure (49), and 3) one of the peaks of RV $dP/dr$ coincides with the peak of LV $dP/dr$ (13, 14, 17, 38). In our study, RV $dP/dt_{max}$ was linearly related to $A_{PP}$ in control and RVPO (Fig. 4B). Thus changes in interventricular synchrony may have changed the amount and timing of the LV contribution to RV $dP/dt_{max}$.

**Table 3. Effects of BiVP optimization**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th></th>
<th>Change</th>
<th></th>
<th>RVPO</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Optimum</td>
<td>Minimum</td>
<td>Change</td>
<td>Optimum</td>
<td>Minimum</td>
<td>Change</td>
</tr>
<tr>
<td></td>
<td>2.7 (0.9)*</td>
<td>2.4 (0.8)</td>
<td>10.2 (4.3)</td>
<td>2.7 (0.6)*</td>
<td>2.4 (0.6)</td>
<td>12.5 (7.5)</td>
</tr>
<tr>
<td>EDP, mmHg</td>
<td>RV: 3.9 (1.6)</td>
<td>3.8 (1.6)</td>
<td>3.7 (11.8)</td>
<td>RV: 5.3 (1.0)</td>
<td>5.3 (1.0)</td>
<td>0.0 (4.3)</td>
</tr>
<tr>
<td></td>
<td>LV: 8.3 (1.6)</td>
<td>8.4 (1.5)</td>
<td>1.3 (2.9)</td>
<td>LV: 6.5 (3.4)</td>
<td>6.8 (3.3)</td>
<td>5.1 (10.2)</td>
</tr>
<tr>
<td></td>
<td>Gradient: 4.3 (0.9)</td>
<td>4.7 (1.2)</td>
<td>0.4 (0.6)</td>
<td>Gradient: 0.1 (1.8)*</td>
<td>1.4 (2.1)</td>
<td>0.1 (1.2)*</td>
</tr>
<tr>
<td>dP/dt_{max}, mmHg/s</td>
<td>RV: 173 (35)*</td>
<td>143 (22)</td>
<td>20.1 (9.5)‡</td>
<td>RV: 247 (60)*</td>
<td>225 (54)</td>
<td>10.5 (5.4)‡</td>
</tr>
<tr>
<td></td>
<td>LV: 652 (112)*</td>
<td>629 (111)</td>
<td>3.9 (1.9)</td>
<td>LV: 468 (51)</td>
<td>489 (80)</td>
<td>3.4 (7.5)‡</td>
</tr>
<tr>
<td></td>
<td>$A_{PP}$: 0.27 (0.12)*</td>
<td>0.03 (0.12)</td>
<td>0.24 (0.11)</td>
<td>$A_{PP}$: 0.00 (0.15)*</td>
<td>0.22 (0.10)</td>
<td>0.22 (0.08)</td>
</tr>
</tbody>
</table>

Values are means (SD) for 6 animals. Change category values are percentages except for Gradient and $A_{PP}$ values.*$P < 0.05$ vs. minimum. †$P < 0.05$ vs. control. ‡$P < 0.05$ vs. LV $dP/dt_{max}$.
The effect of ventricular interdependence is especially important in the response of the RV to RVPO (48). RVPO is known to cause RV free wall dysfunction (21) and a leftward shift of the interventricular septum (7). This constrains LV filling and compromises septal contraction. The direction of changes in the EDP gradient with optimization during RVPO in our study would have been expected to shift the septum leftward and adversely affect LV output. However, CO improved. This implicates butressing of the interventricular septum as \( A_{pp} \) approaches zero during RVPO (simultaneous RV and LV pressure), thus enhancing the effectiveness of septal and RV free wall contraction (16, 61).

Although we would not have anticipated a dependence of CO on \( A_{pp} \) in the control state, positive \( A_{pp} \) did optimize CO. This suggests that RV contractility can be dependent on interventricular synchrony, even with normal ventricular loading. In fact, \( A_{pp} \) was similar to previously reported data in animals with normal hearts in sinus rhythm, including anesthetized pigs [\( A_{pp} = 0.21 \, (0.11) \); unpublished observations] and dogs [\( A_{pp} = 0.38 \, (0.11) \)] (60).

Others have related interventricular synchrony to acute improvements in cardiac function during BiVP. Yu et al. (62) showed decreased \( A_{pp} \) and increased LV \( dp/dt_{max} \) in patients with severe heart failure who responded to BiVP. Alternate indexes have also been utilized during simultaneous (4, 10, 26, 51, 57) and sequential (9, 58) BiVP. However, there have been no studies relating the effect of interventricular synchrony to RV contractility.

Pacing has rarely been used to treat the failing RV. Electrical resynchronization with RV pacing has shown to acutely increase arterial systolic and pulse pressure (23), as well as cardiac index and RV \( dp/dt_{max} \) (15), in patients with congenital heart disease. BiVP has been shown to acutely increase the aortic velocity-time integral and RV \( dp/dt_{max} \), and to decrease the RV-LV preejection period in patients with systemic RV failure (22), and to increase RV ejection fraction in a single patient with previous Mustard repair (11). LV EDP did not increase with optimization, despite increased RV stroke volume, which should have increased LV filling (18). Previously, however, we demonstrated increased ED area with optimization in a similar experiment (43). This may reflect the insensitivity of EDP to small changes in preload.

**Clinical implications.** The present observations emphasize that indexes of LV function, including LV \( dp/dt_{max} \) and regional LV synchrony, are insufficient to assess the efficacy of BiVP during RV dysfunction. Continuous measurement of CO is needed to avoid error (54).

Relevance of the present study to BiVP for the treatment of ventricular dysfunction after cardiac surgery is limited to short-term effects in RVPO. Most clinical heart failure involves LV dysfunction. In that setting, intraventricular synchrony and mitral valve function are known to be important (2). Although short-term hemodynamic improvement is often associated with long-term clinical benefit of BiVP (1, 55), the relation is complex and not well established.

**Methodological considerations.** In previous studies from our laboratory, optimized BiVP improved CO up to 20% during acute RVPO (45); more modest improvements are described here. This reflects a more modest objective of snaring the pulmonary artery: from decreasing CO by 50% to doubling peak RV pressure. Effects of BiVP are dependent on the severity of cardiac dysfunction (24). Therefore, the smaller benefit seen in the present study may reflect a smaller degree of RVPO. Alternatively, greater hemodynamic instability in previous studies may have amplified the apparent benefit of optimization. As well, AV node ablation with ethanol injection into the region of the bundle of His could have caused myocardial damage, affecting regional ventricular contraction and overall function.

A weakness of our study protocol was optimizing AVD and VVD independently. This does not account for the interdependence of these variables, nor does it account for a possible nonlinear cumulative effect. Ideally, all pacing variables should be simultaneously varied, and all possible combinations should be tested (41, 42, 44). Furthermore, we changed AVD and VVD in sequential fashion. In our present studies of BiVP, variables are changed simultaneously in a randomized sequence.

We did not account for the fact that changes in ventricular \( dp/dt_{max} \) could reflect changes in regional ventricular synchrony (8, 29, 37) or that septal contraction could be altered by changes in ventricular activation (20, 33). Tissue Doppler imaging or three-dimensional echocardiography should be employed in future studies to examine these issues.

In conclusion, during BiVP optimization in our model, CO is improved by increased RV contractility mediated by changes in mechanical interventricular synchrony. Afterload increases during RVPO exaggerate this effect, making CO critically dependent on simultaneous pressure generation in the RV and LV, with support of RV contractility by transmission of LV pressure across the interventricular septum. Interventricular synchrony merits further examination during acute studies of BiVP in patients, especially during altered ventricular loading.

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