



Effects of sequential biventricular pacing during acute right ventricular pressure overload

T. Alexander Quinn,¹ George Berberian,² Santos E. Cabreriza,² Lauren J. Maskin,² Alan D. Weinberg,³ Jeffrey W. Holmes,¹ and Henry M. Spotnitz²

Departments of ¹Biomedical Engineering, ²Surgery, and ³Biostatistics, Columbia University, New York, New York

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Quinn, T. Alexander, George Berberian, Santos E. Cabreriza, 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/dt_{max}). Mechanical interventricular synchrony was measured by the area of the normalized RV-left ventricular (LV) pressure diagram (A_{PP}). Positive A_{PP} 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/dt_{max} ($P = 0.002$). During RVPO, CO was maximized with RV-first pacing, which increased RV dP/dt_{max} ($P = 0.007$), but did not affect LV dP/dt_{max} , and decreased the left-to-right, end-diastolic pressure gradient ($P = 0.023$). Percent increase of RV dP/dt_{max} was greater than LV dP/dt_{max} ($P = 0.014$). There were no increases in end-diastolic pressure to account for increases in dP/dt_{max} . In control and RVPO, RV dP/dt_{max} was linearly related to A_{PP} ($r = 0.779$, $P < 0.001$). The relation of CO to A_{PP} was curvilinear, with a peak in CO with positive A_{PP} in the control state ($P = 0.004$) and with A_{PP} 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.

ventricular mechanics; interventricular synchrony; cardiac output; perioperative pacing; cardiac resynchronization therapy

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 Harlak, 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 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ for arrhythmia prophylaxis. To maintain blood volume, 0.9% saline solution was administered intra-

Address for reprint requests and other correspondence: H. M. Spotnitz, Columbia Univ. College of Physicians & Surgeons, 622 W. 168th St., PH 14-103, New York, NY 10032 (e-mail: hms2@columbia.edu).

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venously at $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for 1 h and then at $5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ 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 ($100 \text{ U} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$).

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 clipped 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 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 (25). Immediately after complete heart block, dual-chamber mode (DDD) simultaneous BiVP (VVD = 0 ms) at a heart rate of 90 or 5 beats/min above the intrinsic rate (required during RVPO in 2 pigs at 97 and 110 beats/min) was initiated. After 5 min for normalization of hemodynamics, the AV pacing delay (AVD) was varied between 60 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). After data in the control state were obtained, the pulmonary artery was snared until peak RV pressure doubled, which induced acute RVPO. After 5 min for normalization of hemodynamics, the pacing protocol was repeated. The animals were humanely killed at the conclusion of the experiment.

Data 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 (ADIstruments, Milford, MA) and recorded on a personal computer (Apple Computer, Cupertino, CA). Off-line analysis was performed using custom routines implemented in Matlab (MathWorks, Natick, MA). All signals were smoothed using a five-point moving average. The RV and LV pressure signals were differentiated by a five-point Lagrange interpolating technique (34).

End diastole. In contrast to normal physiology, with near-simultaneous 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/dt_{max}). ED pressure (EDP) for each ventricle was taken at the respective ED point. The transseptal 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/dt_{max} . 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

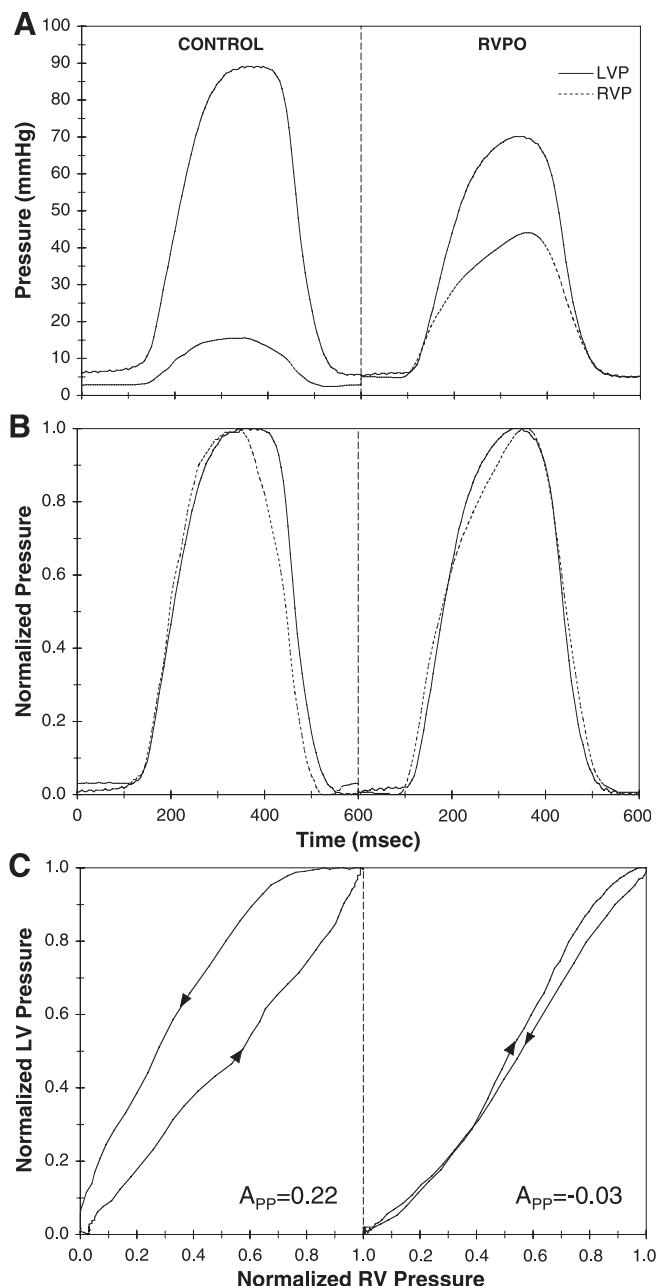


Fig. 1. Representative examples of raw (A) and normalized (B) right ventricular (RV) and left ventricular (LV) pressure (RVP and LVP, respectively) curves and resulting normalized RV-LV pressure diagrams (C) for optimum interventricular pacing delay (VVD) during control and RV pressure overload (RVPO). 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.

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. All variables were averaged over three cardiac cycles at end expiration, defined as the low point in mean arterial pressure during respiratory variation. Values of CO and dP/dt_{max} were normalized by the value during simultaneous BiVP (VVD = 0 ms) in each pig before values were averaged to reduce variability between pigs. The optimum VVD was defined as the setting that produced the

Table 1. Optimization of AVD and VVD

| | Control | | | RVPO | | |
|-----------|-----------------|------------|--------------|-----------------|-------------|--------------|
| | Optimum AVD, ms | VVD, ms | | Optimum AVD, ms | VVD, ms | |
| | | Optimum | Minimum | | Optimum | Minimum |
| 1 | 150 | 0 | -80 | 150 | 60 | -20 |
| 2 | 150 | -20 | -60 | 150 | 40 | -60 |
| 3 | 150 | 20 | -60 | 180 | 20 | -40 |
| 4 | 150 | 40 | -80 | 180 | 40 | -80 |
| 5 | 150 | 0 | -60 | 150 | 40 | -80 |
| 6 | 150 | 0 | -80 | 150 | 20 | -20 |
| Mean (SD) | 150 (0) | 6.7 (20.7) | -70.0 (11.0) | 160 (15) | 36.7 (15.1) | -50.0 (27.6) |

AVD, atrioventricular delay; RVPO, right ventricular (RV) pressure overload; VVD, interventricular pacing delay. Positive VVD indicates RV-first pacing.

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/dt_{max} 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/dt_{max} and A_{PP}. 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

Table 2. Effects of acute RVPO

| Variable | Control | RVPO |
|-------------------------------|-------------|---------------|
| CO, l/min | 2.6 (0.9) | 2.6 (0.5) |
| EDP, mmHg | | |
| RV | 3.9 (1.6) | 5.4 (1.1)* |
| LV | 8.4 (1.3) | 6.7 (3.1) |
| Gradient | 4.4 (0.8) | 0.5 (1.7)* |
| dP/dt _{max} , mmHg/s | | |
| RV | 169 (38) | 240 (63)* |
| LV | 652 (121) | 485 (52)* |
| t _{RVP} , ms | 180 (15) | 276 (15)* |
| t _{LVP} , ms | 238 (17) | 249 (11) |
| A _{PP} | 0.23 (0.10) | -0.10 (0.16)* |

Values are means (SD) for 6 animals. A_{PP}, area of normalized RV-LV pressure diagram; CO, cardiac output; EDP, end-diastolic pressure; dP/dt_{max}, maximum rate of increase of ventricular pressure; t_{RVP} and t_{LVP}, time to peak RV and LV pressure, respectively. Positive A_{PP} indicates RV pressure preceding LV pressure. **P* < 0.05 vs. control.

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 A_{PP} is positive in the control state and negative during RVPO (Fig. 1C).

Optimization of AVD and VVD. Table 1 presents the optimum AVD and the 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.

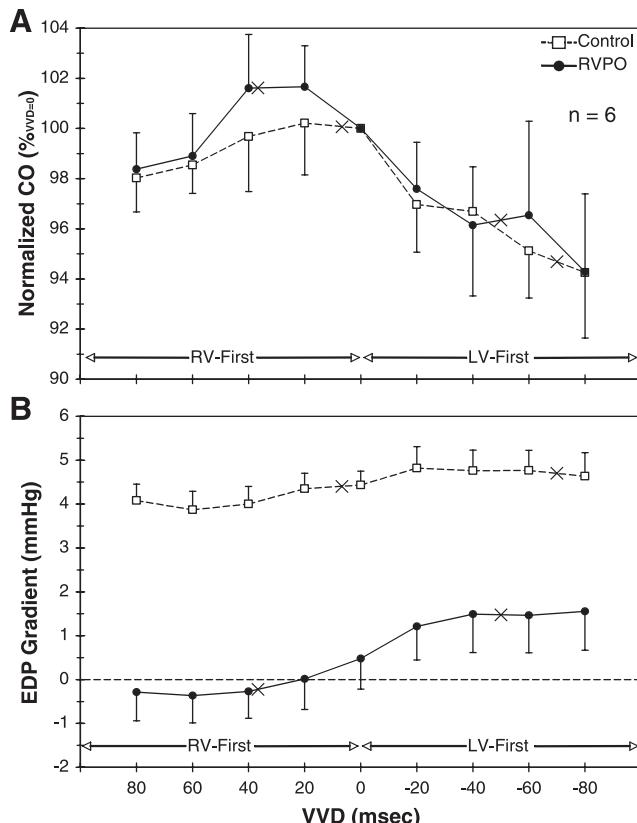


Fig. 2. Effect of VVD on cardiac output (CO, A) and transseptal end-diastolic pressure (EDP) gradient (B) during control and RVPO. ×, Average optimum and worst VVD settings. Positive VVD indicates RV-first pacing. Positive EDP gradient indicates greater LV than RV pressure. Values of CO were normalized by the value during simultaneous biventricular pacing (BiVP) in each pig (%vvd=0). Values are means ± SE.

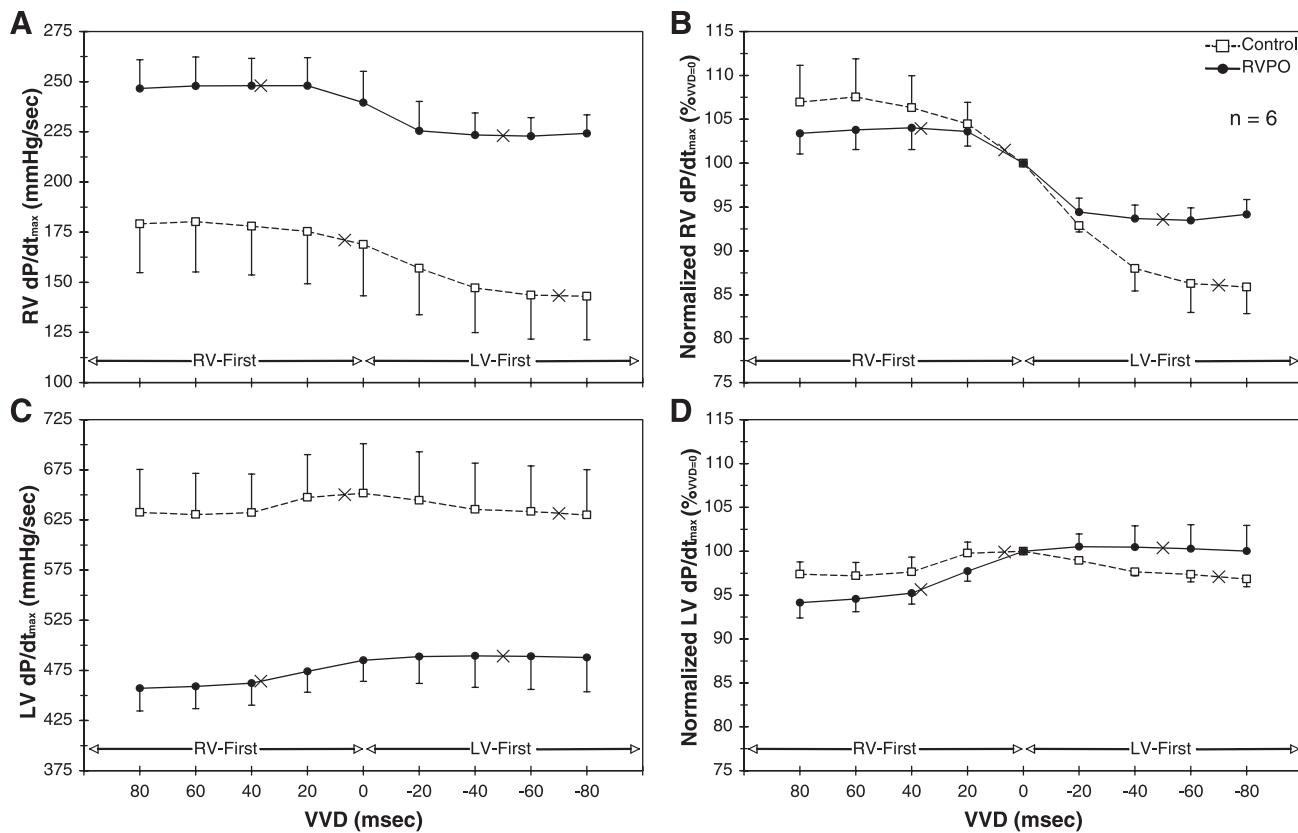


Fig. 3. Effect of VVD on absolute (A and C) and normalized (B and D) RV and LV maximum rate of pressure increase (dP/dt_{max}) during control and RVPO. Values of dP/dt_{max} were normalized by the value during simultaneous BiVP in each pig ($\%_{VVD=0}$). Values are means \pm SE.

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 effect of VVD on average RV dP/dt_{max} . In control and RVPO, RV dP/dt_{max} increased with RV-first pacing and decreased with LV-first pacing ($P < 0.001$). During RVPO, the absolute RV dP/dt_{max} -VVD relation shifted upward (Fig. 3A; $P = 0.040$) because of the increase in RV EDP (35). This led to a smaller change in normalized RV dP/dt_{max} during RVPO (Fig. 3B; $P < 0.001$).

Figure 3, C and D, 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

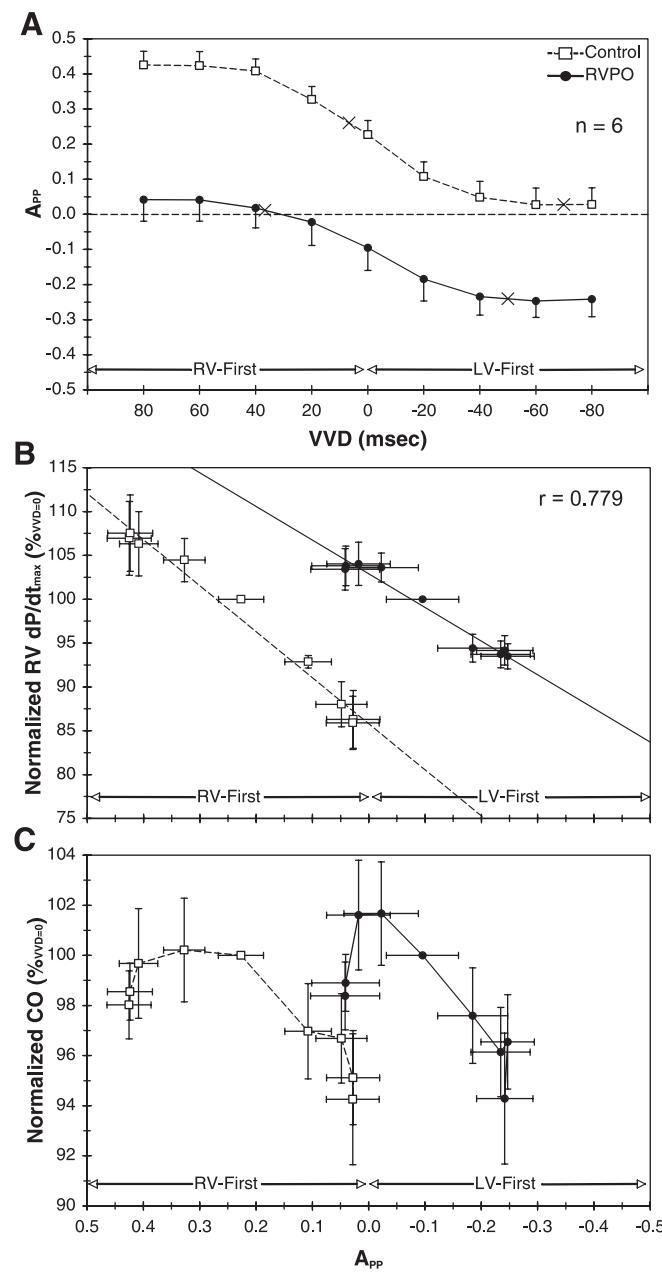


Fig. 4. Effect of VVD on A_{PP} (A) and relation of A_{PP} to normalized RV dP/dt_{max} (B) and normalized CO (C) during control and RVPO. Positive A_{PP} indicates RV pressure preceding LV pressure; zero indicates complete synchrony. Values are means \pm SE.

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 ($VVD > 0$ 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/dt (50, 52), 2) alteration of LV free wall function directly affects RV developed pressure (49), and 3) one of the peaks of RV dP/dt coincides with the peak of LV dP/dt (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

| Variable | Control | | | RVPO | | |
|------------------------|--------------|-------------|-------------|--------------|--------------|--------------|
| | Optimum | Minimum | Change | Optimum | Minimum | Change |
| CO, l/min | 2.7 (0.9)* | 2.4 (0.8) | 10.2 (4.3) | 2.7 (0.6)* | 2.4 (0.6) | 12.5 (7.5) |
| EDP, mmHg | | | | | | |
| RV | 3.9 (1.6) | 3.8 (1.6) | 3.7 (11.8) | 5.3 (1.0) | 5.3 (1.0) | 0.0 (4.3) |
| LV | 8.3 (1.6) | 8.4 (1.5) | -1.3 (2.9) | 6.5 (3.4) | 6.8 (3.3) | -5.1 (10.2) |
| Gradient | 4.3 (0.9) | 4.7 (1.2) | -0.4 (0.6) | -0.1 (1.8)* | 1.4 (2.1) | -1.5 (1.2)† |
| dP/dt_{max} , mmHg/s | | | | | | |
| RV | 173 (35)* | 143 (22) | 20.1 (9.5)‡ | 247 (60)* | 223 (54) | 10.5 (5.4)‡‡ |
| LV | 652 (112)* | 629 (111) | 3.9 (1.9) | 468 (51) | 489 (80) | -3.4 (7.5)† |
| A_{PP} | 0.27 (0.12)* | 0.03 (0.12) | 0.24 (0.11) | 0.00 (0.15)* | -0.22 (0.10) | 0.22 (0.08) |

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 buttressing 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 been 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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