Quantitative assessment of independent contributions of pericardium and septum to direct ventricular interaction

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Baker, A. E., R. Dani, E. R. Smith, J. V. Tyberg, and I. Belenkie. Quantitative assessment of independent contributions of pericardium and septum to diastolic ventricular interaction. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H476–H483, 1998.—In the intact animal, it is difficult to discriminate between the independent effects of series and direct ventricular interaction (DI) or the individual contributions of the pericardium and septum to DI. Left ventricular (LV) venous return (LVVR) and right ventricular (RV) end-diastolic pressure (RVEDP) were varied independently in a right-heart bypass model. LV minor-axis diameters were measured, and the product of the two diameters was used as an index of LV volume (LVVI). At each RVEDP (0, 5, 10, and 15 mmHg), increased LVVR caused an increased LVVI. When RVEDP was increased, increased pump output was required to maintain a given LVVI. RV-to-LV pressure gain (ΔLVEDP/ΔRVEDP) reflects coupling and DI. With the pericardium closed, the gain was dependent on RVEDP; when RV output was increased from 0 to 5 mmHg, the gain was not statistically different from zero, indicating little or no DI. When RV output was increased from 10 to 15 mmHg, the gain was not statistically different from 1.0, indicating a 1:1 coupling of the ventricles. Opening the pericardium reduced the gain, but significant interaction remained. When the septal contribution was accounted for, the remaining interaction was eliminated. In conclusion, DI substantially affects LV volume relations. Considerable increases in RV output may be required to counterbalance increased constraint to LV filling. With the pericardium closed, RV-to-LV coupling is minimal when RVEDP is low and increases to 1:1 coupling when RVEDP is high. Opening the pericardium reduces DI, but significant septum-mediated interaction remains.

ventricular interdependence; ventricular mechanics; diastole; diastolic interaction

BECAUSE THE RIGHT and left ventricles (RV and LV, respectively) function in series, share a common septum, and are enclosed in a relatively incompressible pericardium, changes in function of one ventricle can affect that of the other. Diastolic ventricular interaction involves two components. Interaction via RV output (equal to LV venous return, LVVR) is termed series interaction, and interaction via the septum and pericardium is termed direct ventricular interaction (DI). Diastolic interaction has been studied extensively, and many of its characteristics have been clarified (4, 6, 9, 11, 13, 15, 16, 22, 24, 30). Normally, series interaction is the dominant physiological mechanism. However, increased LV constraint due to increased pericardial pressure (PP) and/or RV end-diastolic pressure (RVEDP) may have substantial hemodynamic effects. The importance of series interaction vs. DI and the relative contributions of the septum and pericardium to DI are not yet clear.

We have previously shown that DI plays an important role in determining the hemodynamic response to acute pulmonary embolism (1–3). After severe acute pulmonary embolization with the pericardium closed, volume loading decreased LV end-diastolic volume and stroke work, although with the pericardium opened, volume loading increased LV end-diastolic volume and stroke work (3). These studies demonstrated that although RV output (i.e., series interaction) is clearly important, constraint to LV filling (i.e., DI) may contribute significantly to the hemodynamic responses to acute pulmonary embolism and subsequent volume loading and unloading.

The relative contributions of series vs. direct ventricular interaction were not addressed in our previous work. In the intact heart, this question has been difficult to resolve because most interventions affect both mechanisms. For example, pulmonary artery constriction or embolism increases RVEDP but also decreases LVVR. In the present study, we used a canine right-heart bypass model in which both pump output (the series component) and RVEDP (a determinant of DI) could be controlled independently to separate the effects of the series and direct components of ventricular interaction. We applied the interventions while the pericardium was closed and again when it was open to discriminate between the pericardial and septal contributions to DI.

METHODS

Animal preparation. After premedication with 0.75 mg/kg morphine sulfate, 11 dogs weighing 19–29 kg were anesthetized, initially with thiopental sodium (10–15 mg/kg iv), and then maintained with fentanyl citrate (50 µg/kg iv over 5 min followed by 20–50 µg·kg⁻¹·h⁻¹). Additional boluses were administered and infusion rates were adjusted as necessary. The animals were ventilated with a 70% nitrous oxide-30% oxygen mixture using a constant-volume respirator (model 607, Harvard Apparatus, Natick, MA).

LV and RV pressures were measured with 8-Fr micrometer-tipped catheters with reference lumens (model PR279, Millar Instruments, Houston, TX) inserted through a femoral artery and an RV cannula, respectively. Aortic pressure was measured with a fluid-filled catheter introduced through the other femoral artery. An electrocardiographic lead and a signal generated by the ventilator to indicate end expiration were also recorded.

A midline sternotomy was performed with the dog in the supine position. The ventral surface of the pericardium was incised transversely along the base of the heart, and the heart was delivered from the pericardium for instrumentation. A flat, liquid-containing balloon was sutured loosely to the anterolateral surface of the LV to measure PP (1). Septum-to-LV free wall and LV anteroposterior diameters were mea-
sured by sonomicrometry (Triton Technology, San Diego, CA) (3).

The dog was then prepared for right-heart bypass (Fig. 1). The vena cavae were cannulated and drained to a reservoir, where the blood was filtered and heated. The circuit was primed with fresh blood from a donor dog. A roller pump (Sarns, Ann Arbor, MI) was used to pump blood from the reservoir to the pulmonary artery, the flow (LVVR) being measured with an ultrasonic flow probe (Transonic Systems, Ithaca, NY) positioned on the pulmonary artery cannula. An 11-mm cannula connected to a height-adjustable reservoir was inserted into the right atrium to drain the coronary sinus flow and to control RV filling pressure. The azygous veins were tied off, and the heart was then returned to the pericardial sac, the edges of which were loosely reapproximated with several individual sutures, with care taken to avoid decreasing the pericardial volume.

Conditioned signals (model VR16, PPG Biomedical Systems, Lenexa, KS) were recorded on a personal computer (IBM, Armonk, NY). The analog signals were passed through anti-aliasing low-pass filters with cutoff frequencies of 100 Hz and were sampled at a frequency of 200 Hz. The digitized data were subsequently analyzed on a personal computer using a software package developed in our laboratory (CVSOFT, Odessa Computer Systems, Calgary, Alberta, Canada).

Experimental protocol. The right-heart bypass model used in this study allowed for independent control of LVVR and RVEDP. Thus series interaction was controlled by adjusting pump output (i.e., LVVR), and DI was varied by changing the height of the RV reservoir (i.e., RVEDP). Initially, LVVR was adjusted so that LV end-diastolic pressure (LVEDP) was \(8\) mmHg.

While RVEDP was maintained at 0 mmHg by adjusting the height of the reservoir above the RV, pump output was varied over a wide range. Over a period of \(4\) min, LVVR was first decreased by reducing the pump output until systemic aortic pressure decreased to \(60\) mmHg and then increased incrementally until LVEDP was at least 20 mmHg. Pump output was then returned to the control rate. To assess the effects of increasing degrees of DI, the height of the reservoir above the RV was then raised to maintain RVEDP at 5 mmHg. LVVR

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**Fig. 1.** A schematic diagram of right ventricular (RV) bypass model. Superior vena cava (SVC) and inferior vena cava (IVC) were cannulated and drained to pump reservoir; pump returned systemic venous blood to pulmonary artery, simulating RV output. Pulmonary artery (PA) flow was measured with an ultrasonic flow probe. A cannula was used to drain coronary sinus flow into a height-adjustable reservoir above RV. Thus series component was controlled by adjusting pump output (equal to left ventricular (LV) venous return), and direct component (RV end-diastolic pressure) was altered by adjusting height of RV reservoir.
was then varied over the same range as described above. The procedure was then repeated with RVEDP maintained at 10 and 15 mmHg.

To assess the pericardial and septal contributions to DI, the pericardium was opened and the entire protocol was repeated. Only data collected at end expiration were analyzed. Transmural LVEDP was calculated in two ways: 1) $\text{LVEDP}_T = \text{LVEDP} - \text{PP}$, and 2) $\text{LVEDP}_T = \text{LVEDP} - \text{PP}$. The product of the LV minor-axis diameters (anteroposterior septum-to-free wall diameter) was used as an index of LV area and, hence, volume (LVVI). LVVR was measured as pump output, and stroke volume (SV) was calculated as pump output per beat. End-diastolic pressure-volume curves (LVEDP-LVVI) were plotted for each dog, and the curves were fitted to second-order equations. Normalized data from each dog were combined for analysis. Baseline LVVI (i.e., 100%) was defined as the LVVI observed at an LVEDP of 5 mmHg with the pericardium open (PP = 0) and RVEDP = 0 mmHg. For a single dog, because of missing data when the pericardium was open and RVEDP was 0 mmHg, 100% LVVI was defined as the volume observed at an LVEDP of 5 mmHg and RVEDP of 5 mmHg with the pericardium open. Other values of LVVI were expressed as percentages of the above-defined baseline value to compare data from different dogs. To assess the relationship between LVVR and external constraint, these data were summarized by recording the SV at each level of RVEDP at LVVI values of 94, 100, and 106%. SV of 100% was defined as the LVVR per beat when the LVVI was 100%, RVEDP was zero, and the pericardium was closed. RV-to-LV end-diastolic pressure gain (i.e., the ratio of the change in LVEDP to the change in RVEDP, a measure of ventricular coupling) was determined at an LVVI of 100% for each increase in RVEDP. With the pericardium closed, pressure gains were calculated for each incremental change in RVEDP (i.e., RVEDP = 0–5, 5–10, and 10–15 mmHg). The pressure gains for each 5-mmHg change in RVEDP were calculated as mean values from paired data points. Pressure gains were also calculated for the pericardium-open data, but because there was no statistical difference between the gains for every 5-mmHg increase in RVEDP, these gains were calculated using linear regression for the entire range of RVEDP values (i.e., RVEDP = 0–15 mmHg).

Statistical analysis. For the pericardium-closed data, to determine if the pressure gain for each incremental change in RVEDP (i.e., RVEDP = 0–5, 5–10, and 10–15 mmHg) was different from each other, different from zero, and different from one, the mean differences from the paired data for each segment were compared using the Student’s paired t-test. To determine if opening the pericardium decreased DI, the RV-to-LV end-diastolic pressure gains for pericardium-closed and pericardium-open data over the interval between RVEDP = 10 and RVEDP = 15 mmHg were compared using the Student’s paired t-test. To determine if the remaining DI was significant, we compared the slope of the pericardium-open data to zero. The slope of the pericardium-open data was also compared with the slope of the $\text{LVEDP}_T$ data using two-way repeated-measures ANOVA to determine whether the gain indicated by the slope of the pericardium-open data was because of RVEDP. A P value $<0.05$ was considered significant.

To determine if changes in the LVVR vs. LVVI slopes at different degrees of external constraint (RVEDP values of 0, 5, 10, and 15 mmHg) were significant, we used two-way repeated-measures ANOVA. To isolate which groups were significantly different from the others, we used a multiple-comparisons procedure (Student-Newman-Keuls method).

Also, to determine if a greater change in LVVR was required to change LVVI from 100 to 106% than from 94 to 100% at a constant RVEDP, we compared the incremental slopes (i.e., LVVI of 94–100 vs. 100–106%) using two-way repeated-measures ANOVA. A P value $<0.05$ was considered significant. All data are presented as the means ± SE.

RESULTS

Independent effects of increasing pump output vs. increasing RVEDP. As illustrated in Fig. 2, the series contribution to ventricular interaction was characterized by the end-diastolic pressure-volume relations (LVEDP-LVVI) when LVVR was varied at constant RVEDP values (0, 5, 10, and 15 mmHg), whereas the direct component was characterized by the shifts in these curves when RVEDP was increased. When RVEDP was maintained constant at 0, 5, 10, or 15 mmHg, increasing LVVR increased LVVI along separate single LVEDP-LVVI curves, reflecting the contribution of the series component of ventricular interaction (Fig. 2A). Each increment in RVEDP shifted the LVEDP-LVVI curve upward and to the left, reflecting the contribution of the direct component of ventricular interaction. Transmural LVEDP-LVVI relations (calculated both ways, Fig. A).

Fig. 2. A: LV end-diastolic pressure (LVEDP)-LV volume index (LVVI) plots in a single dog with pericardium closed with RV end-diastolic pressure (RVEDP) held constant at 0 mmHg (circles), 5 mmHg (triangles), 10 mmHg (squares), and 15 mmHg (inverted triangles). At each RVEDP, as LV venous return increased, LVVI increased along a single curve representing series interaction. Curves shifted upward systematically as RVEDP was increased, representing direct interaction (DI). B: by plotting LV transmural pressure [LVEDP$_T$ = LVEDP – pericardial pressure (PP)], shift in curves was eliminated, indicating that DI had been accounted for. C: calculated LV transmural pressure using both RV and PP [LVEDP$_T$ = LVEDP – (2/3 PP + 1/3 RVEDP)] produced similar curves, implying that PP and RVEDP were similar.
2, B and C) eliminated the effects of constraint to LV filling by DI (pericardial and septal), and the curves became superimposed. In contrast to the pericardium-open behavior (see below), there was no significant difference between the LVEDP*T-LVVI and LVEDP^T-LVVI curves with the pericardium closed.

Figure 3 is derived from Fig. 2A and illustrates the degree to which pump output had to be increased to maintain a constant end-diastolic volume when RVEDP was increased. Each symbol represents a different range of SV values (pump output/beat). As RVEDP was increased from 0 to 15 mmHg, it can be seen that substantial increases in pump output were required to maintain a constant LVVI. The data from each experiment were summarized and combined in Fig. 4. LVVR per beat (in percent) is plotted as a function of LVVI at RVEDP values of 0, 5, 10, and 15 mmHg. Figure 4 indicates that increases in external constraint (RVEDP) resulted in progressive upward shifts of these curves; thus greater LVVR was required to maintain the same LV volume as RVEDP was increased. Also, the slopes of these curves increased as LV volume became larger, than illustrated by the steeper slope from 100 to 106% than from 94 to 100%.

Contributions of the pericardium and septum to DI. When the pericardium was open (i.e., PP = 0 mmHg), increases in RVEDP still shifted the pressure-volume relations upward, but the shifts were smaller (Fig. 5A). To evaluate the degree to which the remaining shift could be attributed to a septum-mediated mechanism, we subtracted the theoretical contribution of the septum to constraint (20); this eliminated the shifts in the LVEDP^T-LVVI relations (Fig. 5B), illustrating that the constraint that was still present with the pericardium open was septum mediated.

RV-to-LV end-diastolic pressure gain. Figure 6 shows the combined RV-to-LV end-diastolic pressure gains from all dogs at normalized LVVI values of 100%. With the pericardium closed (Fig. 6, solid circles), RV-to-LV pressure gain was not statistically different from zero when RVEDP was increased from 0 to 5 mmHg (0.22 ± 0.13). As RVEDP increased, the gain also increased, reaching a slope of 0.9 ± 0.15 (not statistically different from 1) when RVEDP was increased from 10 to 15 mmHg, indicating 1:1 coupling of the ventricles. The gain when RVEDP was increased from 5 to 10 mmHg fell in between these two extremes (0.57 ± 0.18). The difference in the pericardium-closed (Fig. 6, solid circles) vs. pericardium-open gains (Fig. 6, open circles) when RVEDP was 10–15 mmHg was statistically significant (P < 0.005). When the theoretical contribution of the septum was eliminated by subtracting one-third of the value of RVEDP (20) (Fig. 6, open triangles), the pericardium-open pressure gain was not significantly different from zero, indicating that the interaction remaining with the pericardium open could be explained by the septum.

DISCUSSION

The relationships between the series and direct mechanisms of diastolic ventricular interaction have not been adequately characterized previously because of the difficulty in controlling each component independently. We have previously shown that DI is an important determinant of the hemodynamic response to acute RV pressure loading and subsequent volume loading, but we could not quantify the effects of each component of ventricular interaction because both the series and direct mechanisms were affected simultaneously by our interventions (1–3). In the present study, our right-heart bypass model allowed us to manipulate and therefore assess the series and direct...
mechanisms independently, and by opening and closing the pericardium, we were also able to discriminate between the pericardial and septal contributions to DI. At each different RVEDP, the LV end-diastolic pressure-volume relation reflects the results of independent changes in RV output and, thus, series interaction. The shifts in these relations when RVEDP was increased reflect the results of changes in constraint to LV filling (i.e., DI). The shifts with the pericardium closed reflect constraint due to the pericardium plus septum, whereas shifts with the pericardium open are due to the septum alone.

Series vs. direct interaction. The contributions of the series component of ventricular interaction are illustrated by the LVEDP-LVVI relation at each RVEDP (Fig. 2A). When RVEDP was held constant and pump output was increased, LVEDP and volume both increased monotonically along a single curve. The effects of DI are illustrated by the upward and leftward shifts of these relations when RVEDP was increased reflect the results of changes in constraint to LV filling (i.e., DI). The shifts with the pericardium closed reflect constraint due to the pericardium plus septum, whereas shifts with the pericardium open are due to the septum alone.

During acute interventions that affect series interaction and DI simultaneously, the responses are a composite of the effects on both mechanisms. For example, during pulmonary artery constriction, there is a decrease in RV output and an increase in RVEDP; this results in decreased venous return to the LV and increased constraint to LV filling, both mechanisms tending to reduce LV end-diastolic volume. In the present model, we were able to demonstrate the impact of increased constraint to LV filling. Thus we had to increase RV output substantially to maintain a given LV end-diastolic volume (i.e., the same transmural pressure) when constraint was increased. For example (see Fig. 3), to maintain an end-diastolic volume index of 92%, pump output per beat had to be increased from 10 to 20 ml/beat when RVEDP was increased from 0 to 5 mmHg, to 30–40 ml/beat when RVEDP was increased to 10 mmHg, and to 50–60 ml/beat when RVEDP was increased to 15 mmHg, illustrating the dramatic increase in LVVR required to counterbalance the increasing DI. To further quantify the relationship between LVVR and different degrees of external constraint, we calculated the required LVVR to maintain representative smaller, normal, and larger LV end-diastolic areas at different levels of RVEDP (Fig. 4). As an illustration of the importance of this interaction, to maintain a normal LV end-diastolic volume (i.e., LVVI = 100%), when RVEDP was increased from 0 to 15 mmHg, LVVR had to be doubled. This demonstrates the interdependence of the series and direct mechanisms of ventricular interaction in that, as RVEDP is increased, more LVVR is required to maintain the same LVVI. Also, as a reflection of the curvilinear pressure-volume relations, a greater change in LVVR was required to change the LVVI from 100 to 106% than from 94 to 100%. Thus, as we have reported previously in acute pulmonary embolism, direct ventricular interaction can play a pivotal role.
role in the hemodynamic response, although both the series and direct components of the interaction contribute to the associated decrease in LV end-diastolic volume (1–3). To fully compensate for the adverse DI on LV end-diastolic volume, it would be necessary for RV output to increase substantially. The quantitative data from the present study underscore the potential importance of DI in the response to acute RV pressure loading.

Pericardial and septal contributions to DI. After the pericardium was opened (i.e., PP remained 0 throughout), increases in RVEDP resulted in smaller, but definitely present, shifts in the LVEDP-LVVI relations. Thus removal of pericardial constraint reduces but does not eliminate DI. This is consistent with the model proposed previously by Mirsky and Rankin (20). They suggested that the effective external pressure of the LV is a function of both RV and pericardial pressure, each weighted according to the respective surface areas over which they apply. Because the LV free wall constitutes approximately two-thirds of the LV surface and the interventricular septum one-third, the effective external pressure equals approximately two-thirds PP plus one-third RVEDP. Despite our not having measured surface areas or radii of curvature of the septum and LV free wall, application of this formula to our pericardium-open data still appeared to account for the differences between the LV pressure-volume curves, thus providing experimental support for their model. With the pericardium closed, the transmural LVEDP-LVVI relation (calculated using PP only) demonstrated little or no shift and was similar when we calculated transmural LVEDP using the Mirsky and Rankin algorithm (Fig. 2B). This is consistent with the fact that, when the pericardium was closed, RVEDP and PP were similar (1, 28, 29, 31). However, if RVEDP and PP are different, as was the case in our model when the pericardium was open and as can occur in acute RV or LV pressure loading (29), both should be considered when calculating LV transmural pressure.

RV-to-LV end-diastolic pressure gain. RV-to-LV end-diastolic pressure gain is the ratio of the change in end-diastolic pressure in the LV produced by change in pressure in the RV (ΔLVEDP/ΔRVEDP). As indicated by our results, the degree of coupling (RV-to-LV pressure gain) between the two ventricles is dependent on the degree of external constraint, with greater coupling observed at higher RVEDP values than at low RVEDP values. Our data indicate that at low RVEDP values (0–5 mmHg) there is little or no coupling of the ventricles (i.e., the slope was 0.22 ± 0.13 and not statistically different from 0). As RVEDP increases, the heart expands, external constraint increases, and the pressure-volume curve becomes steeper. When RVEDP was increased from 10 to 15 mmHg, our analysis indicated that coupling was effectively complete (i.e., the slope of the RV-to-LV pressure gain was 0.90 ± 0.15 and not statistically different from 1). Not surprisingly, there was an intermediate degree of coupling at intermediate values of RVEDP (5–10 mmHg). Therefore, as external constraint increases, the RV-to-LV end-diastolic pressure gain increases to approximately one. This relationship may be particularly relevant in patients with severe congestive heart failure when ventricular filling pressures frequently exceed those produced in our experimental model. Indeed, Janicki (12) has provided such evidence of pericardial constraint during exercise in patients with varying severity of heart failure.

After the pericardium was opened and the pericardial effects eliminated, the pressure gain decreased but was still significant. As indicated earlier, the remaining gain with the pericardium open represents the residual DI due to the shared septum. Thus, with calculation of LV transmural pressure taking RVEDP into account, RV-to-LV pressure gain became zero as predicted (20).

Although a wide range of RV-to-LV pressure gains have been reported in the literature, our data are consistent with those of others who have reported that opening the pericardium substantially reduces but does not eliminate DI (4, 7, 8, 10, 13, 17, 18, 23, 27). In arrested canine hearts, Maruyama et al. (18) reported RV-to-LV gains of 0.38 and 0.44 with the pericardium intact and 0.28 after pericardectomy, respectively. Be mis et al. (4) closed the pericardium and examined LV filling pressure during incremental changes in RVEDP, finding a gain of 0.45 over the entire physiological range of transmural pressures. Using isolated canine hearts in which they fixed LV end-diastolic volume and varied RVEDP incrementally, Janicki and Weber (13) found that DI was consistently greater with the pericardium closed and that the coupling was greater at larger end-diastolic volumes. Their RV-to-LV gains were 0.26 with the pericardium closed and 0.13 with it opened. Dickstein et al. (8) reported a gain of 0.34 with the pericardium open. Slinker et al. (27) calculated gains from data obtained during caval occlusion and/or pulmonary artery constriction. They discriminated between the components of ventricular interaction by combining caval occlusion with rapid withdrawal of blood from the RV. With this model, they were able to reduce RV end-diastolic volume by 10–15 ml on the next beat without changing pulmonary venous flow. With the pericardium closed, they measured direct pressure gains that ranged from 0.23 to 0.32. Little et al. (17), using chronically instrumented normal dogs with the pericardium removed, demonstrated a RV-to-LV gain of 0.43 after caval occlusion. Caval occlusion and pulmonary artery constriction resulted in a gain of 0.47. Using balloon obstruction of the inferior vena cava that decreased RVEDP to zero, Dauterman et al. (7) demonstrated RV-to-LV gains of 0.53–0.62 in patients undergoing cardiac catheterization. In a preliminary report of patients undergoing open heart surgery, Kieser et al. (14) calculated the difference between pulmonary capillary wedge and central venous pressures as an estimate of LV preload after sternotomy and before and after lung retraction and pericardiectomy. Their results suggest that LV constraint can be demonstrated both before and after pericardiectomy.

Despite widely different techniques and experimental models, there is substantial agreement between our
results and those previously reported. Some of the variation in the reported gains is likely because of the presence of varied degrees of external constraint in the different models. For example, Glantz et al. (10) reported a gain of 0.97 with the pericardium intact. The range of RVEDP values in their study was ~6–30 mmHg with the majority of data obtained at an RVEDP >10 mmHg. In keeping with our results, regression equations calculated for subsets of their data demonstrated that at the higher RVEDP values pressure gains were closer to one than the gains at the lower RVEDP values.

“Natural” end-diastolic pressure-volume relation.
Each LVEDP-LVVI curve generated using our protocol represents manipulations of the individual components of ventricular interaction. Under normal physiological conditions, however, both the series and direct mechanisms operate simultaneously. For example, volume loading simultaneously increases both RV output and RVEDP. The pressure-volume relation obtained during volume loading represents a composite of curves such as ours (Fig. 2A). Boettcher et al. (5) defined such a curve in the intact dog. Compared with the curves from the present study, their pressure-volume relation is very steep. This is consistent with the concept that the steepness of the curve during volume loading in an intact animal reflects a simultaneous increase in both the series and direct effects (as volume increases, pressure increases, not only as predicted by our RVEDP constant single curves but as a result of moving upward from one RVEDP constant curve to another) with the direct effects proportionately greater at higher volumes. In addition, in the intact animal, the curve becomes even steeper because the tachycardia induced by volume loading tends to decrease end-diastolic volume.

Evaluation of the method. Various approaches have been used to study ventricular interaction. Because of the difficulty in separating the direct and series components, one approach has been to eliminate the series contribution to ventricular interaction by using isolated (9, 10, 19, 25) or arrested hearts (21, 30) in which the ventricles were no longer coupled in series. The contributions of DI were evaluated as the pressure or volume in one ventricle was held constant while the pressure-volume relation of the other ventricle was determined. These models allowed for precise control of the ventricular pressures and volumes but were not physiological because the hearts were removed from the circulatory system and often were arrested. Another approach has been a statistical one involving analysis of beat-to-beat changes over a number of cycles in response to manipulations such as caval occlusion or pulmonary artery constriction (17, 26). This did not allow the direct description of ventricular pressure-volume relations. Using a third approach, Slinker et al. (27) have studied ventricular interaction in a dog model in which they separated direct from series interaction by occluding both vena cavae while simultaneously withdrawing blood from the RV and analyzing the change in LVEDP on the next beat. However, they did not have independent control of ventricular volume and, when the pericardium was open, they were unable to remove volume fast enough to decrease RVEDP substantially.

Our method allowed us to separately and independently control and assess the series and direct mechanisms of ventricular interaction in the beating heart in an in situ system over a wide range of ventricular pressures and volumes. We were also able to quantify the pericardial and septal contributions to direct ventricular interaction by doing the same interventions with the pericardium closed and open. Clearly, this model only describes the results of acute hemodynamic changes, and the results cannot be assumed to reflect what might occur in chronic disease states. Under chronic conditions, the pericardium is capable of enlarging and increasing its unstressed volume; changes in ventricular chamber size and wall thickness may also occur. Although we focused primarily on diastolic interaction, any implications regarding systolic interaction would be derived from data obtained when the RV was not loaded physiologically, the pulmonary outflow tract was obstructed, and some degree of tricuspid incompetence may have been caused by the cannula. Finally, LVVR was assumed to be represented by the pump output. Changes in vascular volume of the lungs during the interventions could alter this relationship; however, pump output was altered slowly, allowing for stability to be achieved, and there was little or no hysteresis in the curves obtained first by decreasing and then by increasing pump output.

In summary, we have devised a right-heart bypass model in which series and direct ventricular interaction can be independently controlled. We demonstrated that the position of each LVEDP-volume curve reflects DI and the position along each constant-RVEDP curve is a function of series interaction. LV end-diastolic volume is augmented by LVVR and diminished by pericardium- and septum-mediated constraint; to maintain a given LV end-diastolic transmural pressure and volume, RV output must increase to offset increasing external constraint. In addition, if LV end-diastolic volume is increased, increasingly greater RV outputs are required to increase LV end-diastolic volume further. When the pericardium was closed, RV-to-LV end-diastolic pressure gain depended on RVEDP. When RVEDP was high, coupling was complete. When RVEDP was low, coupling was absent. When RV was intermediate, coupling was intermediate. The pericardium contributes importantly to DI in this model. However, opening of the pericardium resulted in a reduced but still significant RV-to-LV pressure gain that was entirely accounted for by RV pressure. This suggests that the residual DI observed after the pericardium was opened was septum mediated.

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