

Ventricular interaction and external constraint account for decreased stroke work during volume loading in CHF

THOMAS D. MOORE,¹ MICHAEL P. FRENNEAUX,¹ ROZSA SAS,²
J. J. ATHERTON,³ JAYNE A. MORRIS-THURGOOD,¹ ELDON R. SMITH,²
JOHN V. TYBERG,² AND ISRAEL BELENKIE²

²Departments of Medicine and Physiology and Biophysics, University of Calgary, Calgary, Alberta T2N 4N1, Canada; ³University of Queensland, Brisbane Q4029, Australia; and ¹Department of Cardiology, Wales Heart Research Institute, University of Wales College of Medicine, Cardiff CF14 4XN, United Kingdom

Received 26 April 2001; accepted in final form 13 August 2001

Moore, Thomas D., Michael P. Frenneaux, Rozsa Sas, J. J. Atherton, Jayne A. Morris-Thurgood, Eldon R. Smith, John V. Tyberg, and Israel Belenkie. Ventricular interaction and external constraint account for decreased stroke work during volume loading in CHF. *Am J Physiol Heart Circ Physiol* 281: H2385–H2391, 2001.—The slope of the stroke work (SW)-pulmonary capillary wedge pressure (PCWP) relation may be negative in congestive heart failure (CHF), implying decreased contractility based on the premise that PCWP is simply related to left ventricular (LV) end-diastolic volume. We hypothesized that the negative slope is explained by decreased transmural LV end-diastolic pressure (LVEDP), despite the increased LVEDP, and that contractility remains unchanged. Rapid pacing produced CHF in six dogs. Hemodynamic and dimension changes were then measured under anesthesia during volume manipulation. Volume loading increased pericardial pressure and LVEDP but decreased transmural LVEDP and SW. Right ventricular diameter increased and septum-to-LV free wall diameter decreased. Although the slopes of the SW-LVEDP relations were negative, the SW-transmural LVEDP relations remained positive, indicating unchanged contractility. Similarly, the SW-segment length relations suggested unchanged contractility. Pressure surrounding the LV must be subtracted from LVEDP to calculate transmural LVEDP accurately. When this was done in this model, the apparent decrease in contractility was no longer evident. Despite the increased LVEDP during volume loading, transmural LVEDP and therefore SW decreased and contractility remained unchanged.

congestive heart failure; hemodynamics; pericardium

IT IS IMPORTANT TO ASSESS the hemodynamic status accurately in congestive heart failure and to understand how treatment affects left ventricular (LV) end-diastolic volume (LVEDV) because cardiac function is in part dependent on preload. The old observation that phlebotomy increased cardiac output as central venous pressure fell (16) and the more recent observations that stroke work (SW) may increase as pulmonary

capillary wedge pressure (PCWP) is reduced (4, 28) at first sight seem to suggest that volume manipulation may alter contractility and that there is a descending limb of the SW-LVEDV (Starling) relation.

The effective LV distending pressure is transmural LV end-diastolic pressure (LVEDP), which is LVEDP minus the surrounding [pericardial and right ventricular (RV)] pressure. Normally, pericardial pressure and RV end-diastolic pressure (EDP) are low, but in some conditions, may be markedly elevated. In these situations, the pressure surrounding the LV may contribute substantially to measured LVEDP (7), and the effective distending pressure may be considerably lower than the measured LVEDP. It is now also clear that in these situations, changes in LVEDP may not accurately reflect changes in the effective distending pressure (transmural LVEDP). In a model of acute pulmonary embolism (4, 5), volume loading decreased SW despite the increased LVEDP; the opposite occurred during volume removal. This apparent paradox of decreased cardiac function when filling pressure is increased did not represent decreased contractility; rather, it was explained by a greater increase in pericardial pressure and RVEDP than the increase in LVEDP. This resulted in a reduction in transmural LVEDP and thus decreased LVEDV; the decreased LVEDV was responsible for the reduced SW in keeping with Starling's Law despite the increased intracavitary LVEDP. The reverse was true during volume removal. Similar observations were made in patients with chronic obstructive pulmonary disease in whom volume loading decreased LVEDV despite increased PCWP (17).

Data from two studies suggest that a similar phenomenon may also occur in congestive heart failure. In some patients, LVEDV increased during nitroglycerin administration or when central blood volume was reduced with lower body negative pressure, despite the fact that both interventions decrease LVEDP (3, 9). We suggested previously (2) that these findings can be explained by decreased constraint to LV filling and

Address for reprint requests and other correspondence: I. Belenkie, Health Sciences Center, 3330 Hospital Dr. NW, Calgary, Alberta, Canada T2N4N1 (E-mail: Belenkie@ucalgary.ca).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

direct ventricular interaction. However, there are no published studies in which simultaneous cardiac function, pressures, and dimensions were measured to verify that constraint to filling and ventricular interaction are responsible for the apparent paradoxical response to volume loading in congestive heart failure.

Using the canine rapid-pacing congestive heart failure model, we tested the hypothesis that volume loading may decrease and volume removal may increase transmural LVEDP, despite opposite changes in intracavitary LVEDP, and that changes in SW would parallel changes in transmural LVEDP. We also hypothesized that, as in pulmonary embolism and chronic pulmonary disease, ventricular interaction would account for the associated changes in ventricular dimensions. Our results confirm that changes in intracavitary LVEDP may not reliably predict changes in transmural LVEDP in severe congestive heart failure; our results also clarify the mechanism by which this occurs.

METHODS

Experimental model. Rapid ventricular pacing (220–250 beats/min for 4–6 wk) produced severe congestive heart failure (severe LV dysfunction observed echocardiographically, associated with lassitude, dyspnea, and ascites) in six dogs (both sexes, 20–25 kg) as previously described (2, 11, 14, 15, 29, 32). The pacemakers were then turned off, and the dogs were studied acutely. (Four were first placed in a supporting sling and, with the use of local anesthesia, a catheter was advanced to the pulmonary artery to measure PCWP.) Anesthesia was then induced with intravenous fentanyl citrate (0.1 mg/ml) followed by ~2 mg/kg Pentothal Sodium. The animals were then ventilated with a 70% nitrous oxide-30% oxygen mixture with a constant-volume respirator. Anesthesia was maintained with fentanyl at a rate of ~4 mg/h. A midline sternotomy was performed, the pericardium was incised along the base of the ventricles, and the heart was removed from the sac for instrumentation (4). LV, aortic, and RV pressures were measured with 8-Fr catheter-tipped transducers (model SPC-485A, Millar Instruments; Houston, TX) inserted through a carotid artery and a femoral artery and vein, respectively. Right atrial pressure was measured with a fluid-filled catheter inserted through a jugular vein. Pericardial pressure was measured over the lateral surface of both ventricles with flat, fluid-filled balloon transducers (13). Septum-to-LV free wall, LV anteroposterior, and septum-to-RV free wall diameters, as well as LV free wall segment length were measured by sonomicrometry (Sonometrics, London, Ontario, Canada). An ultrasonic flow probe (Transonic Systems; Ithaca, NY) was implanted on the aorta to measure stroke volume (SV). A signal from the respirator was used to identify end-expiratory cardiac cycles, and a single lead electrocardiogram was recorded. The pericardium and chest were closed, and the animals were stabilized.

Experimental protocol. While data were continuously collected, volume loading was performed with 200–750 ml heparinized saline or a solution of 25 mg/l albumin over 1–4 min until the LVEDP was at least 35 mmHg or hemodynamic instability developed. Volume was then removed over a similar period of time to either reduce the LVEDP to 12 mmHg or the systolic aortic pressure to <75 mmHg. The blood-saline mixture was then reinfused until the LVEDP was the same as at the start of the protocol.

Data analysis. Data collected throughout respiration were analyzed. Pericardial pressure measurements were available in

five animals, four from over the LV; pressure from over the RV was used in one animal because of unsuitable tracings over the LV. In *dog 6*, pericardial pressures were technically unacceptable, and right atrial pressure was used as an approximation to calculate transmural LVEDP. In *dog 1*, catheter whip from the pericardial transducer sometimes caused too much artifact so that only the cardiac cycles just before, at, and just after end expiration were used to calculate transmural LVEDP. Data collected during volume removal in three dogs were excluded because of severe hemodynamic deterioration (systolic aortic pressure decreased rapidly to <70 mmHg and SV decreased to <50%). Transmural LVEDP was calculated as LVEDP – pericardial pressure. The transeptal pressure gradient was calculated as LVEDP – RVEDP. SW was calculated as SV × (LV end-systolic pressure – LVEDP) (expressed in mmHg·ml). End-diastolic dimensions were measured at the peak of the R wave on the electrocardiogram.

Statistical analysis. Hemodynamic and dimension changes during volume loading were compared with the Student's paired *t*-test. A probability <0.05 was considered to be statistically significant.

RESULTS

In the four awake dogs in which PCWP was measured, mean PCWP fell from a mean of 25 (range 16–37) mmHg before anesthesia to 16 (range 5–34) mmHg when first measured under anesthesia with the chest open and the pericardium closed. After instrumentation and stabilization with variable amounts of fluid in all six anesthetized animals, LVEDP was 20.9 ± 1.8 mmHg.

Volume loading. Table 1 lists the hemodynamic and dimension data at baseline and during volume manip-

Table 1. Hemodynamic and dimension changes during volume manipulation in heart failure

	Volume Load		Volume Removal	
	Baseline	Peak	Baseline	Peak
LVEDP	20.9 ± 1.8	26.8 ± 2.9*	29.3 ± 2.6	23.3 ± 2.6
RVEDP	15.1 ± 1.6	24.3 ± 2.3†	22.7 ± 1.9	14.7 ± 2.7
PerP	13.6 ± 1.9	21.8 ± 3.2†	24.7 ± 0.3	16.7 ± 2.4
TLVEDP	6.6 ± 0.7	4.5 ± 1.1*	4.7 ± 2.9	6.7 ± 2.0
TSG	6.4 ± 1.1	3.0 ± 1.1†	6.7 ± 4.3	8.7 ± 3.5
SLVFW	50.5 ± 1.4	49.8 ± 1.3*	51.0 ± 2.1	51.5 ± 1.7
SRVFW	42.7 ± 4.8	44.4 ± 4.7†	45.5 ± 8.7	43.9 ± 8.8
LVAP	58.0 ± 2.2	59.8 ± 2.0†	56.5 ± 2.2	55.8 ± 2.0
SegL	13.1 ± 1.5	13.0 ± 1.5	12.5 ± 1.9	12.5 ± 1.9
LVSP	88.2 ± 6.3	82.5 ± 8.5	97.0 ± 8.5	95.7 ± 5.7
RVSP	31.1 ± 1.8	34.9 ± 3.2	37.3 ± 1.5	35.0 ± 1.7
HR	103 ± 14.7	110 ± 16	132.3 ± 7.2	130.7 ± 9.8
SV	11.7 ± 2.8	10.1 ± 2.6*	15.3 ± 4.0	16.5 ± 5.2
SW	418 ± 101	291 ± 78*	483 ± 143	593 ± 167

Data are means ± SD from all dogs are available during volume loading but in only 3 animals during volume removal because of hemodynamic instability in the two remaining dogs. HR, heart rate (beats/min); LVAP, left ventricular (LV) anteroposterior diameter (mm); LVEDP, LV end-diastolic pressure (mmHg); LVSP, peak LV systolic pressure (mmHg); PerP, pericardial pressure (mmHg); RVEDP, right ventricular (RV) end-diastolic pressure (mmHg); RVSP, peak RV systolic pressure (mmHg); SegL, Segment length (mm); SLVFW, septum-to-LV free wall diameter (mm); SRVFW, septum-to-RV free wall diameter (mm); SV, stroke volume (ml); SW, stroke work (ml·mmHg). TLVEDP, transmural LVEDP (mmHg); TSG, transeptal pressure gradient (mmHg); Data collected during volume removal were not subjected to statistical analysis. **P* < 0.01; †*P* < 0.05.

ulation. Figure 1 illustrates the changes in pressures, LV performance, and dimensions during volume loading and removal in a representative dog (*dog 5*). Volume loading increased LVEDP (from 20.9 ± 1.8 to 26.8 ± 2.9 mmHg) but increased RVEDP more (from 15.1 ± 1.6 to 24.3 ± 2.3 mmHg), thus decreasing the transseptal pressure gradient (from 6.4 ± 1.1 to 3.0 ± 1.1 mmHg). As shown in Fig. 2, the increase in pericardial pressure during volume loading (from 13.6 ± 1.9 to 21.8 ± 3.2 mmHg) was similar to the increase in RVEDP. The decrease in transmural LVEDP (from 6.6 ± 0.7 to 4.5 ± 1.1 mmHg) was similar to the decrease in the transseptal pressure gradient. The decreased transseptal pressure gradient and transmural LVEDP were associated with a decreased SV (from 11.7 ± 2.8 to 10.1 ± 2.6 ml) and SW (from 418 ± 101 to 291 ± 78 ml·mmHg). All of the above changes were statistically significant. The changes in peak LV systolic pressure, peak RV systolic pressure, and heart rate were not significant.

Volume removal. The data are from the three animals that remained hemodynamically stable during volume removal. As illustrated in Fig. 1 and listed in Table 1, volume removal reversed the changes caused by volume loading. As LVEDP decreased (from $29.3 \pm$

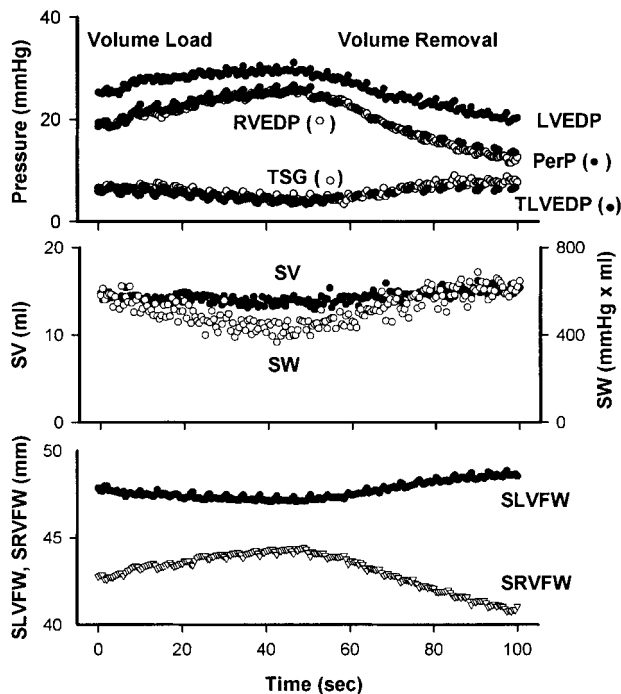


Fig. 1. Hemodynamic and dimension changes during volume loading and removal in a representative animal (*dog 5*). *Top*: changes in left ventricular (LV) and right ventricular (RV) end-diastolic pressure (EDP), pericardial pressure (PerP), transseptal pressure gradient (TSG), and transmural LVEDP (TLVEDP). *Middle*: changes in stroke volume (SV) and stroke work (SW). *Bottom*: changes in chamber dimensions. As LVEDP increased during loading, RVEDP and PerP increased more so that the TSG and TLVEDP decreased. These changes were associated with a decrease in SV and SW, decreased septum-to-LV free wall diameter (SLVFW), and increased septum-to-RV free wall diameter (SRVFW). Changes were reversed during volume removal.

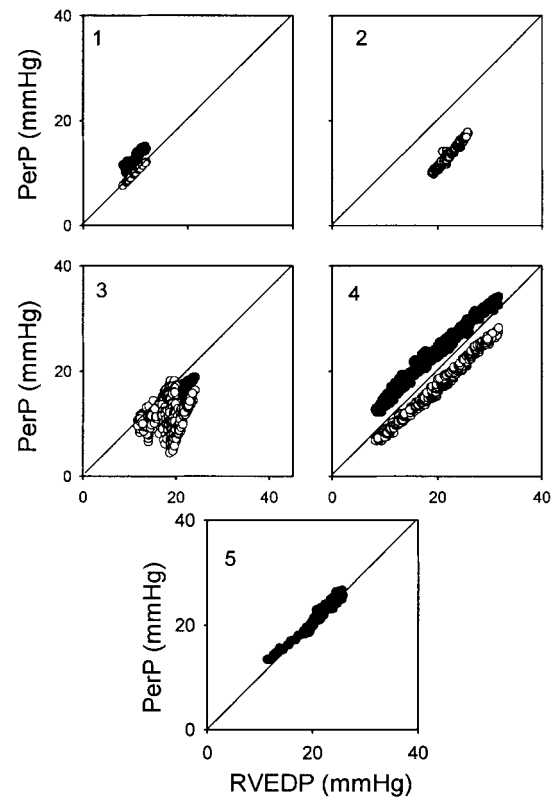


Fig. 2. Plots of PerP versus RVEDP. PerP measurements over both ventricles were available and similar in 3 dogs (*dogs 1, 3 and 4*) as indicated by open and closed circles. Changes in PerP were closely related to changes in RVEDP. PerP was not available in *dog 6*. See Fig. 1 for abbreviations.

2.6 to 23.3 ± 2.6 mmHg), there was also a decrease in RVEDP (from 22.7 ± 1.9 to 14.7 ± 2.7 mmHg), resulting in an increased transseptal pressure gradient (from 6.7 ± 4.3 to 8.7 ± 3.5 mmHg). The decrease in pericardial pressure (24.7 ± 0.3 to 16.7 ± 2.4 mmHg) was similar to that in RVEDP. Transmural LVEDP increased (from 4.7 ± 2.9 to 6.7 ± 2.0 mmHg) and SV and SW increased from 15.3 ± 4.0 to 16.5 ± 5.2 ml and 483 ± 143 to 593 ± 167 mmHg·ml, respectively. Peak LV systolic pressure and heart rate remained unchanged, and peak RV systolic pressure decreased slightly from 37.3 ± 1.5 to 35.0 ± 1.7 mmHg.

Effects of volume manipulation on dimensions. As illustrated in Fig. 1 and listed in Table 1, changes in the transseptal pressure gradient caused the septum to shift predictably. During volume loading, the decreased transseptal pressure gradient caused a leftward septal shift [the septum-to-LV free wall diameter decreased from 50.5 ± 1.4 to 49.8 ± 1.3 mm ($P < 0.05$), and the septum-to-RV free wall diameter increased from 42.7 ± 4.8 to 44.4 ± 4.7 mm ($P < 0.01$)]. The increased transseptal pressure gradient during volume removal caused a rightward septal shift in all three animals (septum-to-LV free wall diameter increased from 51.0 ± 2.1 to 51.5 ± 1.7 mm and the RV dimension decreased from 45.5 ± 8.7 to 43.9 ± 8.8 mm). There was no significant change in segment length during volume loading or removal.

LV segment length. Figure 3 shows the LVEDP- and transmural LVEDP-segment length relations in each animal. As can be seen, transmural LVEDP was consistently lower than LVEDP and segment length was more closely related to transmural LVEDP than LVEDP. There was little change in segment length in *dog 4*, and there was little change in pressure in *dog 1*. In four dogs (*dogs 3–6*), there was considerably more scatter in the LVEDP-segment length relations.

LV function. The SW-LVEDP relations (Fig. 4A) in each animal were negative and, if interpreted in the conventional manner, imply that contractility decreased as LVEDP increased. However, the SW-transmural LVEDP relations were positive in all animals, SW consistently increasing as a function of increasing transmural LVEDP. Figure 4B shows the summary data from all animals in which SW was normalized (100% equals the average of the highest and lowest value for each dog). The SW-LVEDP plots showed considerably more scatter than the SW-transmural LVEDP plots. Figure 5 shows the SW-end-diastolic segment length relations in each dog. In three dogs, the SW-segment length relations had a positive slope, whereas there was little change in segment length in one dog (*dog 4*) and in SW in another dog (*dog 1*).

Pericardial constraint. Pericardial pressure varied considerably between animals and during volume manipulation (Table 1). However, as illustrated in Fig. 2, pericardial pressure was similar to RVEDP, and changes in pericardial pressure (from 13.6 ± 1.9 to 21.8 ± 3.2 mmHg, $P < 0.01$) during volume loading were similar to those in RVEDP (from 15.1 ± 1.6 to 24.3 ± 2.3 mmHg, $P < 0.01$) throughout the range of filling pressures in the five animals in which it was obtained. Transmural RVEDP was low throughout (2.5

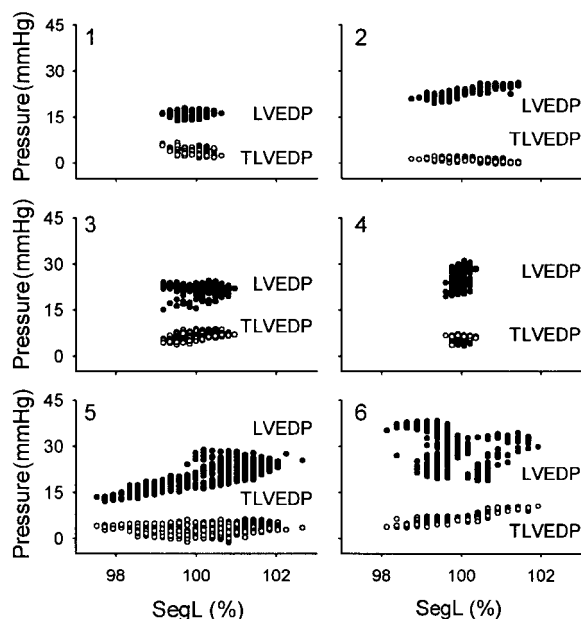


Fig. 3. Plots of LVEDP and transmural LVEDP versus end-diastolic segment length (SegL) during both volume loading in all animals (*dogs 1–6*) and unloading (3 animals). SegL was more closely related to transmural LVEDP than LVEDP.

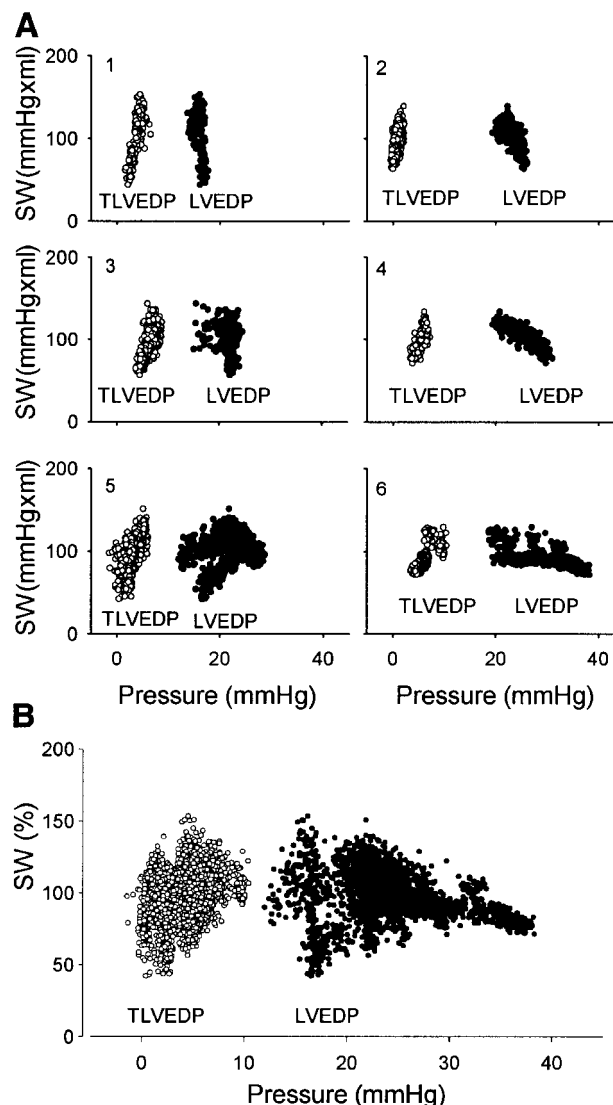


Fig. 4. A: plots of SW versus LVEDP and TLVEDP during volume loading in all animals and unloading (3 animals). Relations between SW and LVEDP all had a negative slope over at least part of the curves. In all animals, there was a single positive SW-TLVEDP relation during both volume loading and removal, suggesting that preload determined LV performance throughout volume manipulation and that there was no change in contractility. Right atrial pressure was used instead of PerP to estimate TLVEDP in *dog 6*. B: summary plot of the data from all the animals. Because PerP in *dog 2* (see Fig. 2) was much lower than RVEDP, RVEDP was used instead to calculate transmural LVEDP for this summary plot only. See Fig. 1 for abbreviations.

mmHg). Pericardial pressure was similar (Fig. 2, open and closed circles) over both ventricles in the three dogs in which both measurements were available.

DISCUSSION

The most important findings of the present study are as follows. First, change in LVEDP (or PCWP) is not a reliable surrogate for estimating change in LVEDV in severe congestive heart failure. Second, when transmural LVEDP was used to reflect LV distending pressure, the negative slope of the SW-PCWP (apparent

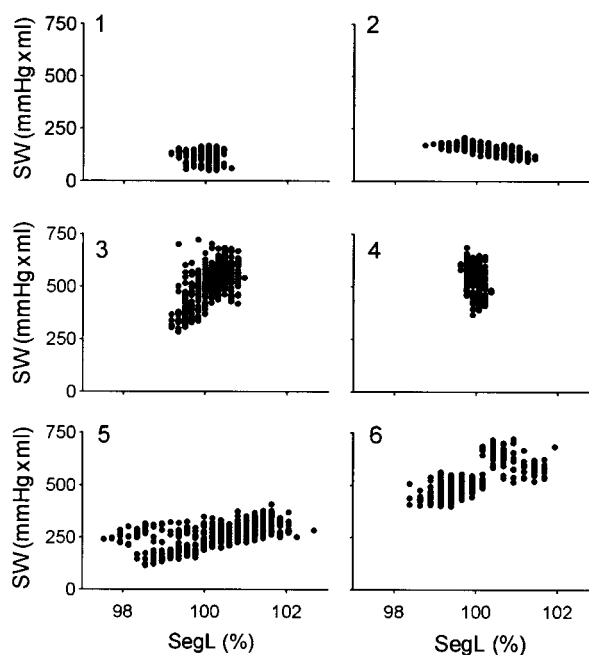


Fig. 5. Plots of SW versus SegL during volume loading in all animals and unloading in 3 animals. In 3 dogs, there is a positive slope of the relation and in 2, there was too little change in one or the other parameter to define a relation.

descending limb of the Starling curve, which implies decreased contractility) was eliminated. Thus contractility was not altered by volume manipulation in this model of congestive heart failure. This is the first demonstration of the potential effect of constraint to LV filling and ventricular interaction during volume loading in congestive heart failure. Although our previous clinical study (26) had suggested that ventricular interaction might explain the previously observed association of improved cardiac function when filling pressure was reduced, it has not been previously verified with simultaneous pressure and dimension measurements.

The effective distending pressure (transmural LVEDP, which determines LVEDV) is equal to measured LVEDP minus the surrounding pressure. We have shown that intracavitary and transmural LVEDP may even change in opposite directions in acute pulmonary embolism (5). The results from the present study show that the same phenomena may also occur in congestive heart failure. Thus, although the negative slope of the SW-LVEDP relations at high LVEDPs suggested that contractility decreased with volume loading, when transmural LVEDP was plotted instead, the apparent decrease in contractility was no longer evident. Indeed, there was a positive SW-transmural LVEDP relation, indicating that systolic performance was reliably predicted by the effective filling pressure, consistent with Starling's Law. The SW-segment length relations provide additional support for the suggestion that contractility is not decreased during volume loading. Our results also demonstrate that ventricular interaction contributes importantly to the

observed changes, the mechanism being similar to that which was previously described in pulmonary embolism and chronic pulmonary disease (4, 5, 17). Common to the three conditions is the presence of both pulmonary hypertension and constraint to LV filling.

LVEDP-LVEDV relation and LV function. According to Starling's Law, SW increases as end-diastolic fiber length or volume increases. Because volume is difficult to measure, LVEDP (or PCWP) is widely used as its surrogate. This is based on the premise that LVEDV changes in the same direction as LVEDP and that, at every LVEDV, there is one value of LVEDP. SW should therefore change in the same direction as LVEDP provided there is no change in contractility or the amount of mitral regurgitation. This is normally a reasonable approximation. In severe congestive heart failure, SW may decrease as LVEDP increases; this "descending limb" of the Starling curve has therefore been attributed to decreased contractility, each observation on the descending limb representing different, progressively downward-displaced ventricular function curves (16, 18). However, this interpretation presupposes that LVEDP is the effective distending pressure and that changes in LVEDP reflect changes in LVEDV. As observed by Katz in 1955 (19), intracavitary and transmural LVEDP are equal only when the pressure surrounding the LV is negligible. When the pressure surrounding the LV is not negligible, external pressure must be subtracted from LVEDP to calculate transmural LVEDP accurately (the effective distending pressure), which determines diastolic fiber length. Thus, if volume loading increases pressure around the LV more than it increases intracavitary LVEDP, transmural LVEDP will decrease (22). This will result in a decreased LVEDV and therefore, reduced SW in accordance with the Frank-Starling mechanism.

We demonstrated these principles previously in a pulmonary embolism model in which volume loading shifted the LVEDP-LVEDV relation upward and leftward, suggesting decreased compliance, and the SW-LVEDP relation downward and rightward, suggesting decreased contractility (4, 5). These apparent changes in compliance and contractility were eliminated when transmural LVEDP was substituted for LVEDP: compliance and contractility remained unchanged. Jardin et al. (17) demonstrated similar ventricular interaction during volume loading in patients with chronic pulmonary disease. The observation by Dupuis et al. (9) that SW increased as PCWP was reduced by nitroglycerin in some of their patients with heart failure can be explained by the same mechanism, but this was not addressed in their report. Whereas one might attribute the improved SW to decreased systemic vascular resistance and/or mitral regurgitation (10), that would not account for the associated increase in LVEDV in these patients. We recently demonstrated that lower body negative pressure (which decreases LVEDP) reduced right atrial pressure and increased LVEDV in almost half of our study patients with severe heart failure (3). In the present study, we have now demonstrated that ventricular interaction explains the apparent paradox-

ical responses in SW to volume manipulation in congestive heart failure; the SW-LVEDP relation implied that a descending limb of the Starling curve was present, but ventricular performance was faithfully predicted by the changes in transmural LVEDP. The SW-segment length relations provide additional support for our position that there is no descending limb of the curve, at least in this model of congestive failure.

Pericardial pressure in congestive heart failure. Volume loading normally increases LVEDV substantially only until LVEDP reaches ~10–15 mmHg, after which the LVEDP-LVEDV relation becomes much steeper because the pericardium limits further increases in cardiac volume (12, 24). Clearly, the pericardium can grow in a time-dependent manner, as reported by LeWinter and Pavelec (21), who showed that constraint became negligible several weeks after creation of an arteriovenous shunt. Because the RV is thin walled, transmural RVEDP is low, and as RVEDP increases above 2–4 mmHg, pericardial pressure increases in a parallel fashion (1). The thicker LV has a higher transmural pressure. In patients with and without LV disease, ~30–40% of measured LVEDP is due to external constraint (8). In the present study, volume loading increased the contribution of external pressure to the measured LVEDP from ~50 to 80%.

We recently reported that pericardial pressure varied widely among animals in the rapid-pacing model of congestive failure (14) as it did in the present study. Of greater importance and in keeping with previous reports, changes in RVEDP paralleled those in pericardial pressure in both studies (4, 5, 25–27). Because there was no change in transmural RVEDP, we speculate that when central venous pressure is acutely increased, this implies increased pericardial constraint, a situation in which changes in filling pressure may not accurately reflect changes in LVEDV. This is consistent with studies in chronically instrumented normal dogs and patients with heart failure; volume loading increased LVEDV and SV only up to LVEDPs of 10–12 mmHg (6, 23, 31), after which there was no further increase or even a decrease in SV (6).

Ventricular interaction. Whereas changes in transmural LVEDP explain the observed changes in SW during volume manipulation, consideration of the associated ventricular interaction and dimension changes provides additional insight into the mechanisms involved. Because the ventricles share the septum and are surrounded by the poorly distensible pericardium, in the presence of pericardial constraint, the volume of one ventricle can increase substantially only if the volume of the other decreases. The transseptal pressure gradient determines end-diastolic septal position; changes in the transseptal pressure gradient shift the septum and, in the presence of constraint, can cause reciprocal changes in the volumes of the ventricles. In the presence of pulmonary hypertension, volume loading is likely to increase RVEDP more than LVEDP (5, 17). If this occurs, the resulting decrease in the transseptal pressure gradient will shift the septum leftward (4, 20) thereby tending to increase RVEDV

and decrease LVEDV. This occurred during volume loading in the present study; the transseptal pressure gradient decreased, RV diameter increased, and septum-to-LV free wall diameter decreased.

Implications. Our results suggest that the use of LVEDP (or PCWP) to estimate changes in LV preload in congestive heart failure may be quite misleading, particularly because the two may even change in opposite directions. The presence of increased jugular venous pressure suggests that pericardial pressure is increased and therefore should alert the clinician to the possibility that changes in PCWP may not reliably predict changes in LVEDV and, therefore, performance. In fact, function may improve as PCWP is reduced (28), and the present study clarifies the mechanism by which this can occur. To optimize benefit from volume manipulation, transmural LVEDP or LVEDV should be assessed. Because of the close relation between changes in right atrial and pericardial pressures (7, 30), PCWP minus right atrial pressure might provide a reasonable estimate of transmural LVEDP, but this would have to be validated in clinical studies. Because improved LV performance is the goal of therapy, perhaps measuring cardiac output directly is a better strategy. However, it is most important to understand the potential for diastolic constraint and ventricular interaction and that changes in filling pressure alone should not be relied upon to predict responses to therapy.

Limitations. Our model does not completely mimic chronic severe congestive heart failure. Failure was of relatively short duration, and pulmonary artery pressure was lower than is commonly observed in severe failure. We therefore speculate that there is potential for even greater ventricular interaction (and therefore, “paradoxical” response to volume manipulation) in severe heart failure than was observed in the present study. That this may be true is suggested by much greater increases in SW observed during tailored therapy in patients than in the present study (28).

Another potential limitation was the presence of a variable amount of pericardial fluid that was drained during instrumentation. This probably resulted in some slackness of the pericardium and might have minimized pericardial constraint and therefore, ventricular interaction. Reproducibility between experiments might have been even better if it had been possible to control for this factor.

In conclusion, we have demonstrated substantial external constraint in this model of pacing-induced congestive heart failure. The observed changes in LV performance during volume manipulation were fully explained by changes in the effective distending pressure and Starling’s Law when preload was appropriately assessed. These results underscore the need to consider the potential effects of pericardial constraint and ventricular interaction on LV filling when assessing the effects of therapy on cardiac function in heart failure.

This study was supported in part by grants-in-aid from the Alberta Heart and Stroke Foundation (Calgary) held by I. Belenkie and by J. V. Tyberg and by grants from the British Heart Foundation (to M. P. Frenneaux, J. A. Morris-Thurgood, and T. D. Moore).

REFERENCES

1. **Applegate RJ, Johnston WE, Vinten-Johansen J, Klopfenstein HS, and Little WC.** Restraining effect of intact pericardium during acute volume loading. *Am J Physiol Heart Circ Physiol* 262: H1725–H1733, 1992.
2. **Armstrong PW, Stopps TP, Ford SE, and DeBold AJ.** Rapid ventricular pacing in the dog: pathophysiologic studies of heart failure. *Circulation* 74: 1075–1084, 1986.
3. **Atherton JJ, Moore TD, Lele SS, Thomson HL, Galbraith AJ, Belenkie I, Tyberg JV, and Frenneaux MP.** Diastolic ventricular interaction in chronic heart failure. *Lancet* 349: 1720–1724, 1997.
4. **Belenkie I, Dani R, Smith ER, and Tyberg JV.** Ventricular interaction during experimental acute pulmonary embolism. *Circulation* 78: 761–768, 1988.
5. **Belenkie I, Dani R, Smith ER, and Tyberg JV.** Effects of volume loading during experimental acute pulmonary embolism. *Circulation* 80: 178–188, 1989.
6. **Boettcher DH, Vatner SF, Heyndrickx GR, and Braunwald E.** Extent of utilization of the Frank-Starling mechanism in conscious dogs. *Am J Physiol Heart Circ Physiol* 234: H338–H345, 1978.
7. **Boltwood CM, Skulsky A, Drinkwater DC, Lang S, Mulder DG, and Shah PM.** Intraoperative measurement of pericardial constraint: role in ventricular diastolic mechanics. *J Am Coll Cardiol* 8: 1289–1297, 1986.
8. **Dauterman K, Pak PH, Maughan WL, Nussbacher A, Arié S, Liu CP, and Kass DA.** Contribution of external forces to left ventricular diastolic pressure. Implications for the clinical use of the Starling law. *Ann Intern Med* 122: 737–742, 1995.
9. **Dupuis J, LaLonde G, Lebeau R, Bichet D, and Rouleau JL.** Sustained beneficial effect of a seventy-two hour intravenous infusion of nitroglycerin in patients with severe chronic congestive heart failure. *Am Heart J* 120: 625–637, 1990.
10. **Faggiono P, Rusconi C, and Ghizzoni G.** Nitrates in heart failure: the hemodynamic effects and clinical implications. *Cardiology* 84: 52–53, 1994.
11. **Farrar DJ, Chow E, and Brown CD.** Isolated systolic and diastolic ventricular interactions in pacing-induced dilated cardiomyopathy and effects of volume loading and pericardium. *Circulation* 92: 1284–1290, 1995.
12. **Flessas AP and Ryan TJ.** Left ventricular diastolic capacity in man. *Circulation* 65: 1197–1203, 1982.
13. **Hamilton DR, DeVries G, and Tyberg JV.** Static and dynamic operating characteristics of a pericardial balloon. *J Appl Physiol* 90: 1481–1488, 2001.
14. **Horne SG, Belenkie I, Tyberg JV, and Smith ER.** Pericardial pressure in experimental heart failure. *Can J Cardiol* 16: 607–613, 2000.
15. **Howard RJ, Stopps TP, Moe GW, Gotlieb A, and Armstrong PW.** Recovery from heart failure: structural and functional analysis in a canine model. *Can J Physiol Pharmacol* 66: 1505–1512, 1988.
16. **Howarth S, McMichael J, and Sharpey-Schafer EP.** Effects of venesection in low output heart failure. *Clin Sci (Colch)* 6: 41–50, 1946.
17. **Jardin F, Gueret P, Prost JF, Farcot JC, Ozier Y, and Bourdarias JP.** Two-dimensional echocardiographic assessment of left ventricular function in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 129: 135–142, 1984.
18. **Katz AM.** The descending limb of the Starling curve and the failing heart. *Circulation* 32: 871–875, 1965.
19. **Katz LN.** Analysis of the several factors regulating the performance of the heart. *Physiol Rev* 35: 91–106, 1955.
20. **Kingma I, Tyberg JV, and Smith ER.** Effects of diastolic transseptal pressure gradient on ventricular septal position and motion. *Circulation* 68: 1304–1314, 1983.
21. **LeWinter MM and Pavelec R.** Influence of the pericardium on left ventricular end-diastolic pressure-segment relations during early and later stages of experimental chronic volume overload in dogs. *Circ Res* 50: 501–509, 1982.
22. **Mirsky I and Rankin JS.** The effects of geometry, elasticity, and external pressures on the diastolic pressure-volume and stiffness-stress relations. How important is the pericardium? *Circ Res* 44: 601–611, 1979.
23. **Parker JO and Case RB.** Normal left ventricular function. *Circulation* 60: 4–12, 1979.
24. **Rabkin SW and Hsu PH.** Mathematical and mechanical modeling of stress-strain relationship of pericardium. *Am J Physiol* 229: 896–900, 1975.
25. **Smiseth OA, Refsum H, and Tyberg JV.** Pericardial pressure assessed by right atrial pressure: a basis for calculation of left ventricular transmural pressure. *Am Heart J* 108: 603–605, 1983.
26. **Smiseth OA, Thompson CR, Ling H, Robinson M, and Miyagishima RT.** Juxtacardiac pleural pressure during positive end-expiratory pressure ventilation: an intraoperative study in patients with open pericardium. *J Am Coll Cardiol* 23: 753–758, 1994.
27. **Smiseth OA, Thompson CR, Ling H, Robinson M, and Miyagishima RT.** A potential clinical method for calculating transmural left ventricular filling pressure during positive end-expiratory pressure ventilation: an intraoperative study in humans. *J Am Coll Cardiol* 27: 155–160, 1996.
28. **Stevenson LW and Tillisch JH.** Maintenance of cardiac output with normal filling pressures in patients with dilated heart failure. *Circulation* 74: 1303–1308, 1986.
29. **Suzuki M, Cheng CP, Ohte N, and Little WC.** Left ventricular spherical dilation and regional contractile dysfunction in dogs with heart failure. *Am J Physiol Heart Circ Physiol* 273: H1058–H1067, 1997.
30. **Tyberg JV, Taichman GC, Smith ER, Douglas NWS, Smiseth OA, and Keon WJ.** The relation between pericardial pressure and right atrial pressure: An intraoperative study. *Circulation* 73: 428–432, 1986.
31. **Vatner SF and Boettcher DH.** Regulation of cardiac output by stroke volume and heart rate in conscious dogs. *Circ Res* 42: 557–561, 1978.
32. **Wilson JR, Douglas P, Hickey WF, Lanoce V, Ferraro N, Muhammad A, and Reichek N.** Experimental congestive heart failure produced by rapid ventricular pacing in the dog: cardiac effects. *Circulation* 75: 857–867, 1987.