

# Influence of Atrial Systole on the Frank-Starling Relation and the End-diastolic Pressure-Diameter Relation of the Left Ventricle

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**SUMMARY** The influence of atrial systole on the left ventricular function curve (stroke volume vs end-diastolic pressure or end-diastolic diameter) and on the left ventricular end-diastolic pressure diameter relation was studied in nine anesthetized, open-chest dogs whose atrioventricular (AV) node had been completely blocked. Measurements were made during volume loading with the pericardium closed and opened and during alternate AV sequential pacing (to permit atrial contribution to ventricular filling) and AV simultaneous pacing (to prevent atrial contribution). When the pericardium was closed, withdrawal of the atrial contribution shifted the stroke-volume end-diastolic pressure relation downward, but did not shift the stroke volume–end-diastolic diameter relation, i.e., it reduced stroke volume for a given end-diastolic pressure according to a reduction in end-diastolic volume. The downward shift of the stroke volume–end-diastolic pressure relation was caused by an upward shift of the end-diastolic pressure–diameter relation, which, for a given end-diastolic pressure, resulted in a smaller end-diastolic diameter and, thus, in a smaller stroke volume. The reason for the upward shift in the end-diastolic pressure–diameter relation was that the atrium remained full and thus increased pericardial pressure by increasing pericardial volume. Opening the pericardium shifted the end-diastolic pressure–diameter relation downward and to the right, shifted the stroke volume–end-diastolic diameter relation upward and abolished the effect of withdrawal of the atrial contribution on these curves.

We conclude that in the presence of an intact pericardium, atrial systole shifts the stroke volume–end-diastolic pressure relation because it shifts the end-diastolic pressure–diameter relation and it improves left ventricular performance by increasing preload.

MORE THAN 350 years after Harvey's<sup>1</sup> observation "that the auricles beat, contract and . . . push blood into the ventricles," Gesell<sup>2</sup> and then Wiggers<sup>3</sup> quantified the effect of atrial systole on left ventricular (LV) function. In 1911, Gesell<sup>2</sup> described an increase in arterial blood pressure of 10–15% caused by atrial systole and in 1923, Wiggers<sup>3</sup> observed that the atrial contribution to LV filling averaged 35%. Their conclusion that atrial systole augmented LV filling and improved LV performance to an important degree has been confirmed over the last 20 years by studies in experimental animals<sup>4–9</sup> and in humans.<sup>10–17</sup> Linden and Mitchell<sup>7</sup> suggested that atrial systole increased LV preload (end-diastolic fiber length), and thus improved LV performance according to the Frank-Starling mechanism.

However, in a recent clinical study, we observed<sup>14</sup> that withdrawal of the atrial contribution to LV filling reduced LV stroke volume without simultaneously reducing filling pressure. Thus, withdrawal of the atrial contribution caused a downward shift of the conventional (stroke volume–filling pressure) ventricular function curve.

The purpose of this study was to determine the reason for the downward shift of the LV function curve. We simultaneously studied the influence of atrial systole on the LV function curve and on the LV end-diastolic pressure–diameter relation. We found that the downward shift in the function curve produced by the withdrawal of atrial contribution is related to an upward shift in the end-diastolic pressure–diameter relation. Our observations suggest that the unemptied atria relatively compromise the pericardial volume, raising pericardial pressure and shifting the end-diastolic pressure–diameter curve upward by the mechanism we hypothesized.<sup>18, 19</sup>

## Methods

### Surgical Preparation

Nine mongrel dogs of either sex that weighed 21.2–30.4 kg (mean 25.9 kg) were anesthetized with sodium pentobarbital, 25 mg/kg i.v. Additional doses were administered as required. After intubation, artificial ventilation was initiated by a constant-volume ventilator (model 607, Harvard Apparatus). Blood gases and pH were checked and corrected by ventilatory adjustments or correction of the fraction of inspired oxygen. The dogs were warmed with a heating blanket.

The femoral vein was cannulated for fluid administration, and a triple-lumen thermodilution catheter was advanced into the pulmonary artery and connected to a thermodilution cardiac output computer (model 9520A, Edwards Laboratories). A fluid-filled catheter was advanced through the femoral artery into the central aorta and connected to a strain-gauge manometer (model P23Db, Gould Satham Instruments, Inc.).

The chest was opened with a median sternotomy.

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An incision (about 3 cm) was made into the pericardium over the right atrial appendage. Unipolar pace-maker electrodes were sutured to the right atrium and right ventricle and connected to a Grass S88 stimulator (Grass Medical Instruments, Inc.). Then, formaldehyde solution (0.1–0.3 ml) was injected into the atrio-ventricular (AV) node to induce complete AV block.<sup>20</sup> Through the same incision, an electromagnetic flow probe (model 501, Carolina Medical Electronics, Inc.) was placed around the aorta. Through another 3-cm incision in the pericardium, the left atrial appendage was pulled out and one ultrasonic crystal was attached to its posterior base as far back as possible and another to its anterior base just above the groove containing the left circumflex coronary artery. In effect, this pair of crystals measured the diameter of the base of the left atrial appendage. Through a 3.5-cm incision in the pericardium over the LV anterior wall, a flat Silastic balloon that contained 0.5 ml saline was slipped under the pericardium toward the LV free wall and apex, and was connected to another pressure transducer. To measure the anteroposterior diameter of the left ventricle, a second pair of ultrasonic crystals was used. The anterior crystal was inserted through the same incision as the Silastic balloon. The posterior crystal was inserted through a separate 0.5-cm incision in the pericardium. Through a 1.5-cm incision in the pericardium and a stab wound in the LV apex, a high-fidelity implantable pressure transducer (model P22, Konigsberg Instruments) was passed into the left ventricle.

From a small branch of a pulmonary vein, a catheter-tip pressure transducer with a reference lumen (model PC-480, Millar Instruments, Inc.) was advanced into the left atrium to measure left atrial pressure.

After the preparation was finished, the pericardium was closed with a running suture, just sufficient to oppose the edges rather loosely.

### Protocol

Normal atrial contribution to LV filling was effected by sequential stimulation of the atria and ventricles. The mean interval between the atrial and ventricular stimuli (PR interval) was 88 msec (mean 60–100 msec). Alternately, atrial contribution was prevented by simultaneous stimulation of atria and ventricles. The pacing mode could be changed instantaneously. The mean heart rate was 112 beats/min (range 107–125 beats/min) and was held constant throughout an experiment.

Because the sinus rate sometimes exceeded the desired heart rate in these AV-blocked dogs, we stimulated the atria with a second paired pulse to maintain control of the atrial contraction at a heart rate just over 100 beats/min. The interval between the first atrial stimulus and the second stimulus (twin) was adjusted very carefully under continuous monitoring of left atrial pressure and diameter. When the interval between these stimuli was too long, the second stimulus led to an effective second atrial contraction against the closed mitral valve during ventricular systole, which

was thus marked by a cannon wave in the left atrial pressure trace. To achieve optimal timing, we began with this long interval, which produced the cannon wave and then shortened the interval progressively until it became so abbreviated that the second contraction could not be detected, either on the left atrial pressure or left atrial diameter tracing. This adjustment was repeated several times during AV sequential pacing and AV simultaneous pacing.

After adjusting the twin pulse, baseline hemodynamic data were recorded in the following sequence: first for 10 seconds during AV sequential pacing and then for at least 30 seconds during AV simultaneous pacing, and finally for 10 seconds during AV sequential pacing. The first 10 seconds of AV sequential pacing was the control period; the second half of AV simultaneous pacing after hemodynamic variables had stabilized was called the stable period. After the baseline data were recorded, volume loading was started with dextran 75 solution (Travenol Laboratories, Inc.) and the recordings were repeated in the same sequence after each increment (about 100 ml) of blood volume. From one data recording sequence to the next, AV sequential pacing was continued. After the last volume load, baseline values were restored by bleeding and the pericardium was opened widely. The volume loading was then repeated, first by reinfusing blood and then by adding dextran solution, and hemodynamic data were recorded as described above.

All directly measured and derived data were recorded on a photographic recorder (model 1858, Honeywell, Inc.) for subsequent analysis. Diastolic pressure was recorded with a gain of 40 mm Hg full scale. Directly measured data were also stored on a tape recorder (model 5600 C, Honeywell). In addition, important hemodynamic variables were continuously monitored on an eight-channel, large-screen oscilloscope (Marcom, Honeywell) and on a trend recorder (model 28, MFE).

LV pressure measured by the Konigsberg micromanometer and left atrial pressure by the pressure sensor of the Millar catheter were equisensitively displayed on the oscilloscope, together with left atrial pressure obtained by connecting the reference lumen of the Millar catheter to a pressure transducer. Then, the stimulator was turned off and during the next asystole, the diastolic traces were superimposed by adjustment of the manual balance of the amplifiers of the Konigsberg micromanometer and the Millar pressure sensor. LV pressure was further ascertained by briefly inserting a 22-gauge needle connected to the pressure transducer. All pressure transducers were fixed at the midlevel of the left ventricle and referenced to atmospheric pressure. Pressures were filtered above 200 Hz except pericardial pressure, which was filtered above 20 Hz.

The cardiac output measured by thermodilution was used to calibrate the cardiac output readings given by the electromagnetic flowmeter. A hybrid computer (Mini AC, Electronics Associates, Inc.) was used for continuous calculation of stroke volume (SV =

$\int \dot{V}_{A_0} dt$ ;  $\dot{V}_{A_0}$  = aortic flow rate) and stroke work (SW =  $\int \dot{V}_{A_0} \cdot P_{LV} dt$ ).

For subsequent data analysis, end-diastole was defined from the  $dP/dt$  trace as the point where the rapid upstroke began (after the a-wave). The interval between the ventricular stimulus and this point was measured on the beats with atrial contribution and was used to corroborate end-diastole in the subsequent beats without atrial contribution.

### Analytical Methods

A multiple linear regression analysis was used to test for a relationship between LV stroke volume and end-diastolic diameter and to test simultaneously for a parallel shift of this relation or for a change of the slope of this relation induced by withdrawal of the atrial contribution or opening the pericardium. The following regression equation was used:

$$SV = a_2 D^2 + a_1 D + a_0 + (b_1 \cdot D + b_0) \cdot A + (c_1 \cdot D + c_0) \cdot P$$

where  $D$  = left ventricular end-diastolic diameter,  $A$  = (0 = atrial contribution; 1 = no atrial contribution), and  $P$  = (0 = pericardium closed; 1 = pericardium open). The first three terms on the right side of the equation describe the relationship between stroke volume and end-diastolic diameter. The quadratic term was chosen to allow for some curvature in the relationship. The parameters  $a_2$ ,  $a_1$ ,  $a_0$  empirically represent the curve. If either  $a_2$  or  $a_1$  are significantly different from zero, then this implies a relationship between stroke volume and end-diastolic diameter. The dummy variables  $A$  and  $P$  represent the withdrawal of the atrial contribution and the opening of the pericardium, respectively. The parameters  $b_1$ ,  $b_0$  and  $c_1$ ,  $c_0$  estimate the respective magnitudes of the changes of LV stroke volume independently caused by the withdrawal of atrial contribution and opening the pericardium from the change due to the change in end-diastolic diameter per se:  $b_1$  and  $c_1$  give the magnitude of the change of the slope, while  $b_0$  and  $c_0$  give the magnitude of the parallel shift of the stroke volume–end-diastolic diameter relation after either intervention. The analysis of these data was performed by using the BMDPIR program, version 2.1.<sup>21</sup>

The augmentation of LV stroke volume by the atrial contribution at a given LV end-diastolic pressure was calculated as the difference between the stroke volume at this end-diastolic pressure with an atrial contribution minus the stroke volume without an atrial contribution. The relation between the absolute or the relative amount of augmentation of stroke volume and end-diastolic pressure was then analyzed by a simple linear regression analysis for all experiments together.

### Results

At a given state of volume loading, we observed transient changes of LV systolic pressure when we switched from AV sequential pacing (atrial contribution to LV filling) to AV simultaneous pacing (no atrial contribution). From its initial value (control period), LV systolic pressure fell rapidly, then rose slightly,

and finally stabilized (stable period) below the initial value (fig. 1). Switching back to AV sequential pacing led to an overshoot increase, which then stabilized promptly at the original level. The stable period was usually reached after 10–15 seconds of AV simulta-

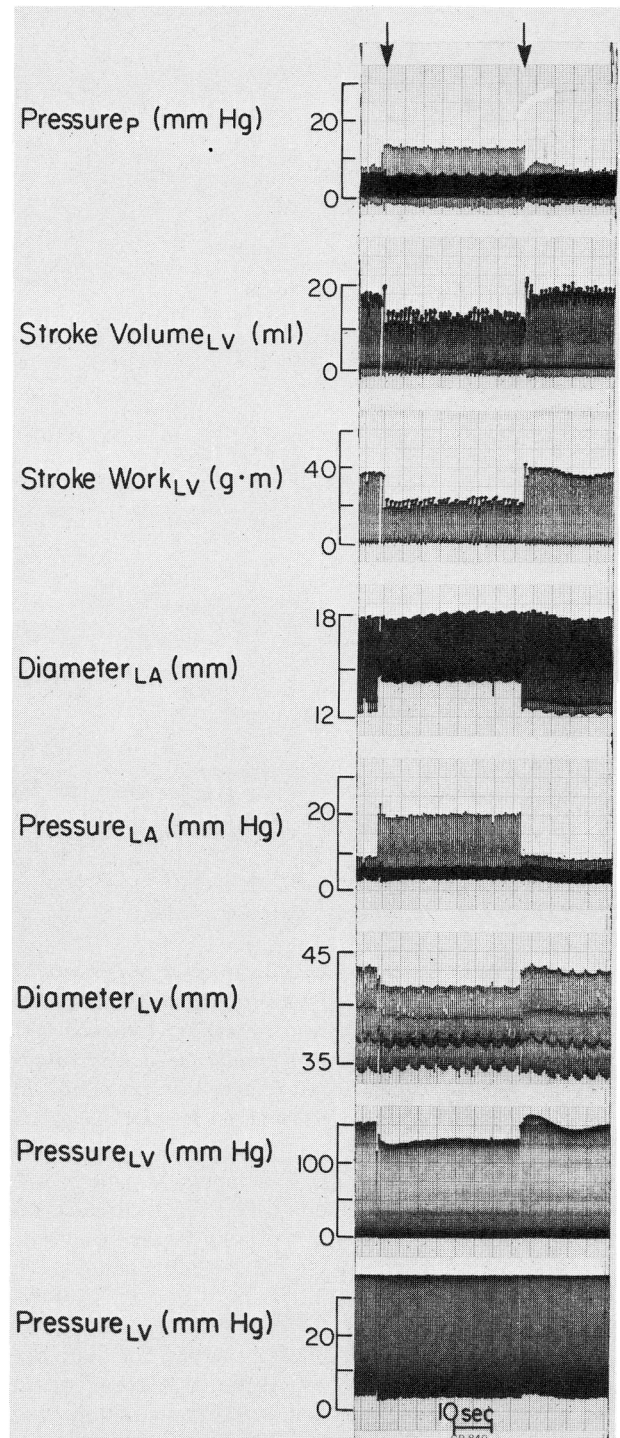


FIGURE 1. Effect of withdrawal of the atrial contribution on left atrial and left ventricular hemodynamic variables in one dog (pericardium closed). Between the arrows, the atria and ventricles are stimulated simultaneously; otherwise, they are stimulated sequentially. The subscript definitions are: LA = left atrial; LV = left ventricular; P = pericardium.

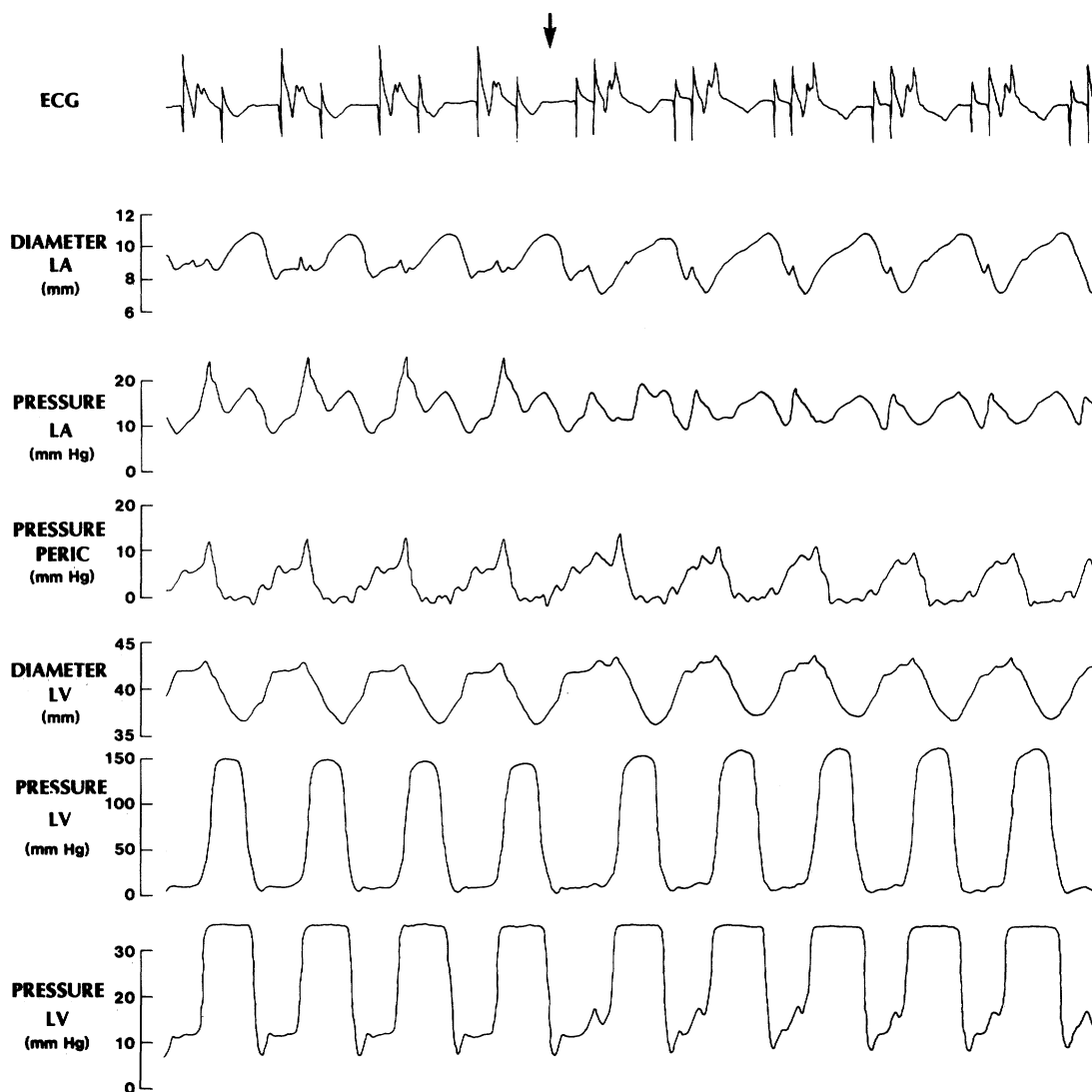


FIGURE 2. Representative tracings of left atrial (LA) and left ventricular (LV) diameter and pressure and pericardial (PERIC) pressure without atrial contribution (left side) and with atrial contribution (right side). The arrow indicates the switch from atrioventricular (AV) simultaneous pacing to AV sequential pacing. The transition diastole was longer than the other diastoles because the ventricular impulse was delayed by the duration of the PR interval. Otherwise, the RR interval was constant. In the ECG trace, the twin pulse is the last in each sequence of impulses. During sequential pacing, LA diameter was less and LV diameter greater at LV end-diastole.

neous pacing. In several experiments in which AV simultaneous pacing was continued for 3 minutes, no further changes in LV systolic pressure were observed. To avoid an influence from these transient changes, we used only data from the initial control period and the stable period.

The shapes of individual left atrial and LV diameter and pressure traces were very different, depending on the presence or absence of an atrial contribution, and the difference appeared immediately after a change in the pacing mode from one beat to the next (fig. 2). The left atrial diameter always increased during LV systole and decreased during LV diastole. However, switching from AV simultaneous pacing to AV sequential pacing enabled the atrial contraction to empty the atrium, so then left atrial diameter at LV end-diastole

became smaller. Simultaneously, LV end-diastolic diameter became larger. In the left atrial pressure trace, the cannon wave, which was due to an atrial contraction against a closed mitral valve, was replaced by a normal a-wave. In the LV pressure trace an a-wave appeared, resulting in a higher end-diastolic pressure, albeit in the presence of a larger LV diameter.

The results of the experiment shown in figure 3 exemplify the major observations of this study. When the pericardium was closed the withdrawal of atrial contribution consistently shifted the relation between stroke volume and end-diastolic pressure downward (fig. 3). After the pericardium had been opened, the whole curve shifted upward and stroke volume became independent of atrial contribution. When we subtracted pericardial pressure from LV end-diastolic pressure

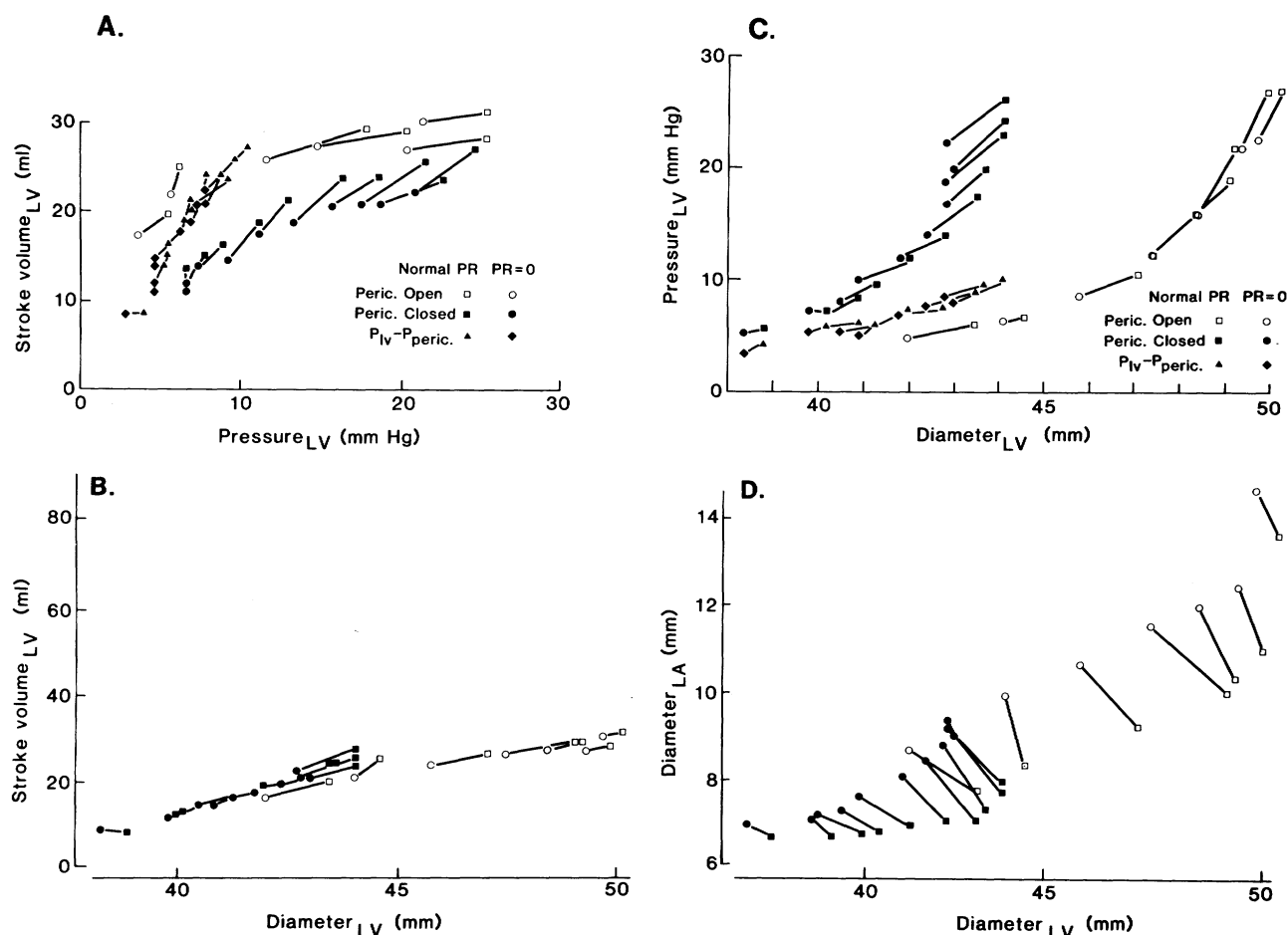


FIGURE 3. Data from experiment 9. (A) Left ventricular (LV) function curve — stroke volume vs LV end-diastolic pressure. (B) LV function curve — stroke volume vs LV end-diastolic diameter. (C) LV end-diastolic pressure-diameter relation. (D) Left atrial diameter (measured at LV end-diastole) vs LV end-diastolic diameter. The lines connect pairs of points with normal PR and without atrial contribution (PR = 0) at the same state of volume loading.  $P_{LV} - P_{peric}$  = transmural LV pressure.

to calculate transmural pressure, these points tended to fall on the curve recorded when the pericardium was open. (In this model when the pericardium was open LV pressure was equivalent to transmural pressure.)

To define the contribution of the Frank-Starling mechanism further, we plotted LV stroke volume against end-diastolic diameter (fig. 3B). All points tended to fall along a single curve, regardless of the presence of the pericardium or atrial contribution.

When the pericardium was closed the withdrawal of atrial contribution always shifted the end-diastolic pressure-diameter relation leftward (fig. 3C). Opening the pericardium shifted the relation rightward and, in this condition, the position of the curve was not affected by atrial contribution. When we compared the calculated transmural pressure-diameter relation (pericardium closed) to the curve recorded when the pericardium was open, the agreement was good.

To assess the effect of atrial contribution on the size of the atrium, we plotted left atrial diameter as a function of LV diameter. At a given LV end-diastolic diameter, left atrial diameter was always larger in the

absence of atrial contribution, whether or not the pericardium was present.

The shifts of the LV end-diastolic pressure-diameter relation just described were found in every other experiment (fig. 4): in each experiment, the LV end-diastolic pressure-diameter relation was shifted upward and to the left after withdrawal of the atrial contribution in the presence of the pericardium. Likewise, opening the pericardium always shifted the curve downward and to the right.

In these experiments, atrial fibrillation sometimes occurred spontaneously (fig. 4). Since this condition represented an alternative means of eliminating the atrial contribution to ventricular filling, we plotted these end-diastolic pressure-diameter coordinates to facilitate comparison. The effect of the withdrawal of atrial contribution appears to be identical, regardless of the means by which effective atrial contraction is eliminated.

When we analyzed the LV stroke volume-end-diastolic diameter relation further by a multiple linear regression analysis with dummy variables (table 1), we

found a high correlation coefficient (in all experiments  $> 0.95$ ), indicating a close association between LV stroke volume and end-diastolic volume. The slope of the regression line was very significantly different

from zero ( $p < 0.001$ ), i.e., the amount of LV stroke volume was dependent on the LV end-diastolic diameter. Since this result was so uniform, the numerical values of the individual slopes are not listed in table 1.

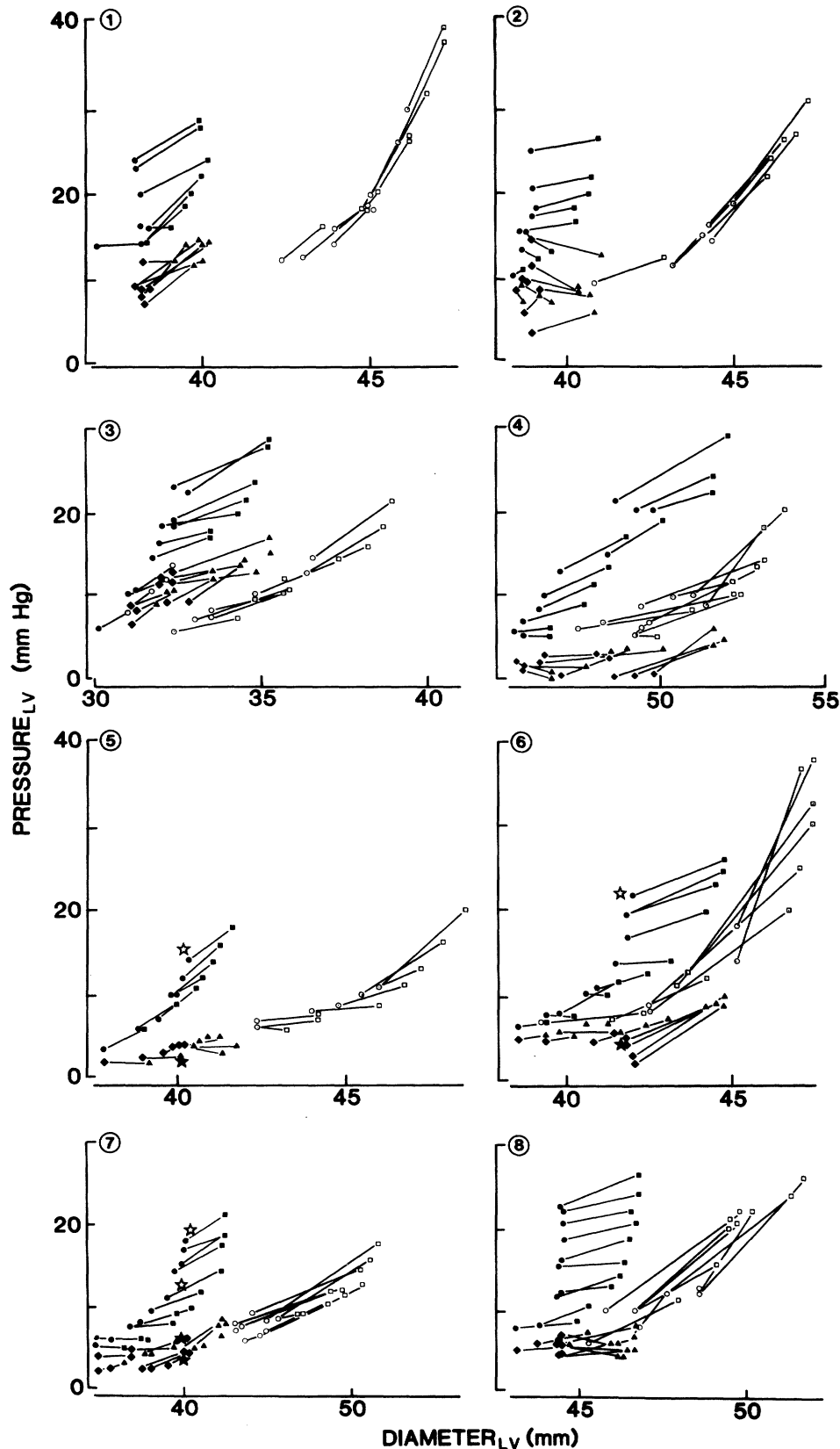


TABLE 1. Results from the Multiple Linear Regression Analysis of the Left Ventricular Stroke Volume–End-diastolic Diameter Relation

Experiment	Multiple correlation coefficient	SEE	n	Change in left ventricular stroke volume (in ml) at a given end-diastolic diameter							
				After withdrawal of the atrial contribution				After opening of the pericardium			
				$b_1(\text{ml}) \pm \text{SE}$	$p$	$b_0(\text{ml}) \pm \text{SE}$	$p$	$c_1(\text{ml}) \pm \text{SE}$	$p$	$c_0(\text{ml}) \pm \text{SE}$	$p$
1	0.99	1.29	34	$-0.03 \pm 0.01$	0.016			$-0.25 \pm 0.04$	0.001		
2	0.95	4.16	27			$-0.13 \pm 2.10$	0.950	$-0.16 \pm 0.11$	0.153		
3	0.97	1.94	38	$-0.08 \pm 0.02$	0.002			$-0.02 \pm 0.03$	0.453		
4	0.97	1.71	38			$-1.03 \pm 0.69$	0.148	$-0.02 \pm 0.02$	0.222		
5	0.99	0.91	30			$0.01 \pm 0.38$	0.980	$-0.03 \pm 0.02$	0.049		
6	0.98	1.35	34	$-0.02 \pm 0.01$	0.202					$1.02 \pm 0.71$	0.160
7	0.97	1.57	44	$0.01 \pm 0.02$	0.423			$-0.05 \pm 0.03$	0.071		
8	0.96	2.19	40	$-0.03 \pm 0.03$	0.199			$-0.01 \pm 0.03$	0.805		
9	0.95	2.07	38	$-0.01 \pm 0.02$	0.300			$-0.08 \pm 0.03$	0.005		

All  $p$  values are two-tailed.  $p$  for  $a_2$  or  $a_1 = 0.001$ .

Missing variables were not computed for the regression equation, since their inclusion did not improve the multiple linear regression coefficient more than 0.01.

Regression equation:  $SV = a_2 \cdot p^2 + a_1 \cdot D + a_0 + (b_1 \cdot D + b_0) \cdot A + (c_1 \cdot D + c_0) \cdot P$ .

Abbreviations: D = left ventricular end-diastolic diameter; A = (0 = atrial contribution, 1 = no atrial contribution); P = (0 = pericardium closed, 1 = pericardium open); n = number of data points;  $b_1, c_1$  = change in left ventricular stroke volume due to a slope change of the stroke volume–end-diastolic diameter relation;  $b_0, c_0$  = change in left ventricular stroke volume due to a parallel shift.

The intercept, i.e., stroke volume at zero diameter, was always negative and was also omitted from the table. In two experiments, withdrawal of the atrial contribution reduced stroke volume by a statistically significant amount due to a slope change of the stroke volume–end-diastolic diameter relation. In one of these experiments and in two others, opening the pericardium reduced stroke volume by a statistically significant amount, also due to a slope change. This reduction was small ( $< 1$  ml) in absolute terms. Neither intervention had a statistically significant effect in any other experiment.

Additionally, we tried to determine (by a simple linear regression) whether the absolute or relative amount of the atrial contribution to LV stroke volume (SV) changed with increasing end-diastolic pressure. We found a significant, positive correlation when the pericardium was closed (absolute atrial contribution:  $SV [\text{ml}] = 0.26 \text{ LV end-diastolic pressure} + 1.36$ ,  $n = 88$ ,  $r = 0.66$ ,  $p < 0.001$ ; relative atrial contribution:  $SV [\%] = 0.31 \text{ LV end-diastolic pressure} + 17.52$ ,  $n = 88$ ,  $r = 0.29$ ,  $p < 0.01$ ). This indicated an increasing augmentation of stroke volume by the atrial contribution with increasing end-diastolic pressure. When the pericardium was opened, no significant correlation was found.

## Discussion

It is generally accepted that atrial systole improves LV performance by means of the Frank-Starling

mechanism, i.e., by increasing LV preload (end-diastolic fiber length).<sup>7</sup> In our clinical study, we observed a downward shift of LV function curve after withdrawal of atrial contribution.<sup>14</sup> To investigate the reason for this downward shift, we compared the relation of stroke volume to end-diastolic pressure and, alternatively, to end-diastolic diameter as measures of preload. We found that withdrawal of the atrial contribution induced a downward shift of the stroke volume–end-diastolic pressure relation when the pericardium was closed, but not when the pericardium was open.

The reason for the downward shift of the stroke volume–end-diastolic pressure relation in the presence of the pericardium can be seen by examining the effect of the atrial contribution on the LV end-diastolic pressure–diameter relation. We found that this relation was shifted upward and to the left after withdrawal of the atrial contribution; i.e., end-diastolic diameter became smaller at a given end-diastolic pressure (fig. 3C). The smaller LV end-diastolic diameter resulted in a smaller stroke volume according to the stroke volume–end-diastolic diameter relation (fig. 3B). Therefore, as LV end-diastolic diameter became smaller for a given end-diastolic pressure, stroke volume also became smaller for this end-diastolic pressure. A smaller stroke volume for a given LV end-diastolic pressure resulted in a downward shift of the stroke volume–end-diastolic pressure relation (i.e., the conventional ventricular function curve).

However, this does not explain how withdrawal of the atrial contribution caused the upward shift of the

FIGURE 4. Left ventricular (LV) end-diastolic pressure–diameter relation for the other experiments performed in this study. The lines connect points with and without an atrial contribution at the same state of volume loading. Symbols are as in figure 3. In three experiments (5, 6 and 7), atrial fibrillation occurred spontaneously. The LV pressure–diameter points (open stars) agree well with the data recorded when atrial contribution was eliminated by simultaneous atrioventricular pacing. Similarly, transmural pressure–diameter points (closed stars) fell near the transmural pressure–diameter relation described when the pericardium was open.



end-diastolic pressure–diameter relation. The cause of this upward shift can be found by considering the effect of withdrawal of the atrial contribution on the atrium itself and by considering that the shift occurred only in the presence of the pericardium.

In the absence of an appropriately timed, effective atrial contraction (compare spontaneous atrial fibrillation, fig. 4), the atrium remained relatively full at LV end-diastole. Thus, left atrial diameter was larger at any LV end-diastolic diameter (fig. 3D). Presumably, this increased pericardial volume, thus accounting for the observed increase in pericardial pressure. As a result, LV end-diastolic pressure, which is the sum of transmural and pericardial pressures, became higher as well.<sup>18</sup> Thus, withdrawal of the atrial contribution shifts the LV end-diastolic pressure–diameter relation upward because it increases pericardial pressure. Therefore, an increase in pericardial pressure (i.e., in effect, a complementary decrease in LV transmural pressure) appears to be the reason for a downward shift of the stroke volume–end-diastolic pressure relation after withdrawal of the atrial contribution.

This hypothesis is supported by the observation that withdrawal of the atrial contribution did not shift either the stroke volume–end-diastolic pressure relation or the end-diastolic pressure–diameter relation, when the influence of pericardial pressure on end-diastolic pressure was eliminated. Thus, we found only one curve when we subtracted pericardial pressure from end-diastolic pressure to obtain transmural pressure and then plotted stroke volume against transmural pressure or plotted transmural pressure against end-diastolic diameter. Similarly, when the pericardium was opened and the measured pressure became equivalent to transmural pressure, we found only one curve for the stroke volume–end-diastolic pressure relation as well as for the end-diastolic pressure–diameter relation. When the pericardium was opened, left atrial diameter continued to be larger after withdrawal of the atrial contribution, but then each chamber could expand freely without affecting pressure in the others, since all external constraint was removed. This interpretation is consistent with the recent study of Maruyama et al.<sup>22</sup> In an *in vitro* study using balloons in each cardiac chamber, they showed that atrial distention elevated the LV pressure–volume relation when the pericardium was intact. When the pericardium was removed, the effect of atrial distention was minimal.

If withdrawal of atrial contribution or opening the pericardium changed stroke volume by other than the Frank-Starling mechanism, we expected a change in stroke volume without a proportional change in LV end-diastolic diameter. As can be seen from the results of the multiple linear regression analysis (table 1), stroke volume was dependent on LV end-diastolic diameter. Although in a few cases, opening the pericardium and withdrawing atrial contribution reduced stroke volume without reducing end-diastolic diameter, this amount was very small and probably was significant only statistically. In some experiments we also observed a tendency toward a flatter slope of the stroke volume–end-diastolic diameter relation after the

pericardium had been opened. This probably only represents the normal flattening of the curve at larger preloads.

It has been suggested that withdrawal of the atrial contribution also reduces LV forward stroke volume because it induces mitral regurgitation.<sup>5, 6, 9</sup> Gilmore et al.<sup>6</sup> and Daggett et al.<sup>5</sup> observed a downward shift of the stroke volume–end-diastolic pressure relation after withdrawal of the atrial contribution when the pericardium was open. Gilmore et al.<sup>6</sup> attributed this downward shift to mechanical impairment caused by the abnormal ventricular depolarization effected to eliminate atrial contribution; they also suggested regurgitation might have reduced stroke volume additionally. However, Daggett et al.,<sup>5</sup> showing the reduction in stroke volume attributable to abnormal depolarization to be small, could suggest only mitral regurgitation as a cause of the reduction of forward stroke volume after withdrawal of the atrial contribution. Their preparation<sup>23</sup> may have been prone to develop mitral regurgitation because of a collapsed right ventricle<sup>5</sup> and blockade of the autonomic nervous system.<sup>5, 6</sup> Although we did not specifically rule out mitral regurgitation, it probably did not play an important role in the reduction of stroke volume after withdrawal of the atrial contribution, because we found no downward shift in the stroke volume–end-diastolic diameter or in the stroke volume–end-diastolic pressure relation when the pericardium was open, when mitral regurgitation likely would have been the greater. Using angiography to detect mitral regurgitation, Braunwald et al.<sup>24</sup> and Williams et al.<sup>23</sup> concluded that a properly timed atrial systole was not necessary for effective mitral closure except, perhaps, when the left ventricle was depressed.

We estimated the pericardial restraining force (i.e., surface pressure<sup>25</sup>) with a flat, liquid-containing balloon placed over the LV free wall near the apex; the pericardium was not sealed. A comparative analysis of the regional and global effects of the pericardium is beyond the scope of this discussion, but our approach is supported by the fact that, for a given end-diastolic diameter, our estimates of transmural pressure agreed well with measured transmural pressure (i.e., LV end-diastolic pressure with the pericardium open).

Removal of the restraining force by opening the pericardium increased LV volume for a given end-diastolic pressure and thus increased LV stroke volume, especially after volume loading. Although this is shown by our data and by the data of others,<sup>26–28</sup> the amount of this increase is not established. Stokland et al.<sup>27</sup> provided an estimate of the effect of pericardiectomy on LV size and stroke volume. Myocardial segment length increased by 4% and stroke volume by 14% when end-diastolic pressure was held at 13 mm Hg by volume loading. However, Shirato et al.<sup>28</sup> presented several experiments in which myocardial segment length increased by 10% or more when the pericardium was open. These latter results are more comparable with our observations.

The results of this study suggest that the downward shift of the LV function curve (stroke volume–filling



pressure) that we observed in our clinical study,<sup>14</sup> as with the downward shift in these experiments, was due to the restrictive properties of the pericardium, i.e., unobserved changes of pericardial pressure shifted the LV end-diastolic pressure-volume relation. However, in some of our patients who were studied after open heart surgery including pericardiotomy, the same downward shift was observed. Although the significance of the pericardium in these patients is less clear, studies have shown that the heart may be externally constrained postoperatively. Even development of severe, life-threatening cardiac tamponade has been reported.<sup>29, 30</sup> These observations suggest that a simple pericardiotomy is not sufficient to eliminate all external constraint on the heart by surrounding structures.

In this experimental study we could not confirm our finding in the clinical study<sup>14</sup> that the atrial contribution to LV stroke volume was less important when filling pressures were elevated since, in these experiments, the atrial contribution increased with increasing end-diastolic pressure.

We observed, however, that the atrial contribution was much less in those patients with a filling pressure of more than 20 mm Hg who had a history of congestive heart failure. Similarly, Rahimtoola et al.<sup>15</sup> reported that the atrial contribution was less in patients with enlarged end-diastolic volumes. Thus, it is possible that in the experimental study we were unable to reproduce the clinical observation of declining importance of the atrial contribution in heart failure patients because the animals in this study had normal left ventricles.

Generally, the amount by which the atrial contribution to LV filling improves LV stroke volume depends on several factors: the increase in LV end-diastolic volume, in turn dependent on the pump function of the atrium and the diastolic pressure-volume relationship, and the augmentation of stroke volume gained for this increase in end-diastolic volume as determined by the slope of the function curve. All of these factors might be altered in the diseased heart, explaining why atrial systole seems important for one patient but not for another.

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