Effects of Left Ventricular Loading by Negative Intrathoracic Pressure in Dogs

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There are many factors, both intrinsic and extrinsic to the left ventricle, that can affect its function when negative intrathoracic pressure is imposed. In this study, we examined whether the left ventricular response to the afterload imposed by negative intrathoracic pressure was similar to that imposed by partial aortic constriction. We used steady-state right heart bypass to control pulmonary venous return to the left ventricle and reflex blockade to maintain constant heart rate and contractility. To impose negative intrathoracic pressure we used a pressure chamber fitted over a midsternal thoracotomy, which allowed steady negative pressure to be applied to all intrathoracic surfaces. Left ventricular volumes were measured from biplane cineradiograms of multiple 1-mm markers implanted in the left ventricular midwall. With cardiac output and heart rate constant, we compared the left ventricular response to two different levels of negative intrathoracic pressure and to increasing aortic pressure by partial aortic constriction. In each case, negative intrathoracic pressure produced a rise in the left ventricular end-systolic and end-diastolic volumes as well as transmural pressures similar to the effects of partial aortic occlusion. Thus, when cardiac output, heart rate, and contractility are maintained constant and all external restraints on the left ventricle are removed, the left ventricle responds in a similar manner to an increase in hydraulic load whether produced by a decrease in intrathoracic pressure or by partial aortic occlusion. (Circulation Research 1988;62: 620–631)

The consensus of many studies is that negative intrathoracic pressure produces a fall in arterial blood pressure, concomitant with a fall in aortic flow. Recently, the notion that the decrease in left ventricular output during negative intrathoracic pressure is due to an increased afterload on the ejecting left ventricle (LV) has gained wider acceptance. Despite this seemingly self-evident concept, however, there has been no unequivocal demonstration of the response of the LV to the pure afterload effects of negative pressure. This is primarily due to the difficulties of accurately measuring or controlling the multitude of competing mechanisms that could also account for the fall in left ventricular output with negative pressure in the intact circulation. Thus, much of the evidence for the afterloading effect of negative pressure is only indirect.

How to best quantify left ventricular afterload continues to engender controversy. Some prefer to express afterload in terms of wall stress or the load on the muscle in the wall, whereas others prefer to express afterload in hydraulic terms that are independent of the ventricle. In this paper we will adopt the latter approach and quantify afterload in terms of aortic input impedance.

We examined whether the left ventricular response to the afterloading effect of negative intrathoracic pressure was similar to that of partial aortic constriction. We thus examined the steady-state effect of negative pressure and aortic occlusion in open-chest dogs on right heart bypass after ganglionic blockade, vagotomy, and pericardiectomy. Left ventricular volume was obtained from the positions of 14–20 stainless steel markers implanted into the wall of the LV. By analogy with the response in the isolated heart, under these highly controlled conditions whereby stroke volume is held constant, an increase in hydraulic left ventricular afterload produced by these interventions should result in an increase in both end-diastolic and end-systolic left ventricular volumes. It did.

Materials and Methods

Six mongrel dogs of either sex, weighing 27–34 kg, were anesthetized with Thiampylal (17.6 mg/kg i.v.), α-chloralose (13.6 mg/kg i.m.), and urethane (136 mg/kg i.m.). The animals were instrumented with a circumferential aortic occluder at the descending aorta just distal to the left subclavian artery, an electromagnetic flow probe (Biotronex, Kensington, Maryland) around the ascending aorta, and a 7F double transducer micromanometer catheter (Millar Instruments, Houston, Texas) introduced via the left common carotid artery so that one transducer was in the left ventricular cavity while the other was in the aorta. The animal was intubated and mechanically ventilated with room air supplemented with oxygen.

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Marker Placement

Fourteen to twenty-two 1-mm-diameter stainless steel markers were placed in the left ventricular myocardium of each animal. This was accomplished by using a 19-gauge needle with its bevel ground off. There was a shim on the shaft to prevent penetration of more than 6 mm from the epicardial surface. After making a small nick in the epicardial surface, the needle was inserted perpendicularly to the epicardial surface to a depth allowed by the shim while the marker was held on with vacuum. Then, vacuum was released and the needle was withdrawn, leaving the marker embedded in the myocardial midwall. To implant septal markers a nonshimmed needle was used to first penetrate the right ventricular free wall and then the septum to embed the marker in the septum. A minimum of three markers were placed in the septal, posterior, anterior, and lateral walls. One apical marker was implanted, and additional markers were placed between these markers in each heart. Fluoroscopy confirmed the myocardial location of the markers after placement. Postmortem examination confirmed that each marker was roughly in the midwall of the LV or interventricular septum and was not located in the interstices of the endocardial surface.

Right Heart Bypass

After placing the markers in the left ventricular wall, right heart bypass (Figure 1) was initiated by placing a 3/8-inch fenestrated venous drainage cannula through the right atrial appendage, through the tricuspid valve, and into the right ventricle. The cannula was connected to a reservoir that was placed approximately 4 feet below the animal. Blood from the reservoir was pumped with a calibrated roller pump (Sarns) through a heat exchanger and an air-trap filter and then into the pulmonary artery. The pulmonary artery cannula was placed through the wall of the right ventricular outflow tract and secured with a purse-string suture, and then the catheter was advanced into the pulmonary artery. Before placing the animal on right heart bypass, the perfusion circuit was washed once with normal saline (0.9%), twice with sodium bicarbonate solution (12.6 g/l), and primed with 2 l of lactated Ringer’s solution. The solution was allowed to warm to 39° C and then heparinized with 5,000 U beef lung heparin. Indomethacin (100 mg) was added to the solution 30 minutes prior to bypass. The animal was then systemically heparinized with 5,000 U beef lung heparin. After slowly equilibrating the animal’s blood with the priming solution, the pump was set to achieve a systolic arterial pressure of approximately 100 mm Hg.

Induction of Negative Intrathoracic Pressure

To induce a controllable steady-state level of negative pressure around the heart, a specially designed box was placed over the midsternal thoracotomy (see Figure 2). This box had a Plexiglas top with holes permitting exteriorization of the various lines and a fitting for large-bore tubing. The sides of the box were constructed from thick rubber and were glued with rubber cement to the skin surrounding the thoracotomy to produce an airtight seal. The rigid top of the box was supported on two edges with pipes attached to the cradle holding the dog to prevent collapse of the box when the vacuum was initiated. Negative pressure in the chamber and thorax was produced by connecting the large-bore tube to a vacuum source that could be regulated to provide different levels of steady negative intrathoracic pressure. In preliminary studies, we noted a large amount of diaphragmatic motion in the direction of the thorax when the vacuum was connected. This diaphragmatic motion resulted in marked translation of the heart. Therefore, a rigid plastic restrainer was placed on the thoracic side of the diaphragm and held in place by cords attached to the table (Figure 2 inset) to prevent this translation. Care was taken to prevent this plate from impinging on the aorta or inferior vena cava.

Study Protocol

Reflex blockade was first produced by bilateral vagotony followed by infusion of 35 mg/kg hexamethonium bromide (Sigma Chemical, St. Louis, Missouri) diluted in 100 ml of saline. The solution was given gradually so that decreases in aortic pressure could be compensated for by increases in the bypass pump speed.

To prevent contact between the lungs and the heart surfaces the endotracheal tube was clamped with the lung volume at functional residual capacity immedi-
FIGURE 2. Schematic of experimental set-up. Chamber is sealed with glue to chest wall by means of rubber skirt. Various lines and catheters are exteriorized as shown. A vacuum hose connected to the chamber allows imposition of negative pressure in the chamber and the thoracic contents. Right inset: Position of animal and axis system relative to biplane x-ray sources and image intensifiers. Left inset: Detail of abdominal restraining plate used to keep the diaphragm from translating when negative pressure is imposed.

ately prior to imposition of negative pressure. Then, vacuum was adjusted so that the box pressure reached a steady negative value (either approximately 10 or 20 mm Hg) for about 20 seconds. Hemodynamic and biplane cineradiographic recordings were made for the last 10 seconds of the run. The box pressure was then returned to atmospheric pressure. When the pressures and flows had stabilized (10–15 seconds), a recording of a control condition was made. Pump speed was not altered between the intervention and its control conditions.

To compare the above response to a maneuver that is known to load the left ventricle, simultaneous hemodynamic and biplane cineradiographic recordings were made during control conditions and during partial aortic occlusion while the lung volume was kept at functional residual capacity and the intrathoracic pressure at atmospheric pressure. The pump speed was not varied between the control state and the aortic occlusion.

After collection of data the heart was arrested with a bolus of saturated potassium chloride solution. All instrumentation was removed, the left atrium was opened, the chordae tendineae of the mitral valve were cut, and the mitral leaflets were sewn together. A prestressed latex balloon was then pulled into the LV through the aortic valve and fixed to the apex. The balloon was then tied tightly by a ligature around the aortic root and inflated with a known volume of water (60 ml). Biplane cine recordings of the heart with its embedded markers were then made at 15 frames per second. These recordings were repeated after withdrawing volume from the balloon in 10-ml increments until the balloon was empty. The heart was then excised from the animal and fixed in 10% formalin for confirmation of marker positions. These data were used to produce calibration curves for each left ventricle as described below.

Magnification and nonflatness of the x-ray fields needed to be taken into account to provide absolute spatial coordinates of each marker. Magnification was accounted for by recording simultaneous biplane images of a precisely machined calibration cube containing several accurately placed markers. Nonflatness of each x-ray field was corrected by an algorithm that fit a polynomial function to the images of precisely aligned grids for both the anteroposterior (AP) and lateral views as previously described.13

Data Acquisition

The instrumented dog was positioned in a biplane x-ray system (GE Sentury system) (Figure 2 inset) so that the left ventricular markers were in the center of the screen during control and vacuum conditions. Once
located, the sources and intensifiers were not moved until completion of the experiment. Biplane cineradiograms were taken at 60 frames per second with a 6-inch AP field and a 6- or 9-inch lateral field. To correct for any frame-to-frame misalignment in the film transport system both during recording and playback, Plexiglas plates with four metal alignment markers were fixed to each image intensifier and were recorded along with the markers (Figure 3) in the heart as previously described. 13

Statham P23dB pressure transducers (Hato Rey, Puerto Rico) at the level of the right atrium measured pressures in the venous drainage and pulmonary artery cannulae and in the thorax ("box pressure"). Aortic flow was measured using a sine wave electromagnetic flow meter (Biotronex) and left ventricular and aortic pressures were measured with the previously described micromanometer. Pressures and flows were recorded continuously on a Gould-Brush strip-chart recorder (Cleveland, Ohio) and on magnetic tape (model 3968A, Hewlett-Packard, Palo Alto, California). A cine marker was recorded from the AP cine camera to synchronize the cine records and hemodynamic records.

**Analysis of Marker Coordinates**

The cine records were analyzed using a previously described, semiautomated marker tracking system. 13 When the desired sequences of film were identified, first the AP and then the lateral images were displayed frame by frame on a 35-mm projector whose screen was viewed by a television camera. Each frame of video image was digitized and the data dumped onto an array processor (DeAnza, Gould) interfaced to a PDP 11/34 computer (Digital Equipment, Marlboro, Massachusetts). The frames containing the images of the calibration cube and dewarp grids were first selected and digitized. Appropriate algorithms to correct for nonflatness and magnification were used to correct all subsequent images of the markers. For those frames containing the markers in the heart, the operator first located each marker on the first frame of the sequence to be analyzed. Using autocorrelation and prediction techniques, the computer then automatically located and marked the center of each marker. The operator could manually correct the position identified by the computer if the algorithm incorrectly located a marker. This was done separately for the AP and lateral views. Synchronization of the two projections was obtained by calculation of the position of the center of mass of the markers on the common axis of the AP and lateral projections. The markers were then paired from the two projections to yield absolute frame-by-frame, three-dimensional coordinates of each marker. Previous studies have demonstrated the spatial resolution of the system to be about 0.2 mm. 13 The marker coordinate data were transferred to an MV 8000 computer (Data General, Westboro, Massachusetts) where another algorithm was used to calculate the volume demarcated by the markers.

**Volume Calculation**

The algorithm for estimating volume from such data has been previously described. 13 Briefly, the centroid of all the markers was first determined. For each marker,
the magnitude of the vector from the centroid to the marker was then calculated. The entire surface was then divided into 30° sectors, and the weighted average of the nearest vectors within a sector were calculated. Cubic spline curves were fitted to all lines with the same circumferential and meridional angles yielding lines of latitude and longitude, respectively. The lines demarcating a sector formed the boundaries for a bicubic surface patch that interpolated the surface locations within the sector. The entire surface was thus interpolated with 614 surface points. From these sectors, the volume was calculated by forming triplets of all the surface points. Tetrahedra were formed from the vertices of each triangle to the centroid, and the volumes of all these tetrahedra were summed yielding the enclosed volume. Typical biplane images of the marker coordinates for one heart along with the interpolated surface for the volume calculation are shown in Figure 3.

A calibration curve for each experiment was obtained by plotting the volumes calculated by the markers against the actual balloon volume in the arrested state. The data used for all six calibrations are shown in Figure 4. The two lower volume points for dog 5 appeared to not form a linear relation with the higher volume points. Since the higher volume points were closer to the in situ values for this dog only, we used only the four higher volume points to obtain a linear calibration line. We verified that the conclusions were not affected whether we used all six points (either linear or nonlinear regression) or the four linear points for the calibration, despite the absolute volumes depending upon the exact calibration line used. For simplicity, the data reported for this dog are those obtained using the four-point linear regression. The results of linear regression analysis of the balloon and marker volumes for each heart are listed in Table 1. The intercept of the regression line represents the approximate volume of myocardial mass enclosed by the markers after diastolic arrest. Assuming that this mass is close to that at end-diastole, we used each linear regression line to correct the marker volumes for the end-diastolic frame to yield an estimate of the end-diastolic cavity volume of the LV.

Since we could not be sure that the volume of myocardium circumscribed by the markers remained constant as the wall thickened during systole, we did not use the arrested heart calibration curve to obtain the end-systolic volume. Rather, since the cardiac output was accurately controlled by the pump setting, dividing this by the heart rate yields the steady-state stroke volume. The end-systolic left ventricular cavity volume was calculated by subtracting this known stroke volume from the above corrected end-diastolic volume.

Hemodynamic Data

In preliminary studies, we verified that the box pressure was the same regardless of where in the chest cavity the catheter was placed. Specifically, when vacuum was imposed the pressure on both the anterior and posterior surfaces of the LV and aorta were the same as the pressure measured in the middle of the box. Hence, all aortic and left ventricular pressures were converted to transmural pressures by subtracting the box pressure.

The hemodynamic information recorded on FM tape was digitized at 4-msec intervals. The hemodynamic information was coordinated with the cine information by use of the cine marker. A minimum of four cardiac cycles were analyzed in each sequence. Using previously detailed methods,15,16 we calculated the following hemodynamic parameters: peripheral vascular resistance (mean transmural aortic pressure divided by mean flow), the first 10 harmonics of the aortic input impedance, and the ratio of the backward to forward

Table 1. Results of Linear Regression Analysis (Y=Ax+B) of Balloon- vs. Marker-Determined Left Ventricular Intracavitary Volumes for Calibration Relations Shown in Figure 4

<table>
<thead>
<tr>
<th>Dog</th>
<th>A</th>
<th>B (ml)</th>
<th>(r)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.819±0.042</td>
<td>43.6±0.72</td>
<td>0.995</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>0.660±0.069</td>
<td>51.4±1.17</td>
<td>0.979</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>0.988±0.034</td>
<td>85.9±0.58</td>
<td>0.998</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>0.793±0.036</td>
<td>55.0±0.62</td>
<td>0.996</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5</td>
<td>1.082±0.031</td>
<td>41.9±0.35</td>
<td>0.999</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6</td>
<td>0.806±0.030</td>
<td>47.2±0.51</td>
<td>0.997</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Y, marker-determined volume; X, balloon volume; A, slope; B, intercept; \(r\), correlation coefficient; \(p\), significance. Standard errors are listed for A and B. Values for dog 5 are the regression for only the four largest volumes shown in Figure 4.
pressure wave components. The details of the methodology and criteria for acceptability of data were identical to those previously employed and are detailed in our previous publications.

The left ventricular end-systolic pressure-volume relation (ESPVR) is an especially useful means to quantify left ventricular function since the relation is more or less linear over a wide range of differing preloads and afterloads when contractility is held constant. Since the contractility should have been maintained constant in our preparation, we quantified the end-systolic and end-diastolic left ventricular responses in terms of the ratio of the respective change (from control to intervention) in transmural pressures to change in volumes. As the studies of the ESPVR on isolated hearts have shown, regardless of the magnitude of the increase in load, this ratio should be the same if the LV responds in the same manner to the different interventions. For this study, end-systolic pressure was defined as the pressure at the nadir of the dicrotic notch.

Statistical Analysis

Because of the relatively small number of samples and the wide scatter in the data, the assumption that the data have a Gaussian distribution may not be warranted. To avoid having any "outlying" data points unduly influencing the statistical comparisons and yet not wishing to arbitrarily delete these data, we employed nonparametric statistical methods to obtain statistically robust descriptions and comparisons. These methods will yield virtually the same conclusions if the data happen to be normally distributed. First, bisquare weighted regression was used to estimate and compare the means for the various interventions. This approach takes into account the scatter of the data and automatically calculates a smooth weighting function that gives more weight to observations near the median and less weight to outlying observations. With this scheme, values that are more than about six standard deviations from the mean will receive no weighting. The effect of each intervention with respect to its control was analyzed by using Wilcoxon's signed-rank test on the change produced by that intervention.

To test for group differences among the interventions, we calculated the Friedman statistic followed by pairwise comparisons if this statistic indicated significantly different effects among the three interventions.

Results

Tracings from a representative experiment illustrating the effects of negative intrathoracic pressure are shown in Figure 5. From top to bottom are the cine marker, aortic pressure, left ventricular pressure, pulmonary artery pressure, aortic flow, box pressure, and right ventricular pressure. This sequence demonstrates the steady-state experimental period with the pressure in the chamber at about -20 mm Hg followed by return of box pressure to atmospheric pressure and a subsequent steady-state control state. The cine marker indicates the firing of the AP camera. Because the shut-off of the cameras provided the most reliable timing signal for coordinating the cine and hemodynamic data, the beats immediately preceding the shut-off of the cameras were used for analysis. Note that heart rate and aortic flow do not change noticeably throughout. A 20-mm Hg decrease in intrathoracic pressure results in a decrease in aortic and left ventricular pressures relative to atmosphere. The transmural pressure, however, of both the aorta and LV rise during negative intrathoracic pressure compared to the control state.

Corresponding hemodynamic data for the aortic occlusion and its control state are shown in Figure 6. Note that during this intervention the control state is first recorded followed by intervention. As with the negative pressure intervention, only steady-state data for the last beats during the filming were analyzed. During aortic occlusion, there is an increase from control values in both aortic and left ventricular pressures. Since box pressures are atmospheric during this intervention, these cavity pressures are also the transmural pressures. As before, there was also no change from the control in heart rate or aortic flow during this intervention.

Representative volume curves calculated from the marker cine data for the runs in Figures 5 and 6 are shown in Figure 7. The volumes illustrated in this figure represent the total volume circumscribed by the markers (cavity plus some myocardium) during three cardiac cycles of each intervention. The maxima and minima of these curves correspond to the respective end-diastolic and end-systolic volumes. The upper panels are data from the negative pressure run and the lower panels are from the aortic occlusion run. The left tracing in each set represents the control condition, and the right-hand figure is the intervention. Note that both interventions increased both the uncorrected end-diastolic and end-systolic volumes from their control levels. The corrected end-diastolic and end-systolic volumes for all of the interventions are listed in Table 2.

Table 2 summarizes the left ventricular pressure and volume data for aortic occlusion and two levels of negative intrathoracic pressure for all six animals. No significant changes in heart rate were induced by any of the interventions. Each intervention produced significant increases in both end-diastolic and end-systolic left ventricular transmural pressure and volume. The Friedman test, however, indicated that there was no difference among these three interventions in the ratios of either the end-systolic or end-diastolic transmural pressure increase divided by the volume increase from control to intervention. Thus, these results indicate that the left ventricular response to each intervention is that of an increased afterload and that over the range of loading imposed, the averaged left ventricular end-systolic and end-diastolic response to the three interventions was the same.

Table 3 summarizes the hemodynamic data. The interventions did not alter characteristic impedance or the backward-to-forward ratio of the pressure compo-
Cine Marker

**FIGURE 5.** Experimental records obtained during and after release of negative intrathoracic pressure. \(P_{\text{a}}\), aortic pressure; \(P_{\text{LV}}\), left ventricular pressure; \(P_{\text{PA}}\), pulmonary artery pressure; \(Q_{\text{a}}\), aortic flow; \(P_{\text{P}}\), intrathoracic pressure; and \(P_{\text{TV}}\), right ventricular pressure. \(P_{\text{M}}\) is decreased to a steady state during which recordings were made. After return to atmospheric pressure, data for control state were obtained. In each case, left ventricular volumes were obtained during the last two to three heart cycles before the cine camera was shut off. The cine marker pulse was used to time the hemodynamic data to correspond to these values.

Discussion

In the present study, by rigidly controlling or eliminating the confounding factors of altered left ventricular filling, contractility, external restraints, and right ventricular filling, and by being able to directly measure the pressures acting at the heart surfaces we have, in effect, achieved the equivalent of the isolated LV. In the isolated LV, it has been shown that the left ventricular ESPVR during negative surrounding pressure is not altered from control conditions if the relation is expressed in terms of transmural pressure. Thus, our results demonstrating that the left ventricular response to the pure afterload effect of negative intrathoracic pressure is similar to that of partial aortic occlusion are not surprising. These results are, to our knowledge, the first time that this response to negative pressure has been unequivocally demonstrated in situ.

Negative intrathoracic pressure afterloads the LV because the distensible circulation is partitioned into intrathoracic and extrathoracic compartments. In the intact circulation, lowering the surrounding pressure of the intrathoracic contents impedes the flow of blood out of the thorax because of increased hydraulic resistance to ventricular emptying. If one considers only the aortic luminal pressure with respect to atmosphere, there would be an apparent fall in aortic pressure and a corresponding fall in the calculated peripheral resistance. The transmural aortic pressure, however, increases due to a larger fall in the surrounding pressure than in the luminal pressure. Equivalently, if one considers the luminal pressure as the upstream pressure and there is a fall in the downstream pressure (in this case the surrounding pressure), there will be an increase in the driving pressure. Thus, at a constant flow, one of the major components of hydraulic afterload, resistance, increases. Because aortic occlusion produced a discrete region of narrowing in the midthoracic aorta, it is not surprising that some differences from the more widespread effects presumably produced by the negative pressure in the aortic impedance spectrum were seen. Our data indicate that there were small differences produced by negative pressure and aortic occlusion in the pulsatile components of hydraulic load. Negative pressure did not affect any of the pulsatile components of load while aortic occlusion increased the first impedance harmonic, indicating either increased reflections and/or
decreased proximal aortic compliance. These differences were subtle, however, since our estimate of reflection magnitude did not show a difference between the two types of interventions. Regardless, our data indicate that the predominant effect of these two types of interventions is on the resistance. It has been shown in the isolated dog heart that, compared with compliance and characteristic impedance, resistance is the largest determinant of stroke volume when contractility, end-diastolic volume, and heart rate are held constant. Consequently, from the standpoint of the LV, as long as stroke volume and heart rate are held constant, when there is increased hydraulic loading, whether the loading is caused by increasing intraluminal pressure or by decreasing surrounding pressure, the LV will respond similarly.

A different interpretation of the afterloading effects of negative pressure was presented by Olsen et al. They used three pairs of sonomicrometers to estimate the left ventricular volume and a micromanometer in a protective sheath placed in the pleural space near the heart to estimate the juxtacardiac pressure. Like previous studies they found a decrease in stroke volume and increase in left ventricular end-systolic volume but they did not find an increase in left ventricular transmural pressure. Thus, despite the LV responding as if it were afterloaded, they could not document an increase in afterload. Consequently, they had to attribute the loading to a so-called "reverse thoracic pump" in which the fall in the ejection pressure of the LV relative to atmospheric pressure was considered as the load.

Since we have clearly demonstrated that negative intrathoracic pressure afterloads the LV, this effect should be present whenever negative pressure is imposed. It is reasonable to ask why the left ventricular response is not always compatible with an increased afterload. The answer must be related to the multitude of factors, both intrinsic and extrinsic to the LV, that can affect its function when negative pressure is imposed, including 1) delayed pulmonary venous transit time; 2) diminished left ventricular filling due to sequestration of blood in the pulmonary vasculature; 3) altered left ventricular compliance due to ventricular interaction mediated by deviations in interventricular septal position; 4) altered external constraints on the LV due to either competition with other intrapericardial chambers for a limited pericardial space or interaction between the lung and LV surfaces; 5) altered left ventricular contractility, and 6) increased LV afterload. The response of the LV represents the net effect of these sometimes competing mechanisms and is determined in part by the phase of the cardiac cycle and the timing and extent of the negative pressure.

Depending upon the conditions, one or more of these mechanisms could dominate, thereby obscuring the effects of the others. For example, when intracardiac...
 volumes are small, one would expect very little ventricular interaction effects so that the afterload effects might be dominant. In contrast, when the intracardiac volumes are large and the pericardial restraining effects are large, one might expect the interaction effects to dominate. If the pericardial effects are dominant, pericardiectomy under these conditions might once again allow the afterload effects to become manifest. There are examples in which the afterloading effect of negative pressure has been obscured by competing effects of other mechanisms. Scharf et al\textsuperscript{30} found a decrease in aortic flow and left ventricular diastolic dimensions and unchanged left ventricular filling and aortic transmural pressures during spontaneous respirations in dogs. They felt these findings were consistent with a decreased left ventricular compliance and filling and not with increased afterload. During loaded respirations, however, there was now an increase in left ventricular diastolic size, along with increases in transmural atrial and aortic pressures. Under these conditions, the results were consistent with a dominant effect of afterload. Similarly, Guzman et al\textsuperscript{30} found an increase in peak left ventricular systolic and end-diastolic pressures relative to airway pressure but no increase in left ventricular cavity area measured by echocardiograms during Mueller maneuvers in supine subjects with presumably large intracardiac volumes. These results are consistent with the afterloading effect being overwhelmed by the larger effect of diminished left ventricular filling and perhaps also decreased compliance mediated by interventricular septal deviation. It is not surprising, therefore, that studies in the intact circulation, under widely different and difficult-to-control conditions, have been unable to unequivocally demonstrate the effect of each specific mechanism.

All of the above considerations pertain to steady-state conditions; during transient conditions the situation becomes even more complicated because of the dynamic interactions of each of the effects. Thus, despite the fact that the afterload should persist as long as the surrounding pressure is negative, its effects could be masked during the ensuing circulatory adjustments. For example, Schrijen et al\textsuperscript{30} demonstrated an increased aortic transmural pressure, an elevated heart rate, no change in left ventricular filling pressure, and a decrease in stroke volume during the first two beats of a deep spontaneous inspiration in dogs. During the next two beats, however, they found a rise in left ventricular filling pressure. The response during the first two beats was attributed to the counterbalancing effects of the increased afterload, which should have increased the filling pressure, with those of the decreased venous return and the reflexly increased heart rate, both of which would tend to decrease filling pressure. By the next two beats, when the reflex effects had disappeared (as indexed by return of heart rate to baseline values), the afterload effect predominated, causing left ventricular filling pressure to increase.

Still another reason for the confusion is the many different methods that have been used to estimate left ventricular volume or, in some cases, the inferences on left ventricular volume or dimensions that have been made without actual measurements of these. For example, Robotham et al\textsuperscript{3} in dogs and Magder et al\textsuperscript{28} in humans found increases in transmural aortic and left ventricular filling pressures during respiration. Based on these data they could infer, but not prove conclusively, that there was an increase in left ventricular afterload. Summer et al\textsuperscript{4} found, in dogs, an increase in one left ventricular end-systolic dimension together with decreased aortic flow and increased transmural aortic and left ventricular diastolic pressures and concluded that negative pressure afterloaded the LV. Obviously, inferring volume changes from a single ventricular dimension, especially in a setting where the left ventricular shape could be changing, may not be reliable. Scharf et al\textsuperscript{30} and Karam et al\textsuperscript{30} found an increase in end-systolic counts and no alteration in end-diastolic counts in radionuclide angiograms during inspirations in humans. These data are also consistent with, but do not conclusively prove, that there is an increase in afterload.

The multiple marker system that we employed allowed extremely accurate determinations of left ventricular volume. First, we used a calibration curve for each heart obtained with the markers located as they were during the experiment. Second, the volume estimation algorithm we used, unlike those used to calculate left ventricular volumes from pairs of

\textbf{FIGURE 7.} Plots of left ventricular volume calculated from the markers for three heart cycles during the interventions shown in Figures 5 and 6. The left panels show the volumes during each control state and the right panels show the volumes during the intervention. Note that these volumes are the marker-determined volumes and not the intracavitary volumes.
sonomicrometers or even from similar markers, does not assume a regular geometric shape. Third, unlike two-dimensional echocardiograms that provide a limited view of the entire ventricle, our volume estimate is obtained from many markers scattered throughout the LV wall. Consequently, our volume estimates should also be more accurate than either of the above methods in settings where the shape of the LV is likely to be altered even though in our particular situation prominent shape changes are unlikely to be a major confounding factor. Because of the high spatial resolution of the marker system we also feel that this system is more accurate than radionuclide methods for estimating absolute changes in ventricular volumes. Our method also enables us to estimate absolute left ventricular volumes rather than the relative volumes that are obtained with other marker systems. Finally, even the conductance catheter system, which offers the potential advantage of on-line analog left ventricular volume signals, may not be suitable under these conditions because of possible changes in parallel conductance caused, for example, by pooling of blood in the pulmonary venous or left atrium, which can be sensed by the catheter as an apparent shift in left ventricular volume. Because of this limitation, it has been suggested that the conductance catheter will accurately measure relative volumes and stroke volumes but not absolute volumes.

Despite these advantages, there are limitations to our method for estimating left ventricular volumes. We have already discussed the potential limitation for obtaining systolic volumes because of the possibility that the amount of myocardium subtended by the cavity volume.

### Table 2. Left Ventricular Response to Two Levels of Negative Intrathoracic Pressure and to Aortic Occlusion

<table>
<thead>
<tr>
<th>Dog</th>
<th>LVEDV (ml)</th>
<th>LVESV (ml)</th>
<th>HR (bpm)</th>
<th>(P_{\text{edv}}) (mm Hg)</th>
<th>(P_{\text{esv}}) (mm Hg)</th>
<th>(\Delta P/\Delta V_{\text{es}})</th>
<th>(\Delta P/\Delta V_{\text{ed}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>110.2</td>
<td>84.5</td>
<td>174</td>
<td>21.9</td>
<td>78.7</td>
<td>-0.5</td>
<td>14.3</td>
</tr>
<tr>
<td>2</td>
<td>131.1</td>
<td>94.9</td>
<td>119</td>
<td>21.0</td>
<td>51.3</td>
<td>-10.9</td>
<td>4.4</td>
</tr>
<tr>
<td>3</td>
<td>105.9</td>
<td>86.7</td>
<td>183</td>
<td>16.7</td>
<td>51.3</td>
<td>-17.6</td>
<td>1.1</td>
</tr>
<tr>
<td>4</td>
<td>80.0</td>
<td>59.8</td>
<td>154</td>
<td>20.5</td>
<td>84.1</td>
<td>-10.5</td>
<td>4.3</td>
</tr>
<tr>
<td>5</td>
<td>109.8</td>
<td>84.2</td>
<td>134</td>
<td>14.5</td>
<td>74.7</td>
<td>-11.5</td>
<td>40.5</td>
</tr>
</tbody>
</table>

**Table Notes:**
- \(C\) is control.
- \(I\) is intervention.
- LVEDV = left ventricular end-diastolic volume (ml).
- LVESV = left ventricular end-systolic volume (ml).
- HR = heart rate (bpm).
- \(P_{\text{edv}}\) = change in intrathoracic pressure (mm Hg).
- \(P_{\text{esv}}\) = mean end-diastolic left ventricular transmural pressure (mm Hg).
- Mean values listed are the bisquare weighted averages.

The data in the table demonstrate the variability in the volume estimates obtained under different loading conditions.
Several alternative mechanisms other than direct left ventricular loading by negative pressure could be postulated to account for the results of our experiment. Since our measurements were made at constant lung volume (without ventilation), hypoxia could potentially cause an increase in left ventricular end-diastolic volume as the heart begins to fail. This is unlikely, however, since if anything, we measured our control data following the experimental negative pressure intervention. The preparation would more likely be hypoxic during our control conditions. A depression of the ventricular inotropic state during negative intrathoracic pressure, induced, for example, by humoral or reflex mechanisms, could account for the increase in left ventricular end-diastolic volume during this experiment. Since the reflexes were blocked, however, we think that in our preparation, reflex-induced alterations in inotropy were unlikely. Moreover, previous studies in the isolated heart have shown no direct changes in contractility following exposure of the LV to negative surrounding pressure. 20 Some studies have proposed that negative pressure may alter the diastolic compliance and hence the systolic function of the LV. 9 This is unlikely in the present study because the mechanism for such a compliance alteration is usually attributed to ventricular interaction mediated by a shift of the interventricular septum, which could not occur in our setting because the right ventricle was collapsed due to the right heart bypass. In fact, our diastolic data indicated no differences in response to the three interventions. We found that the increase in left ventricular end-diastolic volume during negative pressure was small relative to the change in transmural left ventricular end-diastolic pressure. This is because the right ventricle was working on the steep portion of its diastolic pressure-volume relation. This was probably caused by the effects of reflex blockade after which, to maintain acceptable levels of blood pressure, very high vascular volumes and, consequently, filling

<table>
<thead>
<tr>
<th>Dog</th>
<th>$P_{\text{sv}}$</th>
<th>PVR</th>
<th>$Z_1$</th>
<th>$Z_c$</th>
<th>$P_{B/P_f}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>I</td>
<td>C</td>
<td>I</td>
<td>C</td>
<td>I</td>
</tr>
<tr>
<td>Low intrathoracic pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>98.0</td>
<td>99.4</td>
<td>1917</td>
<td>1941</td>
<td>207</td>
</tr>
<tr>
<td>2</td>
<td>71.5</td>
<td>82.6</td>
<td>1273</td>
<td>1470</td>
<td>162</td>
</tr>
<tr>
<td>3</td>
<td>92.5</td>
<td>94.2</td>
<td>1706</td>
<td>1737</td>
<td>156</td>
</tr>
</tbody>
</table>
| 4   | 77.0          | 89.9 | 1745  | 2037  | 120         | 87    | 243   | 188   | ...   | ...
| 5   | 99.4          | 115.3 | 2539  | 2946  | 120         | 134   | 117   | 120   | 0.59  | 0.60  |
| 6   | 98.1          | 105.5 | 2274  | 2446  | 133         | 127   | 156   | 156   | 0.62  | 0.56  |
| Mean* | 93.2         | 98.8 | 1904  | 2023.6 | 143.9       | 134.6 | 195.3 | 170.8 | 0.54  | 0.55  |
| $p$ (C-I) | <0.03 | <0.03 | NS | NS | NS |
| High intrathoracic pressure |
| 1   | 94.0          | 108.6 | 1836  | 2121  | 208         | 213   | 242   | 255   | 0.51  | 0.52  |
| 2   | 58.3          | 82.4 | 1038  | 1467  | 148         | 141   | 277   | 210   | 0.56  | 0.57  |
| 3   | 83.2          | 101.7 | 1536  | 1876  | 122         | 67    | 99    | 37    | 0.57  | 0.72  |
| 4   | 90.2          | 104.6 | 2724  | 3129  | 152         | 163   | 148   | 180   | ...   | ...
| 5   | 90.1          | 96.4 | 2302  | 2463  | 139         | 155   | 97    | 107   | 0.62  | 0.63  |
| 6   | 89.8          | 99.4 | 2082  | 2304  | 323         | 58    | 146   | 57    | 0.60  | 0.71  |
| Mean* | 89.5         | 100.5 | 1944  | 2178.1 | 147.3       | 135.3 | 160.5 | 140.6 | 0.57  | 0.63  |
| $p$ (C-I) | <0.03 | <0.03 | NS | NS | NS |
| Partial aortic occlusion |
| 1   | 66.6          | 114.6 | 1303  | 2241  | 236         | 367   | 256   | 227   | 0.45  | 0.55  |
| 2   | 52.6          | 71.2 | 892   | 1207  | 170         | 178   | 288   | 185   | 0.54  | 0.48  |
| 3   | 85.1          | 119.9 | 1569  | 2211  | 125         | 294   | 109   | 121   | 0.54  | 0.74  |
| 4   | 71.7          | 97.7 | 2166  | 2798  | 143         | 227   | 189   | 141   | ...   | ...
| 5   | 92.6          | 106.4 | 2010  | 2305  | 133         | 171   | 111   | 121   | 0.64  | 0.64  |
| 6   | 88.5          | 119.8 | 2052  | 2777  | 134         | 325   | 142   | 167   | 0.63  | 0.79  |
| Mean* | 79.9         | 112.6* | 1706  | 2415  | 138.1       | 259.3 | 179.3 | 157.8 | 0.57  | 0.64  |
| $p$ (C-I) | <0.03 | <0.03 | <0.03 | NS | NS |
| $p$ (F-test) | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 |

*Mean values listed are bisquare weighted averages.

**Table 3.** Aortic Impedance Response to Two Levels of Negative Intrathoracic Pressure and to Aortic Occlusion

$P_{\text{sv}}$, mean aortic transmural pressure (mm Hg); PVR, peripheral vascular resistance (dyne-sec/cm$^5$); $Z_1$, modulus of first harmonic of impedance (dyne-sec/cm$^5$); $Z_c$, characteristic impedance (dyne-sec/cm$^2$); $P_{B/P_f}$, ratio of backward to forward component of pressure wave.

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volumes of the LV had to be maintained by increasing the pump speed.

In summary, this study demonstrates that the left ventricular response to the relatively pure afterloading effects of steady-state negative intrathoracic pressure (achieved by vagotomy, ganglionic blockade, pericardiectomy, and right heart bypass) is similar to that of partial aortic constriction. In both cases, calculated hydraulic load increases as do both end-diastolic and end-systolic left ventricular volumes. Because of our highly controlled conditions and our very accurate volume estimations, we think that this is the first unequivocal in situ demonstration of this effect. While this load should be present any time negative pressure is imposed around the LV, the response in the intact circulation under physiological conditions could be modulated by the many other competing mechanisms.

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References


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M J Hausknecht, K P Brin, M L Weisfeldt, S Permutt and F C Yin

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