Immediate effect of expiratory loading on left ventricular stroke volume

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ABSTRACT While the steady-state effects of positive pleural pressure on the circulation have been extensively studied, less is known about the immediate effects of positive intrathoracic pressure on cardiac dynamics. Therefore, we performed electrocardiographically gated radionuclide ventriculography with a respiratory gating technique in nine healthy subjects during quiet breathing and during expiration against a 24 cm H2O expiratory threshold load. During expiration, respiratory loading caused an increase in stroke counts by 29.4% (p < .001) due to an increase in end-diastolic counts of 26.1% (p < .001). End-systolic counts also rose 18.8% (p < .05). The ejection fraction did not change significantly. These findings indicate that the increase in left ventricular stroke volume that occurs during the first 1 or 2 beats of a loaded expiration is due to an increase in left ventricular filling and not to augmentation of left ventricular ejection. This immediate increase in pulmonary venous return may reflect increased distensibility of the left ventricle due to decreased filling of the right ventricle. Circulation 75, No. 1, 139-145, 1987.

A SUDDEN INCREASE in pleural pressure such as occurs with coughing or a Valsalva maneuver causes an immediate increase in aortic pulse pressure, but the mechanism for this is not known.1 Although some animal studies have shown that left ventricular stroke volume transiently increases during positive pressure inflation of the lung,2-4 other animal and human studies have shown no increase in stroke volume during the early phase of a Valsalva maneuver1,5-7 in which pleural pressure is increased during an expiratory maneuver at constant lung volume. An increase in pulse pressure could reflect an increase in arterial impedance as well as an increase in stroke volume. We wanted to determine if stroke volume was, in fact, transiently increased during forced expiration, such as might occur during a cough, or with expiratory obstruction of the upper airway. In addition, a knowledge of the physiologic mechanism for changes in pulse pressure or stroke volume may lead to insights with respect to the use of diagnostic respiratory maneuvers in patients with abnormal hemodynamics. If stroke volume is increased, we wanted to determine whether this was due to an increase in end-diastolic volume or to an improvement in left ventricular ejection. In a previous study using techniques similar to those employed here, we had demonstrated that a sudden fall in pleural pressure with loaded inspiration caused a fall in stroke volume attributable to an increase in end-systolic volume, which we proposed was due to the negative pleural pressure impeding left ventricular ejection.3 Therefore, we postulated that the opposite would occur with a sudden elevation of pleural pressure; that is, the increased pleural pressure would increase stroke volume of the left ventricle by assisting ejection.

To determine the mechanism of this increase in pulse pressure with an expiratory increase in pleural pressure, we studied the effects of forced expiration against an expiratory threshold load on left ventricular hemodynamics. Specifically, we measured the immediate effects of expiratory loading on left ventricular stroke volume, end-diastolic volume, and end-systolic volume in nine normal subjects by radionuclide ventriculography gated for both the cardiac and respiratory cycles. Our results indicate that the increase in stroke volume accompanying a sudden expiratory elevation of pleural pressure is due to increased filling of the left ventricle.

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Supported in part by NIH grant Nos. CA32845, HL10342, and HL00914.

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Received July 9, 1985; revision accepted Sept. 25, 1986.
Methods

Population. Nine male volunteers from 18 to 38 years old were recruited from the community, interviewed, examined, and found to be free of pulmonary, cardiovascular, or other disease. The study protocol was approved by the Johns Hopkins Committee on Human Investigations and informed consent was obtained from each subject before the study began.

Expiratory threshold loading. An expiratory threshold load is a useful technique to increase pleural pressure since the subject does not have to be trained to match a target pressure on an oscilloscope or manometer. Figure 1 is a schema of the expiratory threshold loading system used in this study. The expiratory threshold valve consisted of a closed chamber with a weighted plunger. Each subject, breathing through a mouthpiece with the nose occluded, inspired through a low-resistance Otis-McKerrow valve. During expiration each subject had actively developed a positive mouth pressure of 24 cm H2O to lift the plunger and expire.

The characteristics of this threshold valve allowed us to maintain a nearly constant mouth pressure of 24 cm H2O during expiration, irrespective of expiratory flow rates or effort. Since pleural pressure at a constant transpulmonary pressure must change by the same amount as the mouth pressure, we inferred that pleural pressure during expiration was increased by approximately 24 cm H2O during the loading. Studies with esophageal balloons in two subjects showed that the changes in mouth pressure were reflected by changes in esophageal pressure within 4 cm H2O over a range of minute ventilation up to 30 liters/min.

Radionuclide ventriculography. The technique of gated radionuclide ventriculography used in this laboratory is described in detail elsewhere. Labeling of red blood cells in vivo was performed with 20 mCi of 99mTc pertechnetate injected after prior injection of nonradioactive stannous pyrophosphate. With the subject in the supine position, the gamma camera, which had a parallel-hole collimator (Technicare, Solon, OH), was positioned over the precordium and angled approximately 40 degrees in a left anterior oblique position to allow the best visual separation of the left and right ventricles as seen on a persistence scope monitor. A shielded reference sample of 99mTc was affixed to the collimator to normalize the studies for acquisition time and isotope decay. The data acquisition from the cardiac region was synchronized to each subject's electrocardiogram with a physiologic synchronizer (Brattle Instrument Co., Cambridge, MA) interfaced with the signals from the gamma camera to a dedicated minicomputer (Informatex, Norcross, GA). Depending on the heart rate, the cardiac cycle was divided into 60 to 85 msec-time segments and counts imaged during each of these time segments were stored as separate digital images in the computer. For each subject approximately 16 time-segmented digital images were obtained.

Previous studies have shown that gamma ray counts acquired from the left ventricle are proportional to left ventricular volume. The standard error of the regression for repeated studies in the same subject in our laboratory and others ranges from 5% to 6%. To study events occurring only during expiration, we used an additional gating process during expiratory threshold loading (figure 1). Mouth pressure was sensed by a pressure-sensitive switch (Asco, Florham Park, NJ) interfaced with the physiologic (electrocardiographic or ECG) synchronizer to gate the ECG signal to record cardiac events during expiration. Since it was the purpose of our study to examine the effects of a sudden elevation of pleural pressure on left ventricular function, we acquired data for only those beats in which systole (as judged by the R wave on the electrocardiogram) was initiated at peak positive mouth pressure. When the mouth pressure reached 24 cm H2O the gate opened (figure 2). The gate was closed when the mouth pressure fell slightly below this level. Data were acquired for complete cardiac cycles only if the R wave occurred when the expiratory pressure gate was open. Typically one or two cardiac cycle values were acquired during each expiration.

Protocol. The study was performed according to the following protocol.

Expiratory threshold load. Stage I. A 6 min baseline study was performed in all the subjects during quiet supine breathing with ECG gating only and the results were used as the control data. Pilot studies indicated that no change in left ventricular

FIGURE 1. Schematic diagram of the experimental apparatus for respiratory gating of radionuclide ventriculography during loaded breathing.
FIGURE 2. Recording of mouth pressure, respiratory gate, and the electrocardiogram (EKG). Only the data from cardiac cycles occurring during expiration were analyzed. In the first breath on the left side of the tracing, a cardiac cycle was not acquired for study, but one was acquired during the subsequent two breaths.

hemodynamics from inspiration to expiration could be observed with the radionuclide technique, and therefore, data from both phases were pooled for the control data.

State II: Each subject was instructed to breath through the threshold loader for 2 to 3 min to become accustomed to the system. After a short rest period, a 10 min radionuclide ventriculogram was acquired with ECG and expiratory gating with the subject breathing through the expiratory threshold load. During stage II, since the expiratory time comprised only about one-third of the total respiratory cycle, the effective data collection time was approximately 3 min, which has been found satisfactory for radionuclide ventriculography.

*Data processing.* Regions of interest (ROI) over the left ventricle were drawn (figure 3) separately for end-diastole (ROI 1)

FIGURE 3. Radionuclide cardiac image with superimposed ROIs. 1 = end-diastole; 2 = end-systole; 3 = background. In the upper left-hand corner is the reference sample for correction of accumulation time and isotope decay (region 4).
and end-systole (ROI 2) for both the stage I and stage II data acquisitions. Background (ROI 3) counts were taken from a region adjacent to the end-diastolic ROI. An ROI was also constructed for the reference sample (ROI 4). The ROIs were visually defined by an experienced observer. End-diastole was defined as the frame occurring immediately after the R wave. End-systole was defined as the frame with the minimum left ventricular counts after diastole.

For stage I the net end-diastolic counts (EDC) and net end-systolic counts (ESC) were calculated with stage I data as follows:

\[ EDC = ROI\ 1\ counts - ROI\ 3\ counts \times \frac{ROI\ 1\ pixels}{ROI\ 3\ pixels} \]

\[ ESC = ROI\ 2\ counts - ROI\ 3\ counts \times \frac{ROI\ 2\ pixels}{ROI\ 3\ pixels} \]

For stage II, EDC and ESC were calculated with the same formulas used for stage I, but results from stage II were normalized for acquisition time and isotope decay by multiplying by the factor: stage I ROI 4 counts/stage II ROI 4 counts.

Ejection fraction (EF) was calculated as follows:

\[ EF = \frac{EDC - ESC}{EDC} \]

Stroke counts (SC) were calculated as:

\[ SC = EDS - ESC \]

Statistical analysis. Results are expressed as absolute counts and percent of control. Normalized end-diastolic, end-systolic, and stroke counts and ejection fraction during loaded breathing (stage II) were compared with those during quiet breathing (stage I) with Student’s t test for paired variates. Statistical significance was inferred when p was less than .05.

Results

A representative time-activity curve for the control and loaded conditions is shown in figure 4. Loaded expiration caused an increase in stroke counts that was associated with an increase in both end-diastolic and end-systolic counts. End-diastolic counts, end-systolic counts, stroke counts, background counts, and ejection fraction obtained for stages I and II are listed in table 1. Results from stage II expressed as percent of control for each variable for each subject are listed in table 2 and their means are plotted in figure 5. In all the nine subjects, during loaded expiration end-diastolic counts increased significantly, with a mean increase of 26.1% (p < .001). End-systolic counts also rose in seven of nine subjects, but to a lesser extent, with a mean increase of 18.8% (p < .05). Stroke counts increased in every subject, with a mean increase of 29.4% (p < .001). Background counts rose in seven of nine subjects by a mean of 9.7% (p < .05). The ejection fraction did not change significantly.

There was no significant difference in the mean \( \pm SD \) heart rate during stage I and that during stage II (60 \( \pm \) 7 vs 61 \( \pm \) 6 beats/min, p = NS).

Discussion

It has long been recognized that an increase in pleural pressure leads to an immediate increase in aortic pressure and presumably stroke volume. Both animal and human studies have confirmed that positive pressure inflation of the lung may lead to an immediate increase in left ventricular stroke volume,\(^2\) but this has not previously been shown to occur in humans when pleural pressure is elevated during expiration.

This study shows that during the increase in pleural pressure that accompanies active expiration against an
expiratory threshold load there is an immediate increase in left ventricular stroke volume as assessed by respiratory gated radionuclide ventriculography. This increase in stroke volume is due to an increase in end-diastolic volume, as evidenced by the increase in left ventricular end-diastolic counts despite an increase in end-systolic counts.

In a previous study\(^6\) examining the effects of inspiratory threshold loading on left ventricular stroke volume, we found that the decrease in left ventricular stroke volume was due to an increase in end-systolic volume, which we attributed to an increase in left ventricular transmural pressure and wall stress. We therefore postulated that the mechanism of increase in stroke volume with a sudden increase in pleural pressure could be a decrease in left ventricular transmural pressure and wall stress leading to a decrease in left ventricular end-systolic volume. Our data do not support this hypothesis. End-systolic volume was actually increased during expiration against a load in seven of nine subjects. This suggests that the end-systolic wall stress was increased during expiration. Pleural pressure, although elevated, must have risen less than left ventricular pressure, resulting in a net elevation of transmural left ventricular pressure. An alternative explanation for the increase in end-systolic volume is that there is a decrease in left ventricular contractility during expiration. Such a decrease in contractility could be neurally mediated, but this seems unlikely in the absence of changes in heart rate. Although unlikely, it is possible that there were changes in coronary blood flow or acid-base balance that could have affected contractility.

Our data indicate that the increase in stroke volume was due to an increase in pulmonary venous return to the left ventricle during loaded expiration, causing the increase in end-diastolic volume. The increase in venous return to the left ventricle during expiration could reflect one of three mechanisms: (1) a change in pulmonary vascular capacitance during expiration, (2) an increase in the gradient for venous return from the systemic vessels during expiration, or (3) a sudden reduction in back pressure to pulmonary venous return.

Under certain conditions, expiration may be associated with a reduction in pulmonary vascular capacitance leading to increased pulmonary venous return. Although the pulmonary venous return may either increase or decrease during deflation of the lung, conditions associated with a predominant zone III lung tend to cause a decrease in pulmonary venous return during expiration, whereas the opposite is true in the zone II

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<th>ESC I</th>
<th>ESC II</th>
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EDC, ESC, and SC are background corrected. Stage II counts are normalized to the same acquisition time period as those from stage I.

I = control; II = loaded breathing; EDC = end-diastolic counts; ESC = end-systolic counts; SC = stroke counts; BKGC = background counts per pixel; EF = ejection fraction.

<table>
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<td>Stage II values for study variables (% of control)</td>
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lungs. It is conceivable that our subjects developed enough hyperinflation with the expiratory threshold load to have a predominance of zone II conditions in the lung. Expiration would therefore lead to a reduction in radial stress around the extra alveolar vessels and a net reduction of pulmonary blood volume. In addition, blood stored in the pulmonary artery in zone II segments would be released and allowed to return to the left heart. The significant increase in background counts suggests that pulmonary blood volume was not decreased. It is impossible, however, to come to conclusions about this, since lung gas volume was decreasing, which would lead to an increased concentration of pulmonary blood in the gamma camera ROI.

The second possible mechanism of the increase in left ventricular venous return is an increase in the gradient for venous return from the systemic vessels to the right heart being passed through the left heart. This increase in gradient could either result from a reduction in the right atrial pressure or from an increase in the pressure in the small peripheral veins, the mean circulatory pressure. Forced expiration against an expiratory threshold load is associated with an increase in jugular venous and right atrial pressure and thus would not be expected to increase the gradient for peripheral venous return. Moreover, since we measured only the first 1 or 2 beats after the onset of expiration, it is unlikely that a change in systemic venous return could be reflected so quickly in an increase in left ventricular end-diastolic volume.

A third explanation for our findings is that the sudden increase in left ventricular stroke volume is due to increased pulmonary venous return as a result of a reduction in left atrial pressure relative to pulmonary vascular pressure. This could be the result of ventricular interdependence. A sudden reduction of the filling of the right ventricle due to increased pleural pressure could lead to a decrease in left ventricular filling pressure. The mechanism by which this may occur is either a change in geometry of the left ventricle through a reorientation of the septal curvature, or a reduction in the pressure surrounding the left ventricle through a reduction in tension on the pericardium. This would lead to an increased gradient for pulmonary venous return and a consequent increase in left ventricular end-diastolic volume.

Ventricular interdependence may also account for the observed increase in end-systolic volume. If the increase in pleural pressure surrounding the heart were less than the decrease in pericardial pressure due to the decrease in right ventricular volume, it would be possible to have a net decrease in pressure on the surface of the ventricle. This decrease in cardiac surface pressure could lead to an increased transmural pressure and thus an increase in end-systolic volume. Maughan et al. have demonstrated that a decrease in right ventricular volume such as would occur with expiration against a load leads to an increase in end-systolic volume for the same transmural pressure across the left ventricle and pericardium. This mechanism, then, could account for the observed increase in left ventricular end-systolic volume.

Other investigators have studied the effects of a transient elevation of pleural pressure on cardiac dynamics using Valsalva maneuvers and positive pressure ventilation. Elevation of pleural pressure with positive pressure ventilation during inspiration has been associated with either a transient increase or a transient decrease in stroke volume. The present results are in concert with those of Jardin et al., who found with two-dimensional echocardiography that inspiration with a positive pressure ventilator was associated with an increase in left ventricular stroke volume accompanied by an increase in end-diastolic and end-systolic volume, which was attributed to the reduced filling of the right ventricle and interdependence between the ventricles. Scharf et al., using electromagnetic flowmeters, found in dogs that an increase in pleural pressure with positive pressure ventilation caused an initial fall in aortic flow, whereas a step change in pleural pressure with chest compression at constant lung volume caused a rise in aortic flow. They proposed that the predominant mechanism for the reduction in aortic flow was the reduced gradient for systemic venous return to the right heart delayed by the passage through the lungs.

In our previous study of inspiratory threshold loading, we found that the effect of pleural pressure on afterload predominated; in this study the effect of expiratory threshold loading was dominated by the effect of pleural pressure on preload. A possible explanation for this discrepancy is that the negative pleural pressures with inspiratory loading does not cause significant increases in systemic venous return because the vena cava collapses during inspiration when the right atrial pressure becomes subatmospheric. When the pleural pressure is increased, however, the venous return to the right heart is substantially reduced because of the small pressure gradient for venous return from the systemic veins. Inspiratory threshold loading would tend to increase afterload with little cyclical variation in venous return or right ventricle volume, whereas the opposite would be true for expiratory loading.
In summary, we have found that expiratory threshold loading causes an immediate increase in left ventricular stroke volume, accompanied by increases in both end-diastolic and end-systolic volumes, and thus does not appear to augment left ventricular ejection. The mechanism for this may be either decompression of the right ventricle (ventricular interdependence) due to the decreased gradient for venous return, a phase lag in return to the right heart that is delayed through the pulmonary circulation, or a reduction in pulmonary blood volume causing increased pulmonary venous return due to decreased pulmonary vascular capacitance during expiration.

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Circulation. 1987;75:139-145
doi: 10.1161/01.CIR.75.1.139
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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