The Effects of Airway Pressure on Cardiac Function in Intact Dogs and Man

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SUMMARY Ventilation with positive end-expiratory pressure (PEEP) is associated with reduced cardiac output, but the mechanisms involved are controversial. Possible explanations include increased intrathoracic pressure, reflex changes in myocardial inotropism, pulmonary vascular obstruction and abnormal ventricular interaction. Three types of conscious canine preparations were developed to examine simultaneously each of these factors during ventilation with PEEP. In addition, similar measurements were obtained in patients after cardiac surgical procedures and compared with the results of animal experiments. The primary cause of reduced cardiac output during PEEP appeared to be a diminished end-diastolic volume of the left ventricle, and this appeared to be the result of elevated intrathoracic pressure and increased impedance to blood flow through the lungs. Abnormal interventricular septal shifting and reflex autonomic alterations did not appear to be significant in the normal cardiovascular system. These data provide insight into the cardiac effects of PEEP and emphasize the importance of simultaneous quantification of biventricular performance when assessing cardiopulmonary function.

Until recently, most studies of cardiac function have focused primarily on physiologic events within the left ventricle. Measurements of intrathoracic pressures, dimensions and flows have increased the understanding of ventricular dynamics and have improved the care of patients with cardiac disease. However, factors external to the left ventricle significantly influence cardiac performance. For example, during mechanical ventilation, increased intrathoracic pressure may shift a portion of the circulating blood volume away from the chest, decreasing cardiac filling and reducing cardiac output. Other investigators, however, have observed increased right and left atrial filling pressures during ventilation with positive end-expiratory pressure (PEEP) and have hypothesized that depressed myocardial function may be significant. A circulating negative inotropic agent in the blood of dogs ventilated with PEEP has been reported. Alterations in ventricular geometry and septal shifting that could contribute to reduced cardiac output have also been noted. Because the pulmonary vasculature hemodynamically couples the right and left ventricles, alterations in the pulmonary circulation induced by airway pressure could change the functional characteristics of the ventricles in opposite directions and contribute to abnormal ventricular interaction.
The diverse results of previous studies may be related to differences in physiologic conditions or methods. To assess cardiac function in closed-chest subjects, simultaneous measurements of several intrathoracic and intracardiac pressures, ventricular dimensions, and blood flows are required. In the present studies, the effects of mechanical ventilation and PEEP on biventricular cardiac performance were evaluated in the closed-chest, chronically instrumented dog, a preparation that yields a maximum of high-quality physiologic data. Similar, but more limited, studies were performed in humans after cardiac surgical procedures. Using the most precise measurement techniques available, the physiologic effects of increasing airway pressure on biventricular function were examined, and a quantitative assessment of the relative importance of each of the pertinent factors outlined above was obtained.

Methods

Animal Preparations

The experimental preparations used in this study have been described in detail elsewhere. In group 1, 10 adult mongrel dogs (21–31 kg) were instrumented with pulse-transit ultrasonic dimension transducers to measure left ventricular minor- and major-axis diameters and equatorial wall thickness (fig. 1A). A silicone rubber tube (2.6 mm i.d., 4.9 mm o.d., Dow Corning) was implanted in the dorsal left atrium for catheterization of the left ventricle with a micromanometer. Silicone rubber balloon occluders were positioned around both venae cavae, and another silicone rubber tube was placed near the epicardial surface of the heart to permit passage of a micromanometer into the tip of the tube for measurement of pleural pressure. Multiple side holes in the tube allowed free communication from the lumen to the pleural space, while the tube protected the manometer from impact artifacts. In five dogs, Statham TTQ series electromagnetic flow probes were implanted on the ascending aorta.

In group 2, five dogs that weighed 20–25 kg were instrumented with minor-axis anteroposterior diameter and septal–left ventricular free wall diameter dimension transducers (fig. 1B). Aortic blood flow, major-axis diameter and septal–right ventricular free wall diameter were measured as well. Silicone rubber tubes were implanted in the left atrium and in the right ventricular outflow tract for passage of micromanometers into the left and right ventricles. Vena caval occluders were placed, and a pleural tube was positioned near the epicardial surface of the heart.

In group 3 (fig. 1D), pulmonary hemodynamic and vascular impedance data were obtained in nine conscious dogs that weighed 20–28 kg. Each dog was instrumented with an electromagnetic flow probe on the pulmonary artery, a left atrial pressure catheter, a right ventricular silicone rubber introducer, and a pleural introducer catheter. In all animal studies, the pericardium was left open, and bipolar pacing electrodes were sutured to the right atrial appendage.

At the end of each implantation, connectors and devices were either exteriorized dorsal to the incision

![Image](http://circ.ahajournals.org/)

**Figure 1** The experimental preparations. (A) In group 1, the orientation of the dimension transducers allowed the measurement of minor-axis diameter (1-1'), major-axis diameter (3-3'), and equatorial wall thickness (2) in the conscious dog. (B) In group 2, left ventricular minor-axis septal–free wall diameter, right ventricular septal–free wall diameter (4) and ascending aortic blood flow were measured as well. (C) In patient studies, left ventricular diameter and pressure were measured along with left atrial and pericardial pressure. (D) In group 3, pulmonary artery hemodynamics were measured with an electromagnetic flow probe and a micromanometer.
or implanted in a subcutaneous pouch, and the thora-
cotomies were repaired. Each dog received daily intra-
muscular injections of procaine penicillin G (6 × 10⁸
U) and dihydrostreptomycin (0.75 g) indefinitely after
surgery. The chest was aspirated daily through the
implanted pleural tube to prevent pleural effusion; ap-
propriate i.v. fluid or blood was administered for sev-
eral days postoperatively to maintain adequate fluid
balance and hematocrit.

Data Acquisition

Seven to 10 days after implantation, each dog was
studied in the conscious state. Morphine sulfate, 0.3
mg/kg, was administered intramuscularly 1 hour be-
fore study for sedation. Cardiac dimensions were mea-
sured with a custom-built sonomicrometer, which is a
third-generation device modified from the original de-
sign of Kemper and Franklin. Blood flow was mea-
sured with a Statham M4001 gated sine wave electro-

e
defects.

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mothers. All manometers were balanced, calibrated,
and zeroed to atmospheric pressure before each study.
To minimize drift, the manometers were prewarmed in
a 38°C water bath and electrically excited for 24 hours
before use.

Analog dimension, pressure and flow measurements
were recorded on FM tape during each study. Data
were obtained in the resting state in all studies and also
during three transient vena caval occlusions in groups
1 and 2. Diazepam (1 mg/kg) was given intravenously
during sedation. The dog was paralyzed with i.v. sucine
choline (2 mg/kg), intubated, and ventilated with a
Bennett MA-1 respirator. The tidal volume of the res-
pirator was set routinely at 650 ml, the respiratory rate
at 12 breaths/min, and the oxygen concentration at
30%. Pao₂ was measured during each procedure and
was greater than 90 mm Hg in every study. Intratra-
cheal airway pressure was measured with a fluid-filled
polyethylene catheter incorporated into the endotra-
cheal tube and connected to a Statham P23Db trans-
ducer. The end of the catheter was 1 cm beyond the tip
of the endotracheal tube. The manometer was zeroed
to atmospheric pressure and positioned at midchest
level. Each dog in group 1 or 2 was ventilated with 0,
5, 10, 15 and 20 cm H₂O of PEEP produced by a
standard valve on the expiratory circuit of the Bennett
MA-1 respirator. Group 3 dogs were ventilated with 0,
10, 20, and 30 cm H₂O of PEEP. Physiologic measure-
ments were recorded continuously, and 90 seconds
were allowed for equilibration after each change in the
PEEP setting. Experience with longer periods of
equilibration indicated that 90 seconds was enough to
achieve a steady state. Throughout each study, the
heart rate was maintained constant by paired electrical
stimulation of the implanted right atrial electrodes at
10 beats/min above the spontaneous rate using a

custom-designed programmable stimulator.

In three of the group 1 and two of the group 2
studies, 1500 ml of Normsol-R, pH 7.4, were infused
intravenously, and the expiratory airway pressure was
again increased incrementally as the data were record-
ed. Sufficient equilibration time was allowed after the
infusion so that the end-diastolic pressure of the left
ventricle at 0 cm H₂O expiratory airway pressure was
constant to within 2 mm Hg before and after the var-
iation in airway pressure.

Three of the group 2 dogs underwent the initial
PEEP experiment and were then given propranolol, 1
mg/kg, and 2.0 mg of atropine intravenously. After
attenuation of autonomic reflexes, the protocol was
repeated as data were recorded. Results were com-
pared with those before blockade. In three additional
studies, while the dog was being ventilated in the usual
fashion, a side arm on the inspiratory tube of the respi-
ator was opened suddenly to atmospheric pressure for
10 seconds, achieving steady-state conditions at a sta-
table airway pressure of 0 cm H₂O. The tube then was
submerged 15 cm below a column of water, producing
a step increase in airway pressure to 15 cm H₂O. Data
were analyzed dynamically during cardiovascular ad-
aptation to the higher airway pressure.

At the conclusion of each study, calibrations were
recorded on tape and measurements were made to en-
sure that significant drift had not occurred during the
procedure. For the experiments reported, pressure
calibrations changed by less than 0.5 mm Hg and di-

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mension calibrations by less than 0.05 mm. The dy-

namic characteristics of the pressure and dimension
systems used in these studies have been described.⁹

Flow probes were calibrated before and after each
implantation with a gravity-fed saline system. The calibra-
tion constants for each probe changed by less than 6%
from the mean value throughout these experiments.
The calibration curves of the probes were linear to
within 2%. After each dog was sacrificed, atrial, va-


cular and right ventricular tissues were trimmed from
the heart, and right and left ventricular masses were
measured individually.

Clinical Studies

Seven patients underwent median sternotomy for
coronary artery bypass grafting. All gave informed
consent for the procedure. Each had intractable angina
pectoris from multivessel coronary artery disease and
normal left ventricular function. The surgical proce-
dure was performed in the standard fashion, and just
before discontinuing cardiopulmonary bypass, hemi-
spheric ultrasonic dimension transducers,¹² 5 mm in
diameter, were sutured to the anterior and posterior
epicardial surfaces of the left ventricle (fig. 1C). Place-
ment of each transducer took about 1 minute. A Millar
PC-350 micromanometer was passed into the left ven-
tricle through a pursestring suture in the right superior pulmonary vein. The manometer had been prewarmed and calibrated and was periodically recalibrated to the left atrial pressure measurement. Left atrial pressure and pericardial pressure were obtained with fluid-filled catheters. The leads from the transducers and catheters exited the abdominal wall beside the chest tubes, and the operation was concluded in the usual fashion.

After stabilization of cardiopulmonary function, physiologic measurements were obtained in the intensive care unit 6–12 hours postoperatively. Left ventricular minor-axis diameter was measured with the dimension transducers directly coupled to a sonometer. Left ventricular pressure was measured with the micromanometer, and left atrial and pericardial pressures were obtained with Statham P23Db transducers connected to the implanted fluid-filled catheters. The patients were sedated with i.v. diazepam (0.2 mg/kg), and ventilated with a Bennett MA-1 respirator at 0, 5, 10, 15 and 20 cm H₂O PEEP. After recording 60 seconds of data at each PEEP setting on FM tape, the expiratory airway pressure was released suddenly to 0 cm H₂O. At no point during the procedure did a patient have a systolic blood pressure of less than 90 mm Hg, and no untoward effects were noted. Eighteen to 24 hours postoperatively, after one chest tube was removed, the transducers, catheters and micromanometer were extracted from the heart by applying gentle tension to the bioelectric cables as they exited the chest tube track. There were no complications as a result of this procedure.

Data Analysis

Recorded data were directly digitized from analog tape at 5-msec intervals using an ADAC 1012/1016 A/D conversion system coupled to a PDP 11/23 microprocessor. All data during mechanical ventilation were taken from the end of the expiratory pause when the airway pressure had reached a stable value. In group I, the geometry of the left ventricle was represented as a three-dimensional prolate spheroidal shell. The internal volume (V) of the shell was computed using the formula

\[ V = \frac{\pi}{6} (b - 2h)^2 (a - 1.1h), \]

where \( b \) = the external anteroposterior minor-axis diameter, \( h \) = the equatorial wall thickness, and \( a \) = the external major-axis diameter. Stroke volume was calculated as the change in internal shell volume during ejection. Aortic blood flow was computed as the negative rate of change of calculated left ventricular volume during ejection using a third-order orthogonal polynomial approximation. Cardiac output and end-diastolic volume were normalized to the body surface area (BSA) with the equation

\[ \text{BSA (m}^2) = \sqrt{\text{weight, kg}}. \]

The transmural pressure of the left ventricle was computed as the difference between intracavitary pressure and intrapleural pressure. Dynamic left ventricular mass was calculated from the dimension measurement as the computed ellipsoidal shell volume \( \times 1.06 \text{ g/cm}^3 \) (myocardial density).³

In group 2 dogs, dynamic left ventricular internal volume was calculated by subtracting myocardial volume (measured left ventricular mass/1.06 g/cm³) from the external shell volume computed with the equation for a general ellipsoid:

\[ V = (\frac{\pi}{6}) a b c, \]

where \( c \) is the minor-axis septal–left ventricular free wall diameter. The diastolic relationship between \( b \) and \( c \) was determined in the control state over the entire range of ventricular volumes during a transient vena caval occlusion. These data were fitted with a linear regression analysis and were assumed to represent the pure left ventricular relationship because right ventricular diastolic transmural pressure was close to zero throughout the vena caval occlusion. Deviation from this relationship represented septal shifting and ventricular interaction. Again, right and left ventricular transmural pressures were calculated digitally, and transseptal pressure was computed as left ventricular minus right ventricular pressure.

In group 3, pulmonary artery diastolic flow was assumed to be zero. Systolic and diastolic intervals were defined by inspection of the digital data. Computations of pulmonary input impedance and hydraulic power indexes were performed by Fourier analysis of the transmural pulmonary artery pressure and pulmonary artery flow wave forms. Details of the data processing have been described.¹³ Ten to 20 cardiac cycles were analyzed at each level of PEEP. Standard hemodynamic indexes were generated, as was a spectrum of data regarding phasic pulmonary pressure and flow. Mean impedance was defined as the ratio of the zero harmonic pressure and flow moduli and is analogous to pulmonary vascular resistance, excluding left atrial pressure contributions. Characteristic impedance \( Z(0) \) was defined as the average impedance modulus between 7 and 11 Hz. Pulmonary artery input power was calculated as described by Milnor and associates⁴ and expressed in mean, oscillatory and total terms. These data then were converted to units of work (ergs) and normalized for total pulmonary flow.

Results

After sedation and intubation in group I, the paced heart rate averaged 131.8 ± 5.4 beats/min. The average calculated left ventricular mass, 98.3 ± 7.4 g, was not statistically different from the measured left ventricular mass, 96.6 ± 5.3 g (\( p > 0.5 \)), reflecting the accurate placement of the dimension transducers. The calculated mass of the left ventricle varied by an average of 3% from the mean throughout the cardiac cycle (range 1–5%), demonstrating the mutual consistency of the geometric measurements.

Analog data obtained from a sedated closed-chest group 1 dog during mechanical ventilation at an expiratory airway pressure of 0 cm H₂O are illustrated in figure 2A. During mechanical inflation of the lungs, airway pressure and intrapleural pressure increased.
Accompanying the dynamic inspiratory increase in airway pressure were rapid increases in end-diastolic volume, end-diastolic transmural pressure and stroke volume. During the initial phase of expiration when airway pressure was beginning to decrease, end-diastolic pressure, end-diastolic volume, and stroke volume decreased rapidly, usually reaching a minimum before airway pressure returned to 0 cm H₂O. Changes in intrapleural pressure generally paralleled variations in airway pressure, although the total excursion in pleural pressure was considerably less. During end-expiration, airway pressure was stable at 0 cm H₂O, and the physiologic measurements changed very little.

As expiratory airway pressure was increased by 5-cm H₂O increments from 0 to 20 cm H₂O (fig. 2B), both end-diastolic diameters progressively decreased and the wall thickened. Further changes associated with increasing airway pressure included a decrease in stroke shortening, a decrease in peak systolic left ventricular pressure, an increase in intrapleural pressure, and a decrease in the end-diastolic transmural pressure of the left ventricle. After return of expiratory airway pressure to 0 cm H₂O, the physiologic measurements rapidly reverted to control values.

The relationship in the group 1 dogs between expiratory airway pressure and cardiac index is illustrated in figure 3. After each 5-cm increment in expiratory airway pressure, the cardiac index decreased progressively (fig. 3A). The decrease in cardiac index was parallel to the decrease in end-diastolic volume, slope of the regression line, y = 0.066x + 2.73, r = -0.99, SEE = 0.07. The decrease in stroke volume was less (fig. 3B), the slope of the regression line, y = -1.01x + 55.05, r = -0.99, SEE = 1.08.

Figure 2. (A) Analog measurements of left ventricular dimensions and pressures during mechanical ventilation of the unanesthetized dog. The transmural pressure of the left ventricle was obtained by analog subtraction of the pleural pressure from the left ventricular pressure. (B) Effects of steady-state increases in expiratory airway pressure on left ventricular dimensions and pressures in the unanesthetized dog. Calibrations are the same as those in panel A.
way pressure, there was a statistically significant fall in cardiac index, averaging \(-0.33\) l/min/m\(^2\)/5 cm H\(_2\)O airway pressure. The relationship appeared to be an inverse linear one over the range of values tested \((r = -0.99)\). Figure 3 also shows the relationship of the end-diastolic volume index calculated in the 10 dogs to the expiratory airway pressure. There was a similar inverse linear relationship between these variables \((r = -0.99)\), with end-diastolic volume decreasing 5.05 ml/m\(^2\) for each 5-cm increment in airway pressure. Individual values are presented in table 1.

The effects of increasing expiratory airway pressure on left ventricular intracavitary end-diastolic pressure, intrapleural pressure and transmural end-diastolic pressure are shown in figure 4. Increasing airway pressure had no significant effect on intracavitary left ventricular pressure. However, for each 5-cm H\(_2\)O increment in airway pressure, there was a statistically significant increase in intrapleural pressure, averaging 1.1 mm Hg/5 cm H\(_2\)O airway pressure. When changes in intrathoracic pressure were taken into consideration by calculating transmural pressure of the left ventricle, there was a significant fall in end-diastolic transmural pressure with each increment in airway pressure, consistent with the observed decline in end-diastolic volume (table 1).

Left ventricular peak systolic transmural pressure and peak aortic flow velocity measured at the five levels of expiratory airway pressure are represented in table 1. Peak systolic left ventricular pressure and aortic blood flow decreased progressively as airway pressure was increased. The changes were statistically significant at the three highest levels of airway pressure.

A comparison of cardiac index and end-diastolic volume index for the 10 group 1 studies is illustrated in figure 5 as expiratory airway pressure was increased progressively from 0 to 20 cm H\(_2\)O. With this technique, the relationship between the end-diastolic volume index of the left ventricle and the cardiac index appeared to be linear over the range of values evaluated \((r = 0.99)\).

Data obtained in a volume infusion study are shown in figure 6. During the control experiment, the typical linear decrease in end-diastolic transmural pressure and volume of the left ventricle were noted with in-

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**TABLE 1. Left Ventricular Pressure and Dimension Data During Ventilation with Positive End-expiratory Pressure**

<table>
<thead>
<tr>
<th>Airway pressure (cm H(_2)O)</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastolic volume index (ml/m(^2))</td>
<td>54.12 ± 1.85</td>
<td>51.07 ± 1.46*</td>
<td>45.67 ± 1.94*</td>
<td>38.93 ± 1.46*</td>
<td>34.94 ± 2.01*</td>
</tr>
<tr>
<td>Cardiac index (l/min/m(^2))</td>
<td>2.67 ± 0.17</td>
<td>2.49 ± 0.15*</td>
<td>2.08 ± 0.11*</td>
<td>1.69 ± 0.08*</td>
<td>1.42 ± 0.06*</td>
</tr>
<tr>
<td>Transmural LV end-diastolic pressure (mm Hg)</td>
<td>8.61 ± 0.59</td>
<td>7.75 ± 0.59*</td>
<td>6.83 ± 0.65*</td>
<td>5.90 ± 0.81*</td>
<td>5.66 ± 0.51</td>
</tr>
<tr>
<td>Intracavitary LV end-diastolic pressure (mm Hg)</td>
<td>6.32 ± 0.55</td>
<td>6.37 ± 0.55</td>
<td>6.96 ± 0.70</td>
<td>6.71 ± 0.89</td>
<td>7.55 ± 0.67</td>
</tr>
<tr>
<td>Intrapleural pressure (mm Hg)</td>
<td>-2.41 ± 0.33</td>
<td>-1.38 ± 0.33*</td>
<td>0.13 ± 0.47*</td>
<td>0.81 ± 0.50*</td>
<td>1.89 ± 0.52*</td>
</tr>
<tr>
<td>Transmural LV peak systolic pressure (mm Hg)</td>
<td>130.7 ± 5.3</td>
<td>128.6 ± 5.7</td>
<td>122.4 ± 5.7*</td>
<td>111.9 ± 5.9*</td>
<td>102.0 ± 7.7*</td>
</tr>
<tr>
<td>Peak aortic blood flow (ml/sec)</td>
<td>229.4 ± 11.1</td>
<td>218.0 ± 9.3*</td>
<td>194.3 ± 7.0*</td>
<td>160.4 ± 6.1*</td>
<td>126.5 ± 10.1*</td>
</tr>
</tbody>
</table>

Data are mean ± SEM of observations in 10 studies.
*\(p < 0.05\) from the previous level using a paired t test.
Abbreviation: LV = left ventricular.
increasing airway pressure. After infusion, a similar decrease in end-diastolic pressure and volume occurred, but both curves were shifted upward as compared with control. Thus, the effects of airway pressure on end-diastolic pressure and volume could be counteracted by increasing the intravascular blood volume. When cardiac index was compared with end-diastolic volume index, the ventricle appeared to be operating on the same linear relationship throughout the experiment. Likewise, when end-diastolic transmural pressure was plotted vs end-diastolic volume index, the control and infusion values seemed to fall on the same exponential relationship. These findings were consistent in each of the five volume infusion studies.

The typical results of a PEEP experiment performed in a multidimensional preparation are illustrated in figure 7. As expiratory airway pressure was increased incrementally from 0 to 15 cm H2O, both the anteroposterior and septal–free wall minor-axis diameters progressively decreased, while there was a slight fall in the major-axis diameter. Left ventricular intracavitary and intrapleural pressure changed in an identical fashion to the group 1 experiments. The data in figure 7 are from a dog with autonomic blockade. In general, no appreciable difference was noted between the blocked and paced-unblocked experiments. Peak systolic transmural right ventricular pressure increased slightly with each change in expiratory airway pressure, and right ventricular septal–free wall diameter stayed relatively constant.

To better understand the dynamics involved, we performed another experiment (fig. 8). While the dog was ventilated in the standard fashion, the side arm from the inspiratory hose of the ventilator was opened to atmospheric pressure. This lowered airway pressure to 0 cm H2O and pleural pressure became constant at −2 mm Hg. After 10 seconds were allowed to achieve a steady state, the side arm was immersed 15 cm below a column of water, producing a sudden increase in airway pressure to a stable value of 15 cm H2O. Pleural pressure increased and right ventricular septal–free wall diameter initially decreased. The anteroposterior and septal–free wall minor-axis diameters also decreased initially. Over the next three beats, the right ventricular septal–free wall end-diastolic diameter returned almost to the control value, but the anteropos-
Figure 7. Left and right ventricular pressure, dimension and flow measurements during mechanical ventilation with increasing positive end-expiratory pressure from 0 cm H2O (left panel) to 15 cm H2O (right panel). This group 2 dog had undergone autonomic blockade. See text for experimental details.

terior and septal-free wall minor-axis diameters continued to decrease until they reached a steady state.

Figure 9 illustrates the time course of dimensional changes. Beats 1 and 2 are control beats, 3 and 4 the initial beats after the step increase in airway pressure, and the subsequent beats represent equilibration to a new steady state. The left and right ventricular septal-

Figure 8. Effects of suddenly increasing steady-state airway pressure from 0 to 15 cm H2O on biventricular pressures, dimensions and aortic blood flow in a group 2 dog. The time scale is one large box or 5 mm/sec.
free wall diameters are represented as distance from the intervening ventricular septum. With the initial sudden increase in pleural pressure, all chamber dimensions suddenly declined. However after three or four beats, right ventricular end-diastolic diameter gradually returned toward control while left ventricular dimensions continued to fall. A new steady state was achieved within 4–5 seconds, and release of the airway pressure back to 0 cm H₂O resulted in a rapid return of dimensions to control values (fig. 8).

The relative changes occurring in the two minor diameters during this experiment compared with vena caval occlusion data are shown in figure 10. In general, PEEP data were located below the vena caval occlusion curve, reflecting minor degrees of ventricular interaction. However, with increasing airway pressure, the relationship changed in a parallel fashion to the vena caval occlusion, indicating no greater septal shifting or ventricular interaction with increasing levels of PEEP. Thus, when the magnitude of septal shifting is assessed, changes in the septal–free wall diameter must be evaluated relative to changes in other cardiac dimensions.

The results of a typical clinical study are depicted in figure 11. As airway pressure was incrementally changed from 0 to 20 cm H₂O, the anteroposterior minor-axis diameter progressively decreased, a finding similar to that shown in figure 2. Pericardial pressure progressively increased with each increment in airway pressure. Although mean intracavitary left atrial pressure increased considerably with progressive levels of PEEP, the transmural end-diastolic left atrial pressure (which correlated well with transmural end-diastolic left ventricular pressure) progressively fell as airway pressure increased. Despite the more limited measurements in the human subjects, the results were virtually identical to those observed in the dog.

As expiratory airway pressure was increased in the group 3 studies, cardiac output fell significantly (table 2). Although peak pulmonary artery pressure only increased modestly, the mean pulmonary artery pressure changed significantly, from 14.6 ± 1.4 mm Hg in the control state to 28.7 ± 0.8 mm Hg with 30 cm H₂O of PEEP. Accompanying these hemodynamic alterations was a sixfold increase in pulmonary vascular resistance. Pulmonary vascular impedance data are illustrated in figure 12. As airway pressure was increased, mean impedance rose from 645 dyn·sec·cm⁻⁵ with 0 cm H₂O airway pressure to 3009 dyn·sec·cm⁻⁵ at 30 cm H₂O of PEEP, consistent with the changes in pulmonary vascular resistance. However, the characteristic impedance was not altered significantly (table 2). As airway pressure increased, the total work of the right ventricle increased by 30%, and there was a redistribution of work toward the mean term as oscillation about the mean diminished.

**Discussion**

Theories concerning the functional interactions of the heart and lungs can be traced to antiquity. ¹⁵⁻¹⁷ Many of the great physiologists of the nineteenth and twentieth
FIGURE 11. Postoperative left ventricular pressure and dimension data from a patient with normal left ventricular function. Positive end-expiratory pressure was increased from 0 to 20 cm H2O as shown at the top of each panel.

centuries have made significant contributions to this subject,18-25 and there is a large body of knowledge about cardiopulmonary interactions. Over the past 2 decades, considerable effort has been expended to understand the mechanism of decreased cardiac output during ventilation with PEEP. Hypotheses include increased intrathoracic pressure with shifting of the capacitance blood volume toward the systemic venous system,1,2 increasing pulmonary vascular resistance,25 reflex depression of myocardial inotropism,3,4 and abnormal ventricular interaction with shifting of the septum into the left ventricle.5,6 In the group 1 experiments, the steady-state increases in airway pressure decreased the end-diastolic volume of the left ventricle, which seemed to be the primary factor accounting for diminished stroke volume. However, significant questions remained at the conclusion of this study: Was the mechanism of diminished left ventricular diastolic volume related more to increased intrathoracic pressure or to increased impedance to blood flow through the lungs? If changes in ventricular interaction occurred during the PEEP experiment, the prolate spheroid model would not be valid and might yield erroneous results. What were the functional effects of PEEP on the right ventricle?

In the group 2 experiments, increasing expiratory airway pressure resulted in a proportional fall in the anteroposterior and septal–free wall diameters of the left ventricle (figs. 7–10). In all studies, the changes in the two minor-axis diameters during PEEP were parallel to those observed during a vena caval occlusion, suggesting that ventricular interaction, although present in a small degree, did not change significantly during the PEEP experiment (fig. 10). Thus, the prolate spheroid model and the results of the group 1 experiments appear to be valid. The right ventricular septal–free wall diameter remained relatively constant as the airway pressure was increased. To more fully understand these observations, the experiment illustrated in figure 8 was performed. After a 15-cm H2O steady-state increase in airway pressure, right ventricular diameter rapidly decreased, and both left ventricular minor-axis diameters began to fall. Three beats after the increase in airway pressure, right ventricular diameter began to increase gradually toward control levels, while both minor left ventricular diameters continued to decrease. Within 10 beats, a new steady state was achieved. We hypothesized that the initial fall in all cardiac diameters was related primarily to the uniform effects of intrathoracic pressure on ventricular dimensions (fig. 9). Subsequent increases in right ventricular septal–free wall diameter probably were related to the influence of increasing pulmonary vascular resistance on right ventricular afterload, which further

FIGURE 12. Mean (±SEM) pulmonary vascular impedance data from nine sedated group 3 dogs as positive end-expiratory pressure (PEEP) was increased from 0 to 30 cm H2O. Mean impedance increased significantly with each increment in airway pressure whereas characteristic impedance was not altered appreciably.
diminished blood flow through the lungs and decreased left ventricular end-diastolic dimensions. If so, increased intrathoracic pressure accounted for approximately half of the decline in left ventricular end-diastolic volume (fig. 9) and increasing pulmonary vascular resistance accounted for the other half. Because the decreasing venous return to the right ventricle and increasing pulmonary vascular resistance had opposite effects on right ventricular end-diastolic dimensions, there seemed to be only a minimal decrease in right ventricular end-diastolic diameter.

The data in figure 7 were obtained in an autonomically blocked preparation. Thus, the functional changes appeared to be primarily the result of the mechanical effects of airway pressure. In general, no differences were observed between results in intact and blocked preparations. The finding that dimensions returned quickly toward normal after release of PEEP in both group 1 and group 2 preparations also suggested that autonomically mediated reflex changes in myocardial inotropism did not play an important role. Furthermore, alterations in myocardial inotropism in unblocked dogs during PEEP did not appear to be significant, as the linear relationship between end-diastolic volume and stroke volume did not change. It might seem that inotropic influences should have increased heart rate and stroke volume at the higher airway pressures (as declining aortic pressure stimulated the carotid sinus reflex). However, when the dogs were not paced, a very minor slowing of the heart rate was noted at the higher airway pressures, possibly due to a Hering-Breuer type reflex. Thus, the net change in reflex autonomic tone during the PEEP study was probably minimal. Heart rate was controlled in these studies because of the profound influence of contraction frequency on end-diastolic volume and inotropic state.26 Potential differences in myocardial inotropism may have been further minimized by controlling the frequency of contraction. Finally, the demonstration that stroke volume can be returned toward normal by expanding total blood volume in the volume infusion experiments (fig. 6) and in the clinical studies of Jardin et al.6 strongly implicates reduced left ventricular preload as the primary factor causing low cardiac output during ventilation of the normal subject with PEEP.

Intrapleural pressure is difficult to measure. Because of gravitational gradients throughout the chest, esophageal or peripheral pleural pressure measurements may yield inaccurate data. Moreover, in our experience, balloon or fluid-filled catheters increase the magnitude of impact artifacts and baseline pressure shifts. For studies of cardiac physiology, pleural pressure must be measured on the surface of the heart and at approximately the same vertical level as the intracavitary manometer.9,10 Placing the pleural micromanometer within a large-bore silicone rubber tube protected the manometer from motion artifacts. The lumen of the tube freely communicated with the potential space of the pleural cavity via the multiple side holes. The accuracy of this technique was illustrated by the finding that subtracting pleural pressure from intracavitary left ventricular pressure virtually eliminated respiratory variation in the diastolic pressure-dimension relationship.10 Thus, using the pleural pressure on the surface of the heart as the external pressure, decreased transmural filling pressures of both ventricles were observed with PEEP in all animal preparations and in man. Therefore, the increased filling pressures reported previously must have been artifactual, possibly because of inaccurate pleural pressure measurements or the use of mean atrial pressure as the absolute index of ventricular filling. In addition, end-diastolic ventricular and atrial transmural pressures decreased more than mean atrial transmural pressure with increasing levels of PEEP because of diminished atrial contractile force and transport function (fig. 11).
Reliance on intracardiac pressure measurements in the closed-chest subject can be misleading, especially when intrathoracic pressure is changing (fig. 4). Acute or chronic alterations in intrapleural pressure, such as occur with changing patterns of spontaneous respiration or mechanical ventilation, shift all intrathoracic pressure measurements by a proportional degree. Thus, for accurate interpretation of intracavitary atrial, ventricular, aortic or pulmonary arterial pressure, the simultaneous measurement of external pressure and calculation of transmural pressure is required. Intrapleural pressure must be measured very close to the chamber under examination and at an equivalent vertical level because gravitational pressure gradients exist throughout the chest.

Undoubtedly, positive airway pressure increases pulmonary vascular resistance, but pulsatile pulmonary impedance data have not been available. The changes in mean pulmonary vascular impedance appeared to be large during PEEP, while the characteristic impedance was not altered significantly (fig. 12). This finding implies that airway pressure primarily reduced the cross-sectional area of the pulmonary arterioles and capillaries, consistent with the hypothesis of Whittenberger et al.25 Because characteristic impedance remained constant, the lumped properties of the larger pulmonary vessels did not seem to change. Therefore, the primary effect of airway pressure on the pulmonary circulation was to increase the mean pulmonary vascular resistance while the proportion of total right ventricular work due to oscillatory work was reduced (table 2).

In the absence of preload limitations, the right ventricle probably would gain efficiency during PEEP by increasing peak systolic pressure more and shifting significantly toward oscillatory blood flow and work. This would, in effect, take advantage of the relatively low input impedance to store right ventricular energy in the proximal pulmonary vasculature for subsequent use in diastole to overcome the Starling resistor effect of airway pressure. In fact, the opposite occurs, and the right ventricle functions more as a mean pump with each increment in PEEP. The diminished oscillatory work and inability to optimize the distribution of work between mean and oscillatory terms may reflect an imposed limitation on right ventricular end-diastolic volume despite a higher resistance to ejection. This preload limitation forces the right ventricle to perform a greater mean work, precisely the type that is maximally resisted by the mean impedance to pulmonary blood flow. Thus, the beneficial effects of volume loading on left ventricular preload may result partially from augmentation of right ventricular filling, which allows a more oscillatory pulmonary ejection and takes advantage of the lower energy requirements of this mode of function.

In conditions such as cor pulmonale or certain types of congenital heart disease in which varying degrees of right ventricular dysfunction may be present, ventilation with PEEP might further afterload the right ventricle and could precipitate acute cardiac decompensation. Moreover, in the intact dog, adjustments in the ventilatory pattern that increased the average airway pressure, such as increasing tidal volume, respiratory rate, or the inspiratory-expiratory flow ratio, had similar effects as PEEP in reducing transpulmonary blood flow. Cournand et al.1 made similar observations in 1948. Therefore, positive airway pressure should be minimized or avoided, if possible, in cases of right ventricular dysfunction.

In human studies, left ventricular end-diastolic diameter and transmural pressure progressively decreased when airway and pericardial pressures were elevated (fig. 11). Thus, the normal human left ventricle responded to PEEP in a manner similar to that of the dog. Although abnormal ventricular interaction did not appear to be significant in the present study of the normal cardiovascular system, the presence of chronic pulmonary vascular disease or volume overload might result in a more prominent septal shifting, as recently described.6 It would be important to better quantify the relative magnitude of septal shifting in future human studies in a manner similar to that in figure 10. However, in the normal heart, ventricular interaction plays a minor role compared with the increase in intrathoracic pressure and the afterloading effects of airway pressure on the right ventricle.

The shifting of the venous blood volume away from the left ventricle by positive expiratory airway pressure may help to explain the improvement in cardiorespiratory function with mechanical ventilation in patients with pulmonary edema. This intervention would lower the transmural pressure in the venous aspect of the pulmonary capillaries and would reduce the end-diastolic volume of the overloaded left ventricle. In this manner, airway pressure might be analogous to a selective phlebotomy of the pulmonary venous system. This same phenomenon would have detrimental effects on cardiorespiratory function in normovolemic patients who are ventilated with PEEP.

The relationship between end-diastolic volume and stroke volume was linear throughout the PEEP studies. This was a consistent finding over the entire physiologic range of values obtained in the intact dogs. Afterload was not controlled during the experiments, so it is difficult to make definite conclusions. However, the observation that the ventricle was operating at a higher position on the same linear relationship after volume infusion suggested that this was a fundamental property and not an artifact of the PEEP experiment. Most investigators have noted a curvilinear relationship between end-diastolic pressure and stroke volume, with stroke volume asymptotically approaching a maximum as end-diastolic pressure was increased. Others have inferred that this type of relationship also applies when end-diastolic volume is used as the index of filling. However, we suggest that the curved relationship between end-diastolic pressure and stroke volume actually reflects the exponential nature of the diastolic pressure-volume curve and that the relationship between diastolic fiber length and stroke shortening is really linear. However, the uncontrolled nature of the con...
scious preparation makes definitive statements difficult and further investigation of this finding under different experimental conditions is required.

In summary, the primary effect of PEEP on the normal heart is characterized by a simultaneously increased afterload and decreased preload of the right ventricle. As a result of diminished transpulmonary blood flow and probably because of direct pulmonary compressive effects, left ventricular end-diastolic volume becomes markedly reduced. This secondary reduction in left ventricular preload appears to be the major factor accounting for decreased systemic blood flow during ventilation of the normal subject with PEEP.

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