Paradoxical Rise in Left Ventricular Filling Pressure in the Dog during Positive End-Expansory Pressure Ventilation

A Reversed Bernheim Effect

JOHN R. DARSEE, J. RONALD MIKOLICH, PAUL F. WALTER, AND ROBERT C. SCHLANT

SUMMARY Controversy exists whether positive end-expiratory pressure (PEEP) ventilation lowers cardiac output by reducing left ventricular preload, or by a combination of mechanisms. Sixteen open-chest dogs were instrumented for measurement of left and right ventricular pressure, aortic flow, and left ventricular dimensions. With the pericardium intact, PEEP caused the interventricular septum to bulge toward the left ventricular chamber, increased right and left ventricular end-diastolic pressures, but decreased the average of the three left ventricular dimensions. When right ventricular filling pressure was suddenly reduced, the interventricular septum moved back toward the right ventricle, and left ventricular filling pressure fell. With the pericardium removed, PEEP was associated with a decrease in all three left ventricular end-diastolic dimensions but no significant change in left ventricular filling pressure. Although several indices of contractility were decreased during PEEP, all returned to baseline values when left ventricular preload was normalized during PEEP by a rapid infusion of heparinized blood into the left atrium. In conclusion, PEEP decreases preload and significantly alters the shape and compliance of the left ventricle with the pericardium intact. With the pericardium removed, PEEP produces proportional decreases in major and minor axis dimensions, does not appear to affect left ventricular contractility independent of preload, and alters left ventricular compliance to only a small degree. Circ Res 49:1017-1028, 1981

POSITIVE end-expiratory pressure (PEEP) ventilation is used in patients with a variety of respiratory syndromes to increase arterial oxygen tension when oxygen therapy alone is ineffective, or in patients who are at risk for oxygen toxicity as a result of prolonged treatment with a markedly elevated fractional inspired oxygen concentration (Kumar et al., 1970; Falke et al., 1972; Suter et al., 1975). Unfortunately, PEEP is often necessary in patients who are also hemodynamically unstable. Although PEEP is frequently effective in raising the arterial Po2, it may reduce the net transport of oxygen to the tissues (Suter et al., 1975) primarily by decreasing cardiac output (Tucker and Murray, 1972; Powers et al., 1973). Explanations for the decrease in cardiac output have included a decrease in preload (Cournand et al., 1948), subendocardial ischemia (Lozman et al., 1974), a humorally mediated decrease in contractility (Grindlinger et al., 1979), and a reflex depression of cardiac performance resulting from lung hyperinflation (Cassidy et al., 1978); however, there is no general agreement as to the cause.

Indeed, there are several questions regarding the hemodynamic effects of PEEP which have not been answered conclusively. First, it is unclear whether the decrease in cardiac output and stroke volume that occurs during PEEP is exclusively the result of a decrease in left ventricular preload, or a combination of the mechanisms previously mentioned. Second, since it is well known that changes in right ventricular pressure and shape may influence left ventricular pressure and shape, it would be important to determine the extent of this interrelationship during PEEP. Finally, since many studies of the hemodynamic effects of PEEP have utilized a model in which the pericardium was removed, or if present, had been incised and resutured, it would be important to know whether the effects of PEEP on left ventricular pressure and dimensions are the same or different with the pericardium intact as they are with the pericardium removed. The present study was undertaken to answer these questions in the open-chest intact canine model in which the effects of changes in intrathoracic pressure were decreased (although the pressure around the heart may not be precisely atmospheric even with the chest open) and the potential influence of external lung pressure on cardiac filling was minimized by separating the lungs from the heart.

Methods

Animal Preparation and Instrumentation

Sixteen mongrel dogs of either sex weighing 28-37 kg were anesthetized with thiamylal sodium (15

From the Cardiovascular Division, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts, and the Department of Medicine (Cardiology), Emory University School of Medicine, Atlanta, Georgia.

Address for reprints: John R. Darsee, M.D., Harvard Medical School, 180 Longwood Avenue, Room 236, Boston, Massachusetts 02115.

Received July 22, 1980; accepted for publication June 4, 1981.
mg/kg, iv) and morphine sulfate (3 mg/kg, sc), intubated, and passively ventilated with a Harvard respirator delivering room air with a tidal volume of 15 ml/kg at a rate of 12 breaths/min. Basal body temperature was maintained within ± 0.5°C with an external heat blanket. A left thoracotomy was performed in the 5th intercostal space; the lungs were gently retracted from the surface of the pericardium and thereafter restrained 1-2 cm from the heart by a nylon net which did not restrict the filling of the retracted lobes. A micromanometer-tipped pressure transducer (Millar Instruments) was placed into the left ventricle through a 2- to 3-mm slit in the pericardium and a stab wound in the apex. The pericardial slit was closed with 4-0 nylon suture. An identical pressure transducer was placed into the right ventricle through a small opening in the right ventricular wall that had been used to place an ultrasonic dimension crystal into the ventricular septum (as described below). For calibration of the two electronic pressure transducers, a fluid-filled polyvinyl catheter was placed into the aorta from the left carotid artery, and a triple-lumen, balloon-tipped, flow-directed thermodilution catheter (Edwards Laboratories) was placed into the right ventricle from the left jugular vein and then into the pulmonary artery in the “wedge” position. Each fluid-filled catheter was connected to a Statham model P23Db strain gauge positioned at the mid-chest level and referenced to atmospheric pressure and the thermodilution catheter was connected to a cardiac output computer (Edwards Laboratories). The electronic pressure transducer in the left ventricle was calibrated in vivo using pulsatile aortic pressure and pulmonary capillary wedge pressure signals recorded simultaneously through the fluid-filled catheters. The right ventricular pressure transducer was calibrated using the pressure signal obtained with the balloon-tipped catheter in the right ventricular chamber.

A circumferential electromagnetic cuff flowprobe (Carolina Medical Electronics) was placed snugly around the proximal aorta and energized with a Carolina Medical Electronics electromagnetic flowmeter. The electromagnetic flowprobe was calibrated in vivo from cardiac output values obtained simultaneously by thermodilution; values for stroke volume were obtained by dividing cardiac output by the heart rate, and zero flow was verified by briefly occluding the aorta distal to the flowprobe.

**Placement of Ultrasonic Crystals**

A total of three pairs of ultrasonic crystals were utilized to measure the dimensions of the left ventricular chamber. Two pairs of ultrasonic crystals were placed in the myocardium at the subendocardial level (7-8 mm below the epicardium) for measuring the anterior-to-posterior, and the septal-to-free wall dimensions of the left ventricle. The anterior crystal was positioned 12 to 18 mm lateral to the left anterior descending coronary artery and just below the first large diagonal branch. The posterior crystal was positioned approximately 180° around the circumference and the lateral crystal midway between them. To do this, the pericardium was left intact as much as possible. The pair of crystals used to measure the anterior-to-posterior dimension, and the crystal in the lateral left ventricular free wall were placed into the myocardium through small slits (5-7 mm in length) in the pericardium and anchored with 4-0 nylon suture so as to allow the pericardium to slip freely over the epicardium at the site of entry. The upper and lower ends of each pericardial slit were sutured to prevent further tearing of the pericardium; this left a 3- to 5-mm aperture at each of the crystal sites.

A fourth crystal was placed into the ventricular septum by the following method. The blood from the superior and inferior venae cavae (which were closed with a ligature next to their sites of entry into the right atrium) was diverted through large bore (12 mm internal diameter) Tygon tubing to a variable speed roller pump, from which it flowed through similar tubing which passed through the right atrial appendage, across the tricuspid valve, and into the pulmonary artery across the pulmonic valve. Thus, the venous blood bypassed the right ventricle completely. A small slit was made in the pericardium and through the anterior wall of the decompressed right ventricle. An ultrasonic crystal mounted on a coiled spring was turned into the ventricular septum 1-2 cm below the level of the tricuspid ring from the right ventricular aspect of the septum. As previously mentioned, a micromanometer-tipped pressure catheter was placed into the right ventricle through the slit, and the right ventricular wall was closed around it with 3-0 nylon suture. The end of the Tygon tubing was withdrawn from the pulmonary artery to the right atrial appendage, the roller pump was removed from the circuit, and blood was allowed to flow from the venae cavae through the tubing to the right atrium.

Two additional dimension crystals were sutured across the major axis of the heart, one at the endocardial level near the apical dimple (5-7 mm from the insertion site of the pressure transducer) and the other at the endocardial level at the base of the heart in the groove between the left sinus of Valsalva and the left atrium, immediately adjacent to the aortic ring (Fig. 1).

The ultrasonic crystals (Norland Instruments) were piezoelectric transducers, 3 mm in diameter and resonant in the 800 kHz radial mode. A transit-time dimension gauge (Norland Instruments, model N1-202) propagated a burst of ultrasound energy from the transmitting transducer to the receiving transducer. The instrument provided a direct measurement of the transit-time of each ultrasound burst, and generated a proportional analog voltage. The instantaneous distance between the trans-
Several hemodynamic variables were measured continuously throughout the experimental protocol. Left and right ventricular pressures were recorded and also electronically amplified for measurement of end-diastolic (LVEDP) and right (RVEDP) ventricular pressures, respectively. The rate of change of left ventricular pressure (dP/dt) was obtained by electronic differentiation using an operational amplifier connected as a differentiator and having a frequency response of 750 Hz. A triangular wave signal with known rate of change (slope) was substituted for the dimension (PEEP), 15 cm H₂O, for 10 minutes; measured pressures then were recorded at the faster paper speeds, and PEEP was discontinued. After the hemodynamic values had returned to baseline (5-7 minutes later), the experiment was repeated and the results of the two experiments were averaged.

**Effects of Changes in Right Ventricular Filling during PEEP**

After these experiments, the venae cavae then were connected to a fluid reservoir that flowed directly into the right atrium through an adjustable valve (Fig. 1). The height of the reservoir was adjusted at the beginning of the experiment to produce a right ventricular filling pressure that was the same as that obtained without the reservoir in place and without PEEP. Once all hemodynamic variables were stable for a 5-minute period, the dogs were again subjected to 15 cm H₂O PEEP for 10 minutes. Then, while PEEP was maintained, the valve on the right atrial reservoir was turned to produce an abrupt decrease in right ventricular filling pressure, and thus produce immediate tran-
septal pressure and geometry-related effects on the left ventricle. We have previously observed that transmural indocyanine green dye curves are normal for the first 5 beats after systemic venous return is abruptly lowered by clamping one vena cava (Darsee JR, Mikolich JR, unpublished data). Hence, any changes in left ventricular chamber pressure or shape occurring within the first 4 beats after right ventricular filling pressure was suddenly reduced were the result of transeptal effects and not due to a decrease in left ventricular filling volume as would eventually occur once the transit-time and capacitance of the pulmonary vascular bed were exceeded.

Effects of the Pericardium during PEEP

The previous experiments had been performed with the pericardium intact. To evaluate the influence of the pericardium upon cardiac dynamics during PEEP, we excised the pericardial sac widely, as far posteriorly and superiorly as possible, and the dogs were again subjected to PEEP for 10 minutes, after which hemodynamic variables were recorded at a faster paper speed (100 mm/sec) for comparison with pre-PEEP values.

Effects of PEEP on Contractility

A large-bore polyvinyl catheter then was placed into the left atrium for rapid infusions of heparinized blood in order to determine whether PEEP had an effect on several indices of contractility, independent of its assumed effects on preload. The dogs were subjected as a group to PEEP for 10 minutes, after which hemodynamic variables were recorded at a faster paper speed (100 mm/sec) for comparison with pre-PEEP values.

Construction of Starling Curves, End-Diastolic Length-Maximum Velocity Plots, and End-Diastolic Pressure-Length Curves

Starling Curves

Because of the possibility that the shape of the left ventricle might be altered during PEEP from that of an approximate prolate ellipsoid, we did not attempt to calculate the change in end-diastolic volume during PEEP, since the available formulas would not likely yield accurate values. Instead, the average of the three end-diastolic dimensions (septal to free wall, anterior to posterior, and apex to base) was used as an index of preload. Values for stroke volume were plotted against respective values for the average left ventricular end-diastolic dimension during a 500-ml hemorrhage and reinfusion with institution of PEEP briefly at multiple times during the hemorrhage and reinfusion. One curve was constructed using values obtained with the pericardium intact and a second using values obtained with the pericardium removed.

Relationship between End-Diastolic Length and Maximum Shortening Velocity

To determine whether any changes that might have occurred in the maximum velocity of shortening of the left ventricular septal-to-free wall dimension represented a change in contractility during PEEP or were primarily a result of altered end-diastolic length, values for maximum left ventricular shortening velocity were plotted against respective values for septal-to-free wall dimension using values obtained during hemorrhage and reinfusion with PEEP instituted briefly, as described previously.

End-Diastolic Pressure-Length Curves

To determine whether left ventricular diastolic compliance was altered during PEEP, values for the average left ventricular end-diastolic dimension (the two cross-sectional dimensions and the major axis dimension) were plotted against respective values for LVEDP using values obtained during hemorrhage and reinfusion with PEEP instituted briefly at several time periods.

Statistical Methods

For comparisons between baseline values and those obtained during PEEP alone, a paired t-test was used (Downie and Heath, 1974). To compare baseline values with those obtained during PEEP, and with values obtained when either right or left ventricular filling was altered externally, an analysis of variance for repeated measures was used (Winer, 1971). To compare the Starling curves, end-diastolic length-maximum velocity plots, and end-diastolic pressure-length curves obtained before PEEP with those obtained during PEEP, and for comparison with values obtained with the pericardium removed, curve fitting and correlation analysis were used (Downie and Heath, 1974). A one-sample t-test was used (α = 0.01) for comparisons between baseline values to allow for multiple comparisons.

Results

Of the 16 dogs entered into the study, all were successfully instrumented and completed all parts of the protocol. There were no significant differences in any of the baseline hemodynamic values among the 16 dogs, for any of the parts of the experimental protocol.

Location of Ultrasonic Crystals

The locations of the ultrasonic dimension crystals at postmortem examination were similar among the 16 dogs. All crystals were within 2 mm of the
TABLE 1  Hemodynamic Changes during PEEP

<table>
<thead>
<tr>
<th></th>
<th>Pericardium intact</th>
<th>Pericardium removed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>PEEP</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>27 ± 6</td>
<td>18 ± 7*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>106 ± 7</td>
<td>106 ± 10</td>
</tr>
<tr>
<td>RVSP (mm Hg)</td>
<td>26 ± 5</td>
<td>37 ± 9*</td>
</tr>
<tr>
<td>RVEDP (mm Hg)</td>
<td>3.8 ± 1.5</td>
<td>8.3 ± 3.5*</td>
</tr>
<tr>
<td>Δ RVEDP (mm Hg)</td>
<td>4.5 ± 1.8</td>
<td>—</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>126 ± 15</td>
<td>106 ± 9*</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>4.2 ± 2.3</td>
<td>7.2 ± 2.8*</td>
</tr>
<tr>
<td>Δ LVEDP (mm Hg)</td>
<td>3.0 ± 1.6</td>
<td>—</td>
</tr>
<tr>
<td>Septal-to-free wall LV dimension (mm)</td>
<td>31.2 ± 3.6</td>
<td>27.8 ± 2.6*</td>
</tr>
<tr>
<td>Anterior-to-posterior LV dimension (mm)</td>
<td>31.9 ± 4.0</td>
<td>32.2 ± 4.0†</td>
</tr>
<tr>
<td>Apex-to-base LV dimension (mm)</td>
<td>38.9 ± 5.6</td>
<td>34.7 ± 5.9*</td>
</tr>
</tbody>
</table>

* P < 0.01 compared to respective baseline.
† P < 0.05 compared to respective baseline. RVSP = right ventricular systolic pressure; RVEDP = right ventricular end-diastolic pressure; LVEDP = left ventricular end-diastolic pressure; LV = left ventricular; values shown are mean ± 1 SD.

endocardial surface of the left ventricle; thus the signals generated by them served as accurate indices of chamber dimensions. The crystal in the ventricular septum was within 5 mm of the center of the anterior-posterior length of the septum. That the two minor axis dimensions were approximately perpendicular to each other was verified by the observation that the angle between the two lines connecting opposing crystals was not more than 192° and not less than 168° at postmortem examination.

Effects of PEEP Alone

The effects of 15 cm H$_2$O PEEP on ventricular pressures and left ventricular dimensions with the pericardium intact are summarized in Table 1. PEEP was associated with a significant decrease in stroke volume, peak aortic flow, and left ventricular systolic pressure, and a significant increase in right ventricular systolic and end-diastolic pressures and left ventricular end-diastolic pressure but no change in heart rate (Fig. 2). There was also a significant decrease in the septal to free wall and apex to base left ventricular dimensions, but a significant increase in the anterior to posterior left ventricular dimension (Fig. 3).

Effects of Changes in Right Ventricular Filling during PEEP

With the flow of blood from the reservoir to the right atrium unimpeded, the hemodynamic effects of PEEP were not significantly different from those obtained when the reservoir was not a part of the circuit (Table 2). However, when the valve on the reservoir was turned to produce a sudden decrease in flow to the right atrium, there was an abrupt decrease in RVEDP from 8.5 ± 3.1 to 3.8 ± 1.2 mm Hg. The latter value was not significantly different from the baseline value (Table 2). The decrease in RVEDP was associated with a significant decrease in LVEDP (7.2 ± 3.1 to 4.4 ± 0.9 mm Hg; P < 0.01) and anterior to posterior left ventricular dimension (32.3 ± 3.9 to 29.5 ± 3.4 mm; P < 0.01), an increase in the septal to free wall dimension (27.6 ± 2.9 to 29.4 ± 3.1 mm; P < 0.05) (Fig. 4), but no significant change in stroke volume, heart rate, left ventricular systolic pressure, or the apex-to-base left ventricu-
Effects of the Pericardium during PEEP

Some of the changes that occurred during PEEP with the pericardium removed were different from those with the pericardium intact (Table 1). Although there were no significant differences in the PEEP-induced changes in stroke volume, heart rate, right and left ventricular systolic pressures, RVEDP, and apex-to-base left ventricular dimension, the changes in several other variables with PEEP were altered importantly by removing the pericardium (Fig. 5). Instead of increasing as it did with the pericardium intact, the LVEDP did not change significantly with PEEP with the pericardium removed (from 4.3 ± 2.0 to 4.0 ± 1.9 mm Hg; \( P = \text{NS} \)). Furthermore, both minor axis dimensions decreased significantly during PEEP, unlike the case with the pericardium intact in which the anterior-to-posterior dimension actually increased. That the decrease in all left ventricular dimensions was associated with no significant change in LVEDP suggests that left ventricular compliance was also affected to a small degree with the pericardium removed.

Effects of PEEP on Contractility

The administration of PEEP with the pericardium removed was associated with a significant decrease in peak left ventricular dP/dt (2680 ± 292 to 2235 ± 287 mm Hg/sec; \( P < 0.05 \)), the maximum velocity of septal to free wall shortening (66 ± 9 to 54 ± 7 mm/sec; \( P < 0.05 \)), and the velocity of circumferential fiber shortening (1.48 ± 0.19 to 1.21 ± 0.13 circ/sec; \( P < 0.05 \)) (Fig. 6; Table 3). However, since these indices are partially dependent on preload, several other indices were calculated which are either normalized for preload or essentially preload independent. There was no significant change in left ventricular dP/dt at a developed pressure of 40 mm Hg, in the percent systolic shortening of either minor axis dimension, or in the maximum velocity of shortening divided by the septal-to-free wall end-diastolic dimension (Table 3), suggesting that the changes in the indices of contractility mentioned previously were probably a result of changes in preload. This hypothesis was strengthened by the return to baseline of all contractile indices after

### Table 2: Effects of a Sudden Decrease in Right Ventricular Filling during PEEP (with Pericardium Intact)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>PEEP alone</th>
<th>PEEP with sudden reduction in RV filling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke volume (ml)</td>
<td>28 ± 6</td>
<td>17 ± 6*</td>
<td>17 ± 6*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>102 ± 9</td>
<td>103 ± 8</td>
<td>102 ± 8</td>
</tr>
<tr>
<td>RVSP (mm Hg)</td>
<td>28 ± 6</td>
<td>36 ± 9*</td>
<td>35 ± 5</td>
</tr>
<tr>
<td>RVEDP (mm Hg)</td>
<td>3.6 ± 1.4</td>
<td>8.5 ± 3.1*</td>
<td>3.8 ± 1.2</td>
</tr>
<tr>
<td>Δ RVEDP (mm Hg)</td>
<td>—</td>
<td>4.9 ± 1.3</td>
<td>0.2 ± 0.1</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>127 ± 14</td>
<td>104 ± 10*</td>
<td>106 ± 9*</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>4.7 ± 1.3</td>
<td>7.2 ± 3.1*</td>
<td>4.4 ± 0.9</td>
</tr>
<tr>
<td>Δ LVEDP (mm Hg)</td>
<td>—</td>
<td>2.5 ± 0.6</td>
<td>—2.3 ± 0.1</td>
</tr>
<tr>
<td>Septal-to-free wall LV dimension (mm)</td>
<td>31.3 ± 3.4</td>
<td>27.6 ± 2.9*</td>
<td>20.4 ± 3.1*</td>
</tr>
<tr>
<td>Anterior-to-posterior LV dimension (mm)</td>
<td>31.8 ± 3.9</td>
<td>32.3 ± 3.9*</td>
<td>29.5 ± 3.4*</td>
</tr>
</tbody>
</table>

* \( P < 0.01 \) compared to baseline
† \( P < 0.05 \) compared to baseline
‡ \( P < 0.05 \) compared to PEEP with normal right ventricular (RV) filling (analysis of variance for repeated measured; values in right hand column are average of the first four beats after the valve in the right atrial reservoir was turned to reduce RV filling; values shown are mean ± 1 SD. Abbreviations are the same as in Table 1.)
FIGURE 4 Effects of changes in right ventricular filling during PEEP. In the three righthand panels, the changes in pressures and dimensions during the first three beats after the valve on the right atrial reservoir was turned to the partially closed position are shown. With the first beat, there is no change from the steady state during PEEP. However, with the second and third beats, the end-diastolic septal-to-free wall dimension and the apex-to-base dimensions increase slightly while the anterior to posterior end-diastolic dimension decreases substantially. These dimensions, however, are all less than the baseline dimensions and primarily represent a change in left ventricular shape after RVEDP was suddenly decreased. Concomitant with these changes in dimensions are decreases in RVEDP and LVEDP by the second beat after the valve is turned.

the infusion of heparinized blood returned the end-diastolic minor axis dimensions to pre-PEEP values (Fig. 7; and Table 3).

Construction of Starling Curves

In each of the 16 dogs, values for average left ventricular end-diastolic dimension and stroke volume during a 500-ml hemorrhage and reinfusion were utilized to construct a standard Starling curve for each dog. The curves constructed with the pericardium removed were shifted slightly to the right from those with the pericardium intact but were not significantly different. As previously described, values for both variables were also obtained eight additional times during the period of hemorrhage when PEEP was instituted transiently for a 3-minute period. At each point along the Starling curve, the administration of PEEP produced values for stroke volume and average end-diastolic dimension that remained on or near the standard curve, but were always downward and to the left of their respective pre-PEEP values (Fig. 8). This was true both with the pericardium intact and with the pericardium removed. Thus, at any given end-diastolic dimension, PEEP reduced stroke volume and end-diastolic dimension along each dog's standard Starling curve, suggesting that PEEP decreases preload but not contractility, and that the pericardium did not alter the relationship substantially.

Relationship between End-Diastolic Length and Maximum Shortening Velocity

Values obtained during hemorrhage and reinfusion produced a curve for each dog which described the relationship between the maximum left ventricular shortening velocity and the septal-to-free wall left ventricular end-diastolic dimension at a variety
of end-diastolic dimensions. Commensurate values obtained during several 3-minute periods of PEEP also fell on the curve but downward and to the left of the pre-PEEP values (Fig. 9), both with the pericardium intact and with it removed, suggesting that the decrease in this ejection phase index of contractility during PEEP was the result of a change in preload.

**End-Diastolic Pressure-Length Curves**

The relationship between the average left ventricular end-diastolic dimension and LVEDP during hemorrhage and reinfusion established two diastolic compliance curves, one for the pericardium intact and one for the pericardium removed (Fig. 10). With the pericardium intact, the administration of PEEP was associated with values that were significantly displaced ($P < 0.01$ in each dog) from the basic curve in each dog, and were upward and to the left of pre-PEEP values. These observations suggested that, with the pericardium intact, PEEP was associated with a substantial change in left ventricular compliance. The basic diastolic pressure-dimension curve had a more gradual slope with the pericardium removed and did not become steep at greater end-diastolic dimensions as it did with the pericardium intact. Moreover, the administration of PEEP at a variety of end-diastolic dimensions resulted in values that were not significantly displaced from the basic curve, although individual values during PEEP were usually positioned above the basic curve (Fig. 10).

**Discussion**

The results of this study suggest that with the pericardium intact, PEEP is associated with a decrease in stroke volume and average left ventricular end-diastolic dimension supporting the hypothesis that PEEP reduces aortic flow by reducing left ventricular preload. In addition, the shape of the left ventricle appears to be altered substantially during PEEP: the apex-to-base dimension and the septal-to-free wall dimension decrease while the anterior-to-posterior dimension actually increases. Since these changes were accompanied by an increase in RVEDP and right ventricular systolic pressure, the movement of the interventricular septum toward the left ventricle and the rise in LVEDP during PEEP represent a reversed Bernheim effect; that is, the increase in right ventricular filling pressure caused an increase in left ventricular filling pressure, despite the apparent decrease in left ven-
tricular preload. This was confirmed by the observation that a sudden decrease in RVEDP produced by an abrupt reduction in venous return was associated with a decrease in LVEDP and movement of the septum toward the right ventricle prior to the time when the reduction in venous flow to the right heart would affect pulmonary venous return to the left heart. With the pericardium removed, there appeared to be less ventricular interdependence, since PEEP produced a reduction in all three left ventricular dimensions, and did not cause the septum to be pushed toward the left ventricle as much as with the pericardium intact. The observation that LVEDP did not decrease significantly during

![Diagram with labels: Aortic Pressure, LV Velocity, Septum to Free Wall LV Dimension, Anterior to Posterior LV Dimension, dP/dt, LVP, LVEDP, Graphs showing changes in pressures and velocities.]

**Figure 7** Effects of normalizing preload with a rapid infusion during PEEP. With the same decrease in contractile indices during PEEP as shown in Figure 6, a 30-second infusion of 100 ml of heparinized blood into the left atrium (beginning when LV dP/dt and LV velocity had reached a nadir) increased both LV end-diastolic dimensions, peak LV dP/dt, and LV velocity to pre-PEEP values.

**Table 3** Effects of PEEP on Isovolumetric and Ejection Phase Indices of Contractility (Pericardium Removed)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>PEEP alone</th>
<th>PEEP with left atrial infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak LV dP/dt (mm Hg/sec)</td>
<td>2680 ± 292</td>
<td>2235 ± 287*</td>
<td>2706 ± 304</td>
</tr>
<tr>
<td>LV dP/dt at D P&lt;sub&gt;0&lt;/sub&gt; (mm Hg/sec)</td>
<td>1922 ± 206</td>
<td>1886 ± 212</td>
<td>1911 ± 200</td>
</tr>
<tr>
<td>Maximum velocity of septal-to-free wall shortening (mm/sec)</td>
<td>66 ± 9</td>
<td>54 ± 7*</td>
<td>67 ± 8</td>
</tr>
<tr>
<td>Velocity of circumferential fiber shortening (circ/sec)</td>
<td>1.48 ± 0.19</td>
<td>1.21 ± 0.13*</td>
<td>1.50 ± 0.23</td>
</tr>
<tr>
<td>Percent shortening of septal-to-free wall dimension (%)</td>
<td>32.3 ± 4.6</td>
<td>31.9 ± 3.5</td>
<td>32.8 ± 4.4</td>
</tr>
<tr>
<td>Maximum velocity of shortening/septal-to-free wall end-diastolic dimension (sec&lt;sup&gt;−1&lt;/sup&gt;)</td>
<td>2.2 ± 0.9</td>
<td>2.2 ± 0.8</td>
<td>2.2 ± 0.8</td>
</tr>
<tr>
<td>Percent shortening of anterior to posterior dimension (%)</td>
<td>26.8 ± 3.5</td>
<td>26.0 ± 3.1</td>
<td>26.9 ± 3.4</td>
</tr>
</tbody>
</table>

* P < 0.05 compared to baseline; values in the right hand column are the average of the first five beats after the left atrial infusion was completed; LV dP/dt = rate of change of left ventricular pressure; D P<sub>0</sub> = developed left ventricular pressure of 40 mm Hg; circ/sec = circumferences per second. Values shown are mean ± SD.
PEEP suggests that, at least to some degree, the increased RVEDP is still transferred to the left ventricle through the septum even in the absence of the pericardium. Thus, ventricular interdependence is not solely a result of the two chambers occupying a closed sac with limited space for acute expansion.

That contractility was not significantly changed by PEEP was demonstrated by the lack of change of several contractile indices that are essentially independent of preload. Even those contractile indices which did change with PEEP (peak left ventricular $dP/dt$ and the maximum velocity of minor axis shortening) returned to pre-PEEP values after preload (end-diastolic dimensions) returned to baseline following a rapid left atrial infusion. Further evidence that little or no change in left ventricular contractility occurred during PEEP was provided by the observation that the coordinate values for average left ventricular end-diastolic dimension and stroke volume fell on or very near the basic Starling curve in each dog when PEEP was instituted at any end-diastolic dimension. Furthermore, PEEP did not alter the relationship between end-diastolic dimension and shortening velocity at any point along the basic end diastolic length-maximum velocity plot.

Finally, the relationship between left ventricular end-diastolic pressure and average end-diastolic dimensions (diastolic compliance) was altered substantially during PEEP with the pericardium intact, but to only a minor degree with the pericardium removed.

Several groups of investigators over the last 30 years have suggested that the decrease in cardiac output that occurs with PEEP ventilation is due to a reduction in venous return (Cournand et al., 1948; Braunwald et al., 1957; Morgan et al., 1966; Kumar et al., 1970; Suter et al., 1975). Recent studies by other investigators have confirmed this observation (Fewell et al., 1980), and our own studies suggest that pulmonary venous return to the left heart is decreased by PEEP.

Scharf and colleagues (1977) observed that PEEP was associated with an increase in right atrial, pulmonary arterial, and left atrial pressure when measured relative to atmospheric pressure, but increased relative to pleural pressure only when end-expiratory lung volume was allowed to increase. They also suggested that the rise in left atrial pressure (and thus LVEDP) may indicate a degree of left ventricular dysfunction associated with in-
increasing end-expiratory lung volume, although they did not suggest a mechanism. The elaboration of a negative inotropic substance by the lung has also been postulated as a possible cause of decreased contractility and cardiac output during PEEP (Liebman et al., 1978; Grindlinger et al., 1979). However, other investigators have observed that, following the institution of PEEP, changes in right ventricular performance preceded any detectable change in left ventricular performance by 2–3 heart beats, suggesting that the humoral agent, if present, is not the initiating factor (Fewell et al., 1980).

A similar theory was proposed by other investigators who suggested that a reflex depression of ventricular function resulted from hyperinflation of the lung (Glick et al., 1969; Cassidy et al., 1978). Although this reflex mechanism may influence cardiac function, it was no longer operative after 15–25 seconds in the studies in which it was described. A more recent investigation provided evidence that both right and left ventricular preload are decreased during PEEP (Fewell et al., 1980). This is in accordance with the results of our study, although the methods used to reach this conclusion were different.

In a study of the changes in canine left ventricular size and configuration with PEEP by Scharf and coworkers, a somewhat different method of measuring left ventricular dimensions yielded results that were different from the results in our study (Scharf et al., 1979). Using lead markers in the myocardium to study the shape of the heart during cinefluorography, they found that the septal-to-free wall dimension actually increased while the anterior-to-posterior dimension decreased during PEEP. The differences in their results may be related to the fact that the pericardium was not left intact; the edges were only loosely approximated after having been incised widely. Furthermore, their studies were performed following closure of a midline sternotomy. The effects of this type of closure on left ventricular dimensions are unknown, but may be partially responsible for the different results. Perhaps most importantly, cardiac output was kept nearly constant with PEEP in the study by Scharf et al., whereas, cardiac output was allowed to change in the present study.

The alteration in left ventricular diastolic compliance during PEEP observed in the present study confirms the observations of Scharf et al. (1979) and of Haynes et al. (1980) who felt that diastolic pressure-volume relations were shifted in the direction of increased stiffness, at least in part resulting from right ventricular dilation and ventricular interdependence. In the present study, when the pericardium was removed, left ventricular diastolic compliance was not altered to the same degree with PEEP. The interdependence of the right and left hearts is well established for the diastolic characteristics of the two chambers (Elzinga et al., 1974) and has recently been elucidated for the systolic function of the two pumps (Elzinga et al., 1980). As early as 1910, Bernheim postulated that changes in the shape or compliance of the left ventricle could compress the right ventricle, thereby limiting right ventricular performance (Bernheim, 1910); the syndrome or effect now bears his name. The opposite situation in which changes in right ventricular shape or compliance affect the function of the left ventricle, is termed the “reversed Bernheim effect.”

More recently, investigators quantitatively examined the effect of filling either the left or right ventricle on the distensibility of the opposite ventricle (Taylor et al., 1967). They found that the magnitude of this influence on the ventricular pressure-volume relation varied directly with the degree of filling of the other ventricle; it was minimal at the normal physiological levels of ventricle filling, but became significant at abnormally elevated end-diastolic volumes or pressures. The capability of right ventricular filling to decrease left ventricular distensibility became apparent at an LVEDP in
excess of 4 mm Hg. Their experiments were performed with the chest open and the pericardium removed; it seems likely that the interrelationship they observed would be even more pronounced with the pericardium intact.

The effects of alterations in the diastolic filling pressure of the right ventricle on left ventricular geometry and filling pressure have also been studied in the isolated, supported canine heart (Bemis et al., 1974). The shape of the left ventricle was studied by placing endocardial radiopaque markers in the ventricular septum, the anterior wall, the posterior wall, and the free wall in a plane perpendicular to the long axis. They found that increments of 5 mm Hg in the RVEDP increased the LVEDP by 2.3 mm Hg, decreased the septum-to-free wall distance by 4.5%, and increased the anterior-to-posterior dimension by 4.4%. They concluded that LVEDP and left ventricular end-diastolic dimensions were significantly related to RVEDP and that left ventricular end-diastolic geometry was increasingly distorted at greater elevations of RVEDP.

From the results of the present study in the open-chest dog, it appears that PEEP is associated with a change in left ventricular geometry and an increase in LVEDP with the pericardium intact, resulting from a reversed Bernheim effect from the dilated right ventricle. With the pericardium removed, the relationship is still present but to a much lesser degree. The decrease in left ventricular stroke volume is a result of a PEEP-induced decrease in left ventricular preload, and not to a change in the contractile state of the sarcomeres.

Acknowledgments

We thank Nancy Watters for secretarial assistance.

References


Bernheim PI (1910) De l'asystolie veineuse dans l'hypertrophie du cœur gauche par stenose concomitante du ventricle droit. Rev Med 30: 786-801


Lieberman PR, Patten MT, Nanny J, Hechtman HB (1979) The mechanism of depressed cardiac output on positive end-expiratory pressure (PEEP). Surgery 83: 595-598


Paradoxical rise in left ventricular filling pressure in the dog during positive end-expiratory pressure ventilation. A reversed Bernheim effect.
J R Darsee, J R Mikolich, P F Walter and R C Schlant

doi: 10.1161/01.RES.49.4.1017

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/49/4/1017

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/