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Canine Left Ventricular Volume Response to Mechanical Ventilation with PEEP

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To determine the cause of decreased cardiac output (CO) resulting from the use of PEEP, hemodynamic and pulmonary parameters and radiographic estimates of left ventricular volumes were observed in nine dogs under three conditions: control, PEEP (15 cm H_2O), and PEEP with intravascular (IV) volume expansion. Volume expansion was sufficient to return the CO to control values. Cardiac index (CI), stroke volume index (SI), left ventricular volumes, and the left ventricular stroke work index (LVSWI) all decreased approximately 30 per cent with the application of PEEP. Ejection fraction remained unchanged. With IV volume expansion, the CI, SI, left ventricular end-diastolic volume index, and LVSWI returned to approximate control values. The transmural left ventricular end-diastolic pressure (TMLVEDP) did not change significantly. The authors therefore conclude that reduced left ventricular preload is the cause of decreased cardiac output by PEEP and that indirect evidence of preload (transmural left ventricular end-diastolic pressure) is not an adequate assessment of the force-length relationship under the conditions stated. (Key words: Heart: cardiac output; contractility. Ventilation: positive end-expiratory pressure.)

POSITIVE END-EXPIRATORY PRESSURE (PEEP) is an effective technique for management of respiratory failure. However, the application of PEEP may cause decreased cardiac output (CO). The decreased CO may be treated pragmatically with intravascular volume expansion or inotropic drugs. Nonetheless, the appropriate management of patients with respiratory failure who have decreased CO as a result of PEEP remains controversial, mainly because of our incomplete understanding of the mechanisms by which PEEP reduces CO. Data presented by Qvist *et al.*[1] and Braunwald *et al.*[2] supported reduction of venous return or preload. Equally convincing data by Liebman *et al.*[3] and Cassidy *et al.*[4] supported reduction of ventricular function. Hobelmann *et al.*[5] and Cassidy *et al.*[6] emphasized the associated increased pulmonary vascular resistance (PVR) which places the right ventricle (RV) in jeopardy of failure. Powers and Dutton[7] argued for RV failure as a result of decreased myocardial perfusion.

Previous investigators measured hemodynamic variables in an effort to infer left ventricular (LV) filling and the position of the LV volume on the Frank-Starling force-length curve. This approach, of necessity, has been indirect.

The objective of this study was to measure pertinent hemodynamic and pulmonary data, and to radiographically estimate LV volumes under three conditions: control, PEEP (15 cm H_2O), and PEEP with intravascular volume expansion sufficient to return the CO to control values. If decreased contractility results from PEEP, then with the application of PEEP, a larger LV diastolic volume would be required to restore a constant cardiac output. If, however, the LV volumes remain constant at the same CO despite PEEP, a decrease in LV contractility would be precluded.

Methods

Nine mongrel dogs weighing 14–25 kg (18.2 ± 4) were anesthetized with sodium pentobarbital (30 mg/kg), intubated, and mechanically ventilated with a fixed I-E ratio of 1:2, and a respiratory rate of 20 breaths/min. Pa_{CO_2} was maintained at 39 ± 4 torr by adjusting the tidal volumes. Anesthesia was maintained with 70 per cent N_2O in 30 per cent O_2 and hourly intravenous (iv) administration of pentobarbital, 3.0 mg/kg. Muscle relaxation was maintained with administration of pancuronium, 0.025 mg/kg, every 30 min, after a loading dose of 0.1 mg/kg.

PULMONARY DATA

End-tidal CO_2 was continuously sampled from a 2-mm (ID) tube in the distal end of the endotracheal tube and analyzed by an infrared capnograph. Airway pressures were measured through an adaptor in the endotracheal connector. Esophageal pressures (P_{eso}) were measured via a saline-filled catheter placed behind the left atrium during fluoroscopy. The low-pressure transducers were calibrated with a water manometer. Gas flows were measured by a pneumotachograph with a differential transducer and electronically integrated for tidal volumes. PEEP was produced by placing a weighted ball valve on the respiratory port.

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TABLE 1. Values of Physiological Variables*

	Condition		
	1	2	3
Pa_{O_2} torr	134 ± 14.0	149 ± 11†	158 ± 15‡
Pa_{CO_2} torr	39.3 ± 3.4	39.3 ± 2.7	38.9 ± 4.3
*p*H	7.35 ± 0.03	7.35 ± 0.03	7.35 ± 0.04
Temperature °C	37.4 ± 0.43	37.2 ± 0.43	37.2 ± 0.43
Hematocrit (Per cent)	32.3 ± 4.30	30.7 ± 3.3	30.1 ± 3.8
Heart rate, beats/min	169 ± 7	169 ± 7	169 ± 7
PEEP (cm H_2O)	0	14.4 ± 0.7	14.4 ± 0.8

* Values are means ± SD.
† $P < 0.01$ compared to control (1).
‡ $P < 0.001$ compared to control (1).

HEMODYNAMIC DATA

A 6.7 French pigtail catheter was inserted via a femoral artery for LV pressure measurements and for contrast injection. A flow-directed, pulmonary artery catheter was placed via a femoral vein for measurement of central venous pressure (CVP), pulmonary artery pressure (PAP), pulmonary capillary pressure in the wedged position (PCWP), and for thermodilution CO determination (in triplicate). A catheter was placed in the abdominal aorta for systemic blood pressure measurement and for obtaining arterial blood samples. A transvenous pacing wire was placed in the right atrium via a femoral vein to maintain a constant heart rate. Pacemaker and atrial function was verified by continuous monitoring of the electrocardiogram. The transducers were calibrated with water or mercury manometers and zeroed to the mid-thorax after final positioning.

TABLE 2. Hemodynamic Variables*

	Condition		
	1	2	3
P_{eso} (torr)	−1.6 ± 0.3	1.9 ± 0.3†	2.4 ± 1.8
MAP (torr)	132.0 ± 5.0	125 ± 4.3‡	134 ± 3.4
SI (x-ray) ml/m²	20.8 ± 1.8	15.4 ± 1‡	22.1 ± 1.8
SI ml/m²	20.7 ± 1.1	14.5 ± 0.7†	20.7 ± 1.1
CI l/m²	3.5 ± 0.17	2.5 ± 0.1†	3.5 ± 0.14
SVR units	48.0 ± 2.6	63 ± 2.3†	48 ± 2.3
LVEDVI ml/m²	42.3 ± 3.2	30.6 ± 2.2†	39.0 ± 2.3
LVESVI ml/m²	21.7 ± 1.6	15.6 ± 1.5§	16.9 ± 1.1¶
EF	0.49 ± 0.02	0.49 ± 0.03	0.56 ± 0.02‡
LVSWI $g \cdot m^{-2} \cdot beat^{-1}$	35.4 ± 2.1	22.9 ± 1.3†	36.0 ± 1.8
TMLVEDP torr	6.6 ± 0.8	6.0 ± 1	7.8 ± 0.9
TM$\overline{PAP}$ torr	13.4 ± 0.6	16.0 ± 0.9‡	17.6 ± 0.8†
TM$\overline{PCWP}$ torr	6.0 ± 0.6	7.0 ± 1	9.9 ± 1.2†
PVR units	2.7 ± 0.3	4.8 ± 0.3†	3.0 ± 0.5
TM$\overline{CVP}$ torr	4.5 ± 0.6	6.0 ± 0.8‡	7.2 ± 1.3‡

* Values are means ± SEM.
† $P < 0.001$, ‡ $P < 0.02$, § $P < 0.005$, and ¶ $P < 0.05$, as compared to the controls (1).

RADIOGRAPHIC DATA

The animals were placed supine in a cradle so that a right anterior oblique projection could be obtained. Single plane cine ventriculograms were recorded during contrast injection. Volumes were calculated using the Dodge regression formula[8] by two experienced cardiovascular radiologists working independently and utilizing their own tracings.

EXPERIMENTAL PROTOCOL

After cannulation, whole blood (15 ml/kg) was removed, stored in heparin and kept warm for later reinfusion. Concurrently, lactated Ringer's solution (45 mg/kg) was administered to maintain intravascular volume. The animals were allowed to stabilize prior to the study periods. Observations were made under three conditions: 1) Control ZEEP; 2) PEEP 15 cm H_2O; and 3) PEEP with volume expansion (15 ml/kg blood and sufficient lactated Ringer's solution to return the CO to the control value). The hemodynamic and ventilatory data were recorded on polygraphs immediately prior to angiography. Transmural pressures (TM) were calculated as the difference between the P_{eso} and the measured pressure. Formulas used for calculations were:

$$\text{body surface area (BSA)} = 0.112 \text{ body weight}^{2/3}$$

and

$$\text{left ventricular stroke work index (LVSWI)} = (\text{MAP} - \text{transmural left ventricular end-diastolic pressure}) \times .0136 \times \text{SI}.$$

The remaining indices were calculated by dividing the appropriate variable by the BSA in m^2. The ejection fraction (EF) was calculated by dividing the radiographic estimates of LV end-diastolic volume (LVEDV) by the radiographic estimated stroke volume (SV).

Paired *t* tests were used to test significance of differences between conditions 1 and 2, 2 and 3, and 1 and 3. Both the paired *t* test and linear regression were used to compare stroke volumes calculated from thermodilution CO, with the stroke volumes determined by ventriculography.

Results

Temperature, *p*H, Pa_{CO_2}, hematocrit, and heart rate remained essentially constant throughout the course of the experiment (table 1). The Pa_{O_2} increased with PEEP and with volume expansion. The mean esophageal pressure (P_{eso}) changed from negative to posi-

tive with PEEP, and increased slightly with volume load (table 2). With the application of PEEP, MAP decreased slightly, stroke index and cardiac index decreased 30 per cent, and systemic vascular resistance increased. These variables returned to control levels with volume expansion (table 2). The SI calculated from thermodilution was compared to the SI obtained by ventriculography, and no significant difference was found ($P > 0.3$). The correlation coefficient was 0.76 ($P < 0.001$).

Left ventricular, end-diastolic volume index (LVEDVI) decreased approximately 28 per cent with PEEP and returned to 90 per cent of the control value with volume expansion. The ejection fraction did not change with application of PEEP and increased slightly but significantly with volume loading. The transmural LVEDP did not change significantly.

The transmural mean pulmonary artery pressure (TM$\overline{PAP}$) increased 20 per cent with PEEP, and further increased with volume load. The transmural mean capillary wedge pressure (TM$\overline{CWP}$) did not change with PEEP but increased with volume load. These changes resulted in an 80 per cent increase in calculated pulmonary vascular resistance (PVR) with PEEP, and a decrease in PVR to control levels with volume expansion. The transmural mean central venous pressure (TM$\overline{CVP}$) increased 30 per cent with PEEP, and a further 20 per cent with volume load.

Discussion

The decrease in cardiac output which occurred with PEEP in this study was associated with a decrease in LVEDVI and with corresponding decreases in SI, LVESVI, and LVSWI. The ejection fraction remained constant. The direct implication of this finding is that the decrease in cardiac output results from decreased, left ventricular filling with PEEP. However, no decrease in TMLVEDP occurred with the application of PEEP despite the 28 per cent decrease in LV filling. The lack of substantial change in transmural filling pressures with PEEP has been previously observed by Cassidy *et al.*[4] and others.

There are several factors which may account for the significantly decreased filling without significant change in filling pressure. It is reasonable to assume that intrapericardial pressure measures the external force against which the LV must fill, and Cassidy *et al.*[4] have demonstrated that esophageal pressures which we measured, are not significantly different from intrapericardial pressures in a given animal. We calculated transmural LVEDP as the difference between LVEDP and esophageal pressure. However, both LVEDP and esophageal pressure are difficult to measure with precision, and conclusions based on small changes in the difference between the two are likely to be inaccurate. Thus, we assume that the lack of statistical significance of the decrease in TMLVEDP with PEEP represents the inability to obtain adequate measurement precision, since at low volumes, left ventricular filling varies widely with small changes in LVEDP.[9,10] Additionally, in a study not complicated by PEEP, Alderman and Glantz[11] found that in the presence of acute hemodynamic changes, LVEDP may not reflect LVEDV.

After application of PEEP, when the intravascular volume is increased to return the cardiac output to control values, the LVEDVI also returns to approximately control levels. There is a small and insignificant increase in the TMLVEDP, the implication of which is obscured by the difficulty of accurate measurement of TMLVEDP. With volume expansion and PEEP, the ejection fraction of the dogs we studied increased from 0.49 to 0.56, with an associated decrease in LVESVI. Grossman *et al.*[12] have demonstrated that in awake humans decreased LVESV is associated with increased inotropy. It is possible that changes in contractility indeed occurred with PEEP, possibly related to autoregulation.[13] Another possible interpretation of the decreased LVESVI is that the effective afterload is reduced by PEEP.[14]

Scharf *et al.*[15] measured LV contractility in dogs under a variety of conditions, primarily using radiopaque markers in animals subjected to thoracotomy. They also found no decrease in LV contractility with PEEP, although they found a small but significant increase in transmural mean left atrial pressure required to sustain a constant CO. The increase in transmural filling pressure observed by Scharf *et al.*[15] is 1.3 torr greater than the increase we observed. Pressures measured by Scharf *et al.*[15] were atrial pressures, and may reflect decrease atrial compliance during ventricular systole rather than decreased LV compliance as they suggest.

We observed only small increases in the TM$\overline{CVP}$ and TM$\overline{PAP}$, suggesting that volume expansion is not associated with right heart failure under these conditions. We cannot be certain of the validity of our measurements of PVR since the tip of the pulmonary artery catheter was not shown to be at or below the level of the atrium, and position of the catheter is important under these conditions.[16] However, the TM$\overline{PCWP}$ does not differ greatly from the TMLVEDP in our experiments, suggesting the errors, if any, are small.

We conclude that PEEP decreased CO mainly because of decreased LV preload and that there may

be a slight increase in LV contractility in the anesthetized dog with volume expansion. There is no decrease in the LV contractile state as a result of PEEP. The decreased LV preload is not readily detected by hemodynamic measurements. Recent studies in humans correspond with this analysis. Cassidy *et al.*[6] used echocardiography to demonstrate decreased LV filling in humans subjected to PEEP. Furthermore, in humans with respiratory failure treated with PEEP, intravascular volume expansion adequate to cause a significant increase in cardiac output was associated with only a small and statistically insignificant increase in PCWP.[17] The cause of the decreased LV preload which we observed is presumably related to right ventricular preload or contractility and cannot be precisely determined from this study. Regardless of the cause of decreased LV preload with PEEP, volume expansion restores the LV preload and CO to approximate control value without hemodynamic evidence of right ventricular failure.

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