Biventricular Volumes and Function in Patients with Adult Respiratory Distress Syndrome Ventilated with PEEP*

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The ventricular volume and function changes induced by the addition of 12 cm H₂O of positive end-expiratory pressure (PEEP) during mechanical ventilation were studied in 11 patients with the adult respiratory distress syndrome. Cardiac output was measured by thermodilution and ventricular ejection fraction by the multiple gated equilibrated cardiac blood pool scintigraphy. Right and left end-diastolic volumes were then calculated by dividing stroke volume by ejection fraction. The PEEP caused a 14 percent decrease of the cardiac output secondary to a decrease in stroke volume. On the basis of the relationship between stroke volume and ventricular end-diastolic volume, we conclude that reduction in preload was the major component of the decrease in cardiac output. After removal of PEEP, we observed a rebound phenomenon characterized by higher values for stroke volume and cardiac output than before the application of PEEP.

Patients with the adult respiratory distress syndrome (ARDS) often need positive end-expiratory pressure (PEEP) during mechanical ventilation in order to increase the arterial oxygen tension (PaO₂). Arterial hypoxemia is due to an acute pulmonary parenchymal failure in these patients, secondary to major surgery or severe trauma. Continuous positive pressure ventilation can improve the arterial PaO₂ mainly by maintaining a higher functional residual capacity and by decreasing the pulmonary venous admixture. However, PEEP usually decreases the cardiac output (CO), and in some patients, also decreases the systemic oxygen transport (cardiac index times arterial oxygen content).

The mechanism of reduced CO is not entirely clear. A number of investigations suggest that a decrease in venous return to the right heart secondary to the increased intrathoracic pressure plays the major role. Others suggest a decrease of myocardial contractility in the presence of constant or increasing transmural atrial pressure. Additional explanations of the reduction in CO include right ventricular failure caused by an increase in pulmonary vascular resistance, myocardial failure caused by a deleterious action of the increased intrathoracic pressure on the coronary circulation, compression of the left ventricle caused by a leftward displacement of the interventricular septum, and the presence of a negative inotropic agent induced by PEEP.

Since conclusions about the effects of PEEP have, for the most part, utilized pressure to reflect ventricular preload, a concept which is untenable with current physiologic reasoning, it was the purpose of this study to more specifically assess the effects of PEEP on global myocardial function utilizing volume measurements to reflect preload instead of diastolic pressures. We measured CO by thermodilution, left and right ejection fraction (EF) by multiple gated equilibrium radionuclide angiograms, and then calculated right and left end-diastolic and end-systolic volumes. The simultaneous recording of the right and left ventricular volumes by Tc-99m scintigraphy provided data on volume changes of each ventricle and allowed estimation of "ventricular interference," as previous studies suggested.

We found that the decrease in CO induced by PEEP mediated more through a reduction in biventricular volumes than any inherent change in contractility.

Patient Population

Ten men and one woman, age range 19 to 59 years (mean: 35 years) were included in this study. Mechanical ventilation was required for the treatment of acute respiratory failure secondary to severe trauma (six patients), fat embolism (two patients), sepsis (two patients), and extracorporeal circulation (one patient). The ARDS was characterized in all cases by severe pulmonary failure, with an acute onset requiring mechanical ventilation. All had marked arterial hypoxemia, a venous admixture greater than 30 percent of the CO at an inspired oxygen concentration (FiO₂) of 0.5, and signs of an increased pulmonary capillary permeability for fluid and plasma proteins. This was diagnosed by the auscultation of diffuse interstitial crackles and fine rales over both lung fields, bilateral homogeneous pulmonary opacification on the chest x-ray film, and the appearance of great amounts of yellowish pink bronchial fluid. Protein analysis of this bronchial fluid and blood plasma revealed a similar pattern on electrophoresis for the two liquids in all patients, and bronchial fluid

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to plasma protein ratio between 0.84 and 0.96 (mean 0.91). Four of 11 patients manifested a mean pulmonary capillary wedge pressure (PCWP) equal to or greater than 20 mm Hg, suggesting that a probable hydrostatic, in addition to a permeability, cause of pulmonary edema was present. Patients with known left or right heart disease and/or chronic obstructive pulmonary disease were excluded from this study.

**METHODS**

Measurements were made during the first 48 hours after the onset of ARDS. Volume controlled ventilators were used in the controlled mode to deliver a tidal volume (TV) of 12 to 15 ml/kg of body weight. Successive studies were performed during the three following ventilatory periods: (1) mechanical ventilation without PEEP; (2) mechanical ventilation with 12 cm H2O of PEEP; and (3) again mechanical ventilation without PEEP. Each ventilatory period lasted 40 minutes. All investigations, invasive and noninvasive, were begun 20 minutes after application or removal of PEEP. Pressure measurements were made at end-expiration.

The FICO was adjusted to obtain a PaCO2 above 70 mm Hg (9.3 kPa). Arterial carbon dioxide tension (PaCO2) was maintained between 35 and 45 mm Hg (4.6 to 6 kPa), and the pH was between 7.35 and 7.45. For each patient, respiratory frequency, TV, and FICO were kept constant throughout the three study periods. As a part of routine clinical management, all patients had an arterial cannula inserted into the radial artery for continuous measurement of blood pressure and sampling for blood gas determination. A superior vena cava catheter was introduced percutaneously to measure the central venous pressure (CVP). A Swan-Ganz catheter was also placed percutaneously to monitor the pulmonary pressures, the PCWP, and to determine the CO by the thermodilution method. We did not attempt to measure the transmural PCWP because of three major reasons: (1) PCWP may not be an accurate reflection of the left atrial pressure during PEEP, (2) changes in pleural pressure may not reflect the changes in extrapleural cardiac pressure; and (3) transmural pressure transmitted to the myocardium may differ for each ventricle.

Throughout the study, patients received an infusion of glucose at a constant rate (1.5 ml/kg/hr). They were sedated with morphine (1 mg/hr), diazepam (1 mg/hr), and if needed, they received pancuronium to avoid movements during investigations.

Informed consent was obtained by the physician in charge of the patient, and the protocol was approved by the Committee on Ethics and Human Research of our institution.

Thirty minutes before the beginning of the scintigraphic study, 10 mg of stannous pyrophosphate was given intravenously. Twenty minutes later, a bolus of 25 mCi of 99mTc sodium pertechnetate was injected percutaneously in an antecubital vein. After complete mixing throughout the vascular space, multiple ECG-gated equilibrium radionuclide angiograms were performed with the patient in the supine position under a mobile 37 photomultiplier gamma camera.

The single crystal scintillation detector was placed in a 40° to 50° left anterior oblique (LAO) position. In each case, the degree of obliquity used was that which provided the best separation between the left and the right ventricle. In addition, a caudal tilt to 10° of the detector head was used for a better separation between the right atrium and the right ventricle.

The multiple-gated equilibrium cardiac blood pool scintigrams were performed twice, and the data were collected for a four-minute period and stored on a magnetic diskette of a Nova computer for future processing.

The peak of the R wave was used as the physiologic gate. After each cardiac cycle, the length of the R-R interval was automatically examined to determine whether it lies within a physician-selected temporal best-length window. Cycles falling outside this window were rejected. The computer divided the R-R interval into 12 equal time periods (frames) and then assembled data from all cardiac cycles in the given acquisition period.

A left ventricular region of interest was selected by drawing a contour around the left ventricle at end-diastole, then a computer algorithm automatically determined the left ventricular border. Generation of a time activity curve was accomplished by determining the left ventricular counts for each frame corrected for background activity. The background activity was determined by a flat background subtraction based on correlations with contrast ventriculography. The left ventricular ejection fraction (EF) was calculated by the formula

$$EF = \frac{EDC-ESC}{EDC}$$

where EDC is left ventricular end-diastolic counts and ESC, left ventricular counts at end-systole. Laboratory normal for left ventricular EF is 71 ± 6 percent.

Two right ventricular regions of interest were selected by manually drawing a contour around the right ventricle, one in the end-systolic and the other in the end-diastolic phase of the cardiac cycle. A third crescent-like area immediately surrounding the right ventricle was selected to determine the background activity. The right ventricular ejection fraction was calculated by dividing the background-corrected stroke counts (counts at end-diastole minus counts at end-systole) by the background corrected end-diastolic counts. This method has been shown to correlate well with the first pass scintigraphy method. Normal value for right ventricular EF is not available in our laboratory because of the sensitive influence of the pulmonary afterload on the right ventricular EF.

Using the Swan-Ganz catheter to measure cardiac output and pressures at the same time as performance of radionuclide angiography, the following parameters were calculated:

$$SVI (ml/beat/M^2) = \frac{CI \times 1,000}{HR}$$
$$SVRI (dyn sec/cm^2/m^2) = \frac{BF - CVP \times 80}{CI}$$
$$PVRI (dyne sec/cm^2/m^2) = \frac{PA - PCWP \times 80}{CI}$$

where BP is mean arterial blood pressure (mm Hg); HR, heart rate (best/min); PAP, mean pulmonary artery pressure (mm Hg); PCWP, mean pulmonary wedge pressure (mm Hg); CVP, central venous pressure (mm Hg); CI, cardiac index (L/min/m^2); SVI, stroke volume index (ml/beat/m^2); SVRI, systemic vascular resistance index (dyn sec/cm^2/m^2); and PVRI, pulmonary vascular resistance index (dyn sec/cm^2/m^2).

Ventricular end-diastolic volume indices were derived by dividing the SVI by the EF.

Arterial oxygen content (CaO2) was calculated assuming each gram of saturated hemoglobin 1.34 ml O2, systemic oxygen transport index was then calculated as the CI (L/min/m^2) × CaO2 (ml/min).

The t-test for paired samples was used to compare group mean values and the method of least squares for the calculation of linear regression.

**RESULTS**

**Application of 12 cm H2O of PEEP**

The PEEP produced a significant increase in PaO2 (98 ± 11 mean ± standard error of the mean to 126 ± 20 mm Hg, 13.1 to 16.8 kPa, p < 0.05), but no change in PaCO2 and pH. The average increase in CI was 14 percent (4.3 ± 0.4 to 3.7 ± 0.4 L/min/m^2, p < 0.0005) which resulted from a decreased SVI, whereas HR was
FIGURE 1. Effects of PEEP on left and right ventricular ejection fraction and volume (mean ± SEM).

unchanged (111 ± 6 to 112 ± 6 beat/min). Oxygen transport index decreased from 657 ± 59 to 584 ± 53 ml/min/m² (p < 0.0025).

Mean systemic arterial blood pressure (BP) remained stable with PEEP (87 ± 3 to 84 ± 4 mm Hg), but CVP increased significantly (14 ± 2 to 18 ± 2 cm H₂O, p < 0.0005).

Systemic arterial resistance index did not change significantly (1,444 ± 126 to 1,547 ± 139 dynes·sec·cm⁻²/m²).

Mean pulmonary artery pressure was already elevated before PEEP but did not change significantly (30 ± 3 to 31 ± 2 mm Hg). The PCWP did not increase after initiation of PEEP (18 ± 3 to 19 ± 1 mm Hg).

Pulmonary vascular resistance index, already increased without PEEP, showed a further but nonsignificant increase with PEEP (237 ± 37 to 303 ± 62 dynes·sec·cm⁻²/m², NS). Both left and right ventricular EF remained unchanged on PEEP (Fig 1).

The ventricular end-diastolic volume indices are also presented in Figure 1. Left ventricular end-diastolic volume index (LVEDVI) and right ventricular end-diastolic volume index (RVEDVI) both decreased significantly after institution of PEEP, respectively from 56 ± 5 to 48 ± 4 ml/m² (p < 0.0025) and from 83 ± 8 to

end-diastolic volume index (ml/m²)

FIGURE 2. Effect of PEEP on right ventricular function curve for each patient (solid lines). Group means indicated by notched line.

end-diastolic volume index (ml/m²)

FIGURE 3. Effect of PEEP on left ventricular function curve for each patient (solid line). Group means indicated by notched line.
71 ± 7 ml/m² (p < 0.0025). Left ventricular end-systolic volume index (LVESVI) decreased from 17 ± 3 to 14 ± 2 ml/m² (p < 0.025) and right ventricular end-systolic volume index (RVESVI) decreased also from 42 ± 5 to 37 ± 4 ml/m² (p < 0.05).

To assess the ventricular function, we used the relationship of the SVI versus RVEDVI, and SVI versus LVEDVI (Fig 2 and 3). These relationships were both significant before (SVI = 14.19 + 1.74 RVEDVI; R² = 0.66, p < 0.01 and SVI = 1.59 + 1.38 LVEDVI; R² = 0.81, p < 0.001) and after PEEP (SVI = 16.12 + 1.63 RVEDVI; R² = 0.62, p < 0.01 and SVI = 5.71 + 1.26 LVEDVI; R² = 0.80, p < 0.001), so that the decrease in SVI reflected the decrease in ventricular end-diastolic volume indices.

**Removing PEEP**

Cardiac index rose to higher than the baseline levels determined before PEEP was applied (3.7 ± 0.4 to 4.6 ± 0.4 L/min/m², p < 0.025). Heart rate, PAP, and PCWP remained unchanged. Blood pressure increased slightly but significantly (p < 0.05); and CVP decreased again to the same level as at the beginning of the study (Table 1).

The SVRI decreased from 1547 ± 139 to 1371 ± 124 dynes·sec·cm⁻²·m² (p < 0.05).

The left EF increased significantly and reached a higher level than before PEEP. The right EF, however, decreased, and there was a significant difference from the values before PEEP (Fig 1).

The LVEDVI and RVEDVI increased again, and RVEDVI was higher than before PEEP (Fig 1).

The LVESVI did not increase significantly (14 ± 2 to 15 ± 3 ml/m²), but RVESVI increased again to higher values than before PEEP (37 ± 4 to 52 ± 6 ml/m², p < 0.001).

**Discussion**

We examined the effects of 12 cm H₂O PEEP on ventricular volume and function in 11 patients with ARDS. The four principal findings of this study are as follows: (1) PEEP induced a significant decrease in CO, SVI, and both left and right ventricular end-diastolic volumes. (2) An unchanged RVEDVI/LVEDVI ratio indicated that the PEEP-induced decrease in SVI was not primarily related to unequal ventricular volume changes. (3) The decrease in SVI with 12 cm H₂O PEEP followed the decrease in both right and left ventricular end-diastolic volume indices, suggesting that no major changes in ventricular function occurred during PEEP. (4) After discontinuation of PEEP, CO and SVI increased to a higher level than before addition of PEEP.

As expected, in all our patients, 12 cm H₂O of PEEP caused a fall in CO secondary to a decreased stroke volume. All patients except one had a HR over 95 beats per minute (mean 110 ± 6 beats per minute) during mechanical ventilation without PEEP and did not change during PEEP. We would expect an increase in heart rate to compensate for a decrease in CO, and the lack of this possible compensatory mechanism remains unclear. Although the same observation was made by many authors, others noted an increased HR during PEEP, but which was insufficient to improve CO significantly.

The PEEP induced a significant decrease in both left and right ventricular end-diastolic volumes so that the decrease in stroke volume was primarily due to a decrease in ventricular preload. To explain the decrease in stroke volume with PEEP, Lauer et al suggested a ventricular interdependence with a distended right ventricle interfering with left ventricular loading. Recently, Jardin et al showed with echocar-
diography a leftward shift of the interventricular septum during PEEP, and they concluded that decreased cardiac output was due to restriction of left ventricular filling.

We observed, after PEEP was initiated, a change in the configuration of the heart, but because the multiple-gated equilibrium cardiac scintigraphy can only adequately assess changes in volume (total counts) but not exactly in shape, we did not measure any chamber size. Therefore, to separately assess the ventricular response to PEEP, we calculated a RVEDVI/LVEDVI ratio (Fig 4). During mechanical ventilation without PEEP, seven of the 11 patients had an abnormally high RVEDVI/LVEDVI ratio (>1.5) which suggests a relative degree of right ventricular enlargement. After PEEP was initiated, only three of the seven patients with abnormally high RVEDVI/LVEDVI ratio showed a further increase of this ratio. We were then unable to demonstrate any significant relationship between RVEDVI/LVEDVI ratio and PEEP. We conclude that introduction of 12 cm H2O of PEEP did not induce, in our patients, a significantly different volume response between the two ventricles. In particular, there was no evidence of a PEEP-induced relatively increased RVEDVI responsible for a decreased LVEDVI. These results are in contrast with observations in other studies where left ventricular performance was restrained by right ventricular loading (ventricular interference). Three major reasons as follow can be invoked for these different observations: (1) 12 cm H2O of PEEP may not have been a high enough end-expiratory pressure to induce a significant right ventricular enlargement; (2) patients did not receive, during mechanical ventilation, a volume replacement therapy to improve the cardiac performance; and (3) ventricular end-diastolic volumes were low at the beginning of the study.

To assess myocardial function, we did not utilize the Frank-Starling relationship using a pressure to represent preload because of the difference in pressure-volume relationships in ARDS patients. However, like Calvin et al., the measurement of ventricular end-diastolic volumes allowed construction and comparison of population Frank-Starling ventricular function curves before PEEP and after PEEP (Fig 2 and 3). The decrease in SVI followed the reduction in ventricular end-diastolic volume indices; we therefore suppose that only minor changes in myocardial function occurred with PEEP.

After PEEP was discontinued, the mean values of CO, stroke volume, RVEDVI, RVESVI, and left ventricular EF returned to a higher level and right EF to a lower level when compared with the initial period of mechanical ventilation without PEEP. The RVEDVI/LVEDVI ratio increased significantly, reflecting a relative dilatation of the right ventricle after removal of PEEP. This cannot clearly be explained and needs further investigation.

In conclusion, this study demonstrates that the addition of 12 cm H2O PEEP in patients with ARDS induces an equivalent decrease in right and left ventricular end-diastolic volumes. This seems primarily due to a PEEP-induced decrease in ventricular preload. These results are in accordance with those obtained by Fewell et al.7 in the dog using the same level of PEEP. The lack of correlation between RVEDVI/LVEDVI ratio and addition of PEEP seems to indicate that ventricular interference is not the major cause for decreased CO at this level of PEEP.

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