

Local and Global Function of the Right Ventricle in a Canine Model of Pulmonary Microembolism and Oleic Acid Edema: Influence of Ventilation with PEEP

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Right ventricular (RV) dysfunction may occur due to increased RV afterload and, hence, might also contribute to the decrease in cardiac output following institution of PEEP in patients with adult respiratory distress syndrome (ARDS). To test this hypothesis, the authors examined the influence of PEEP on local and global RV function in 12 anesthetized dogs with experimental ARDS (eARDS) induced by pulmonary microembolization with glass beads and oleic acid. Local RV function was analyzed in the RV inflow tract (RVIT) and RV outflow tract (RVOT) by assessing both diastolic segment length, systolic segment shortening, and segment work (sonomicrometry). Global RV contractility was quantified by measuring maximum rate of pressure rise ($dRVP/dt_{max}$) and maximum velocity of contractile element shortening (V_{max}). In eARDS, despite a fivefold increase in pulmonary vascular resistance, there was no change in cardiac index (CI), global RV contractility, RVIT and RVOT work, and RVIT shortening, whereas RVOT shortening decreased from 12.4 to 7.4% ($P < 0.01$). Diastolic segment length increased in RVIT ($P < 0.05$) but not in RVOT. PEEP of 10 cmH₂O did not alter global RV contractility, RVIT and RVOT shortening, and RVIT work but reduced RVOT work (-35%; $P < 0.01$) and CI (-11%; $P < 0.001$). Cardiac index further decreased during PEEP of 20 cmH₂O (-38%; $P < 0.001$), while global RV contractility remained intact despite decreased RVIT and RVOT shortening (-32% and -69%; $P < 0.05$) and work (-26% and -59%; $P < 0.01$) in the presence of reduced fiber preload in both regions. From these findings, it was concluded that 1) the decreased CI during mechanical ventilation with PEEP at constant right ventricular end-diastolic pressure (RVEDP) is not caused by depressed global RV contractility in dogs with eARDS and a normal myocardium prior to insult. Decreased diastolic segment length and segment shortening during PEEP suggest that 2) PEEP reduces stroke volume by the Starling mechanism rather than by ischemia of the RV free wall. Finally, regionally incongruent changes of fiber preload indicate that 3) local differences in RV wall compliance are likely to occur subsequent to eARDS and PEEP. (Key words: Heart, right ventricle; myocardial contractility. Lung, ARDS; PEEP. Measurement technique: sonomicrometry.)

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IN PATIENTS SUFFERING FROM the adult respiratory distress syndrome (ARDS), ventilation with PEEP usually reverses hypoxemia but may considerably depress cardiac output.¹ The mechanisms, however, contributing to low cardiac output during PEEP are not yet fully understood.²⁻⁴

While low levels of PEEP may predominantly decrease right ventricular (RV) preload by intrathoracic pressure rise and reduction of venous return,⁵ high levels of PEEP⁵⁻⁷ and ARDS⁸⁻¹¹ were found to predominantly increase RV afterload, thereby impeding RV ejection and increasing RV wall stress and O₂ consumption. Hence, it has been speculated that high levels of PEEP (similar to acute pulmonary hypertension¹²⁻¹⁴) might compromise cardiac output by causing global RV failure due to ischemia and dysfunction of the stressed RV free wall.^{2,15-17} However, a redistribution of myocardial blood flow in favor of the RV free wall has been found in pulmonary artery hypertension¹⁸⁻²⁰ and during PEEP,²¹⁻²⁴ making ischemia of the RV free wall unlikely.

In view of these contradictory results, we reexamined RV function during ventilation with PEEP in an experimental model of ARDS (eARDS) accentuated by high pulmonary vascular resistance. In our study, special interest was placed on the evaluation of *local* RV function as related to *global* RV contractility. We thereby aimed to answer the following questions: first, what are the effects of PEEP on local RV function and, do different regions within the RV free wall respond uniformly to the application of PEEP? Second, does PEEP impair global RV contractility, thereby acting as the mechanism for the reduction of cardiac output in patients with ARDS and in whom PEEP is used?

Methods and Materials

ANIMAL PREPARATION

Studies were performed in 12 foxhounds of either sex (20.2 ± 4.2 kg). All animals received humane care in compliance with National Institutes of Health guidelines,²⁵ and the institutional animal care and use committee approved this study.

After preanesthetic medication with propiomazine (1-1.5 mg/kg im), anesthesia was induced by intravenous (iv) injection of pentobarbital (20 mg/kg), piritramide

(0.75 mg/kg), and alcuronium (0.25 mg/kg) and maintained by infusion of pentobarbital ($5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). Additionally, an infusion of piritramide ($150 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) and alcuronium ($75 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) was started after termination of surgical preparation. For fluid loss replacement, Ringer's solution ($5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) was administered iv. A warming pad was used to keep core body temperature between 35.5 and 36.8° C. The trachea was intubated and the lungs mechanically ventilated at a rate of 12 cycles/min with a tidal volume (V_t) of 15–18 ml/kg using 100% O₂ (Siemens Servo™ C, Siemens-Elima, Solna, Sweden). The V_t was adjusted to obtain an initial arterial P_{CO₂} between 35 and 40 mmHg.

Fluid-filled catheters (PP270, Portex, Hyth, UK) were positioned in the descending aorta and superior vena cava via the left femoral artery and the right external jugular vein, respectively. A thermistor-tipped, flow-directed catheter (Swan-Ganz™, TD Cath. 93A-131-7F, Edwards, Anasco, Puerto Rico) was inserted into the pulmonary artery via the right external jugular vein. After a right thoracotomy (5th intercostal space) and pericardiotomy, prewarmed and precalibrated tip manometers (Millar Instruments, Houston, TX) were inserted into the RV via an atrial stab incision and into the left ventricle (LV) via the right carotid artery. For measurement of intrathoracic pressure (P_{th}), a tip manometer was fixed at the right atrial level of the pericardial surface. The tip of the catheter was held in a heparinized silicon tube to protect it from motion artifacts. The lumen of the tube communicated freely with the pleural cavity through multiple side holes.

For measurement of local RV contraction, two pairs of miniaturized (\varnothing 1.5–2 mm), piezoceramic ultrasonic transducers (provided by Dr. W. Heimisch, Deutsches Herzzentrum, Munich, FRG) were implanted in the long axis of the inflow tract (RVIT) and outflow tract (RVOT) of the RV free wall (fig. 1) according to the direction of

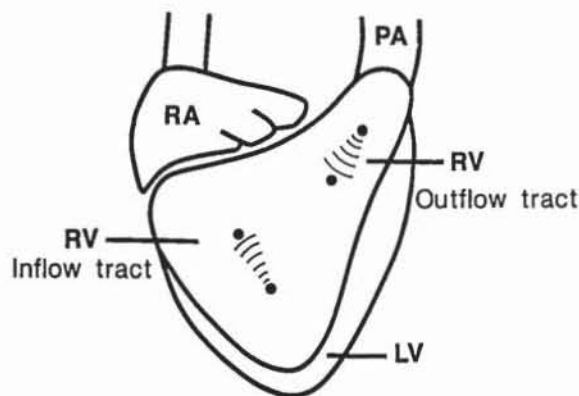


FIG. 1. Position of crystals. Sites of implantation of ultrasonic crystals in the RV free wall. RV = right ventricle; LV = left ventricle; RA = right atrium; PA = pulmonary artery.

main fiber shortening in both regions.^{26–28} The RVOT crystals were placed 20–25 mm proximal to the pulmonic valve. Each crystal was inserted via a stab incision. Subsequently, to prevent increased lung volume and lung weight during eARDS and PEEP from influencing the position of the sonomicrometers and the accuracy of the length measurements, crystals were secured with an epicardial purse-string suture. At the end of surgical preparation, the pericardium was closed by a running suture to avoid constraint to the myocardium. Thereafter, the chest was closed air tight, the lungs were reinflated, and any remaining air was removed by a chest drain. The correct localization of all crystals was confirmed at post-mortem inspection.

MEASUREMENTS

Hemodynamics

All measurements were performed with the dogs in the left lateral position. Mean aortic (AOP_{mea}) and pulmonary artery pressures (PAP_{mea}) were recorded (Hellige Servomed™, Freiburg, FRG) using Statham P23Db transducers (Gould-Statham, Oxnard, CA) referred to the right atrium. ECG, ventricular pressures, P_{th} , and sonomicrometric data were sampled every 4 ms, digitized in real time (A/D Converter C1000, Cosima Corp., Salem, OR), and stored for subsequent evaluation using a PDP 11/03 computer system. Data were analyzed with interactive software developed in our laboratory. All signals were evaluated at end-expiration using an average of three consecutive beats. In the RV, mean (RVP_{mea}), maximal (RVP_{max}), and end-diastolic pressures (RVEDP) were assessed.

The P_{th} was subtracted from the left and right ventricular, pulmonary arterial, and central venous pressures to obtain transmural pressures. The rate of RV pressure rise ($dRVP/dt$) was derived from the RV pressure curve by differentiation. Cardiac output was obtained in triplicate by the thermodilution technique (Cardiac Index Computer, model SP 1435, Gould-Statham, Oxnard, CA). The coefficient of variation of triplicate measurements averaged 3.4%, 2.9%, 2.9%, and 3.6% at control, eARDS, PEEP of 10 cmH₂O (P_{10}), and PEEP of 20 cmH₂O (P_{20}), respectively.

The following parameters were calculated:

$$CI = 10 \cdot CO \cdot BW^{-0.75} \text{ (according to Holt } et al.^{29})$$

$$SI = CI \cdot 1,000 \cdot HR^{-1}$$

$$PVR = (PAP_{mea} - LVEDP) \cdot 79.9 \cdot CO^{-1}$$

$$RCDP = AOP_{mea} - RVP_{mea}$$

$$TTI_{RV} = F_{sys} \cdot T_{sys} \cdot HR$$

where CI = cardiac index, CO = cardiac output, BW = body weight, SI = stroke index, HR = heart rate, PVR = pulmonary vascular resistance, LVEDP = LV end-diastolic pressure, AOP_{dia} = diastolic aortic pressure, RCDP = right coronary driving pressure, TTI_{RV} = RV tension-time index, F_{sys} = area beneath the systolic RV pressure curve, and T_{sys} = systolic ejection period.

As parameters of global RV contractility, the maximal rate of pressure rise (dRVP/dt_{max}) and the maximal velocity of contractile element shortening (V_{max}) were assessed. The V_{max} was obtained by linear extrapolation ($r > 0.9$) of the calculated velocity of shortening of contractile elements in the isovolumetric phase.^{30,31}

Lung Function

Arterial and mixed venous blood were analyzed for P_{O₂}, P_{CO₂}, and pH (ABL3, Radiometer, Copenhagen, Denmark). Effective pulmonary compliance (C_{eff}) and expiratory resistance (R_{exp}) were assessed by a Lung Mechanics Calculator 940 (Siemens-Elema) connected to the respirator. Intrapulmonary shunt (\dot{Q}_s/\dot{Q}_T) was calculated as

$$\dot{Q}_s/\dot{Q}_T = (Cc_{O_2} - Ca_{O_2}) / (Cc_{O_2} - Cv_{O_2})$$

where $Cc_{O_2} = Hb \cdot 1.39 + 0.0031 \cdot (P_B - 47 - Pa_{CO_2})$; Cc_{O₂}, Ca_{O₂}, and Cv_{O₂} are O₂ contents in ideal (100% saturated) pulmonary capillary, systemic arterial, and mixed venous blood, respectively; P_B is barometric pressure; and Pa_{O₂} and Pa_{CO₂} are arterial P_{O₂} and P_{CO₂}, respectively.

Sonomicrometry

Myocardial segment lengths were measured at end-diastole (L_{dia}) and end-systole (L_{sys}). End-diastole was defined as the beginning of the upstroke of dRVP/dt and end-systole as the point of maximal negative dRVP/dt.³² In addition, maximum and minimum segment lengths (L_{max} and L_{min}) were determined. All values for length were normalized by assuming L_{dia} at control to be 10 mm. To quantify the pattern of local segmental motion, the percentage of systolic fiber shortening (S_{sys}) and proto-systolic elongation (E_{sys}) were defined as follows:

$$S_{sys}(\%) = (L_{dia} - L_{sys}) \cdot 100 / L_{dia}$$

$$E_{sys}(\%) = (L_{max} - L_{dia}) \cdot 100 / L_{dia}$$

Additionally, pressure-length loops (PL-loops) were constructed in each experiment by plotting phasic changes of segment length against phasic changes of RV pressure during one cardiac cycle by computer. The PL-loop area of each segment reflects the mechanical work carried out by the segment under consideration³³ and was determined (in units of mmHg · mm) from paper images of the mon-

itor screen using a digital planimeter. Active systolic shortening causes the loops to rotate in a counterclockwise direction. If paradoxical systolic segment elongation (= E_{sys}, clockwise rotation of loops) occurred, this was assigned a negative loop area value and was subtracted from total loop area to obtain an estimate of effective segmental work.³³

EXPERIMENTAL PROTOCOL

After surgery, the animals were isovolemically hemo diluted with 6% dextran 60 (Makrodex® 6%, Schiwa, Glandorf, FRG) to a hematocrit of 30% to achieve identical baseline values of hematocrit and hemoglobin concentration in all animals. The removed blood (9.7 ± 2.3 ml/kg) was used for transfusion during PEEP and for replacement of blood samples taken for laboratory analyses. Hematocrit and hemoglobin did not change throughout observation time.

Following a stabilization period of 30 min, control measurements were performed. Thereafter, the lungs were embolized by injection of a single dose of oleic acid (0.01 ml/kg) into the right atrium followed by repetitive doses of nonsiliconized glass beads (Ø 100 µm; 0.5 to 1 g every 3–5 min, total of 0.5 ± 0.1 g/kg) suspended and thoroughly mixed in 1 or 2 ml of 6% dextran 60. Embolization was terminated when PAP_{mea} had reached a peak level of 35–40 mmHg. These procedures resulted in a standardized model of eARDS accompanied by pulmonary hypertension.³⁴ In this model, PAP decreased to 30 mmHg within 70 min after the last application of glass beads but then (similar to other cardiorespiratory variables) showed no further change for at least 80 min.³⁴ The second set of measurements (eARDS) therefore was obtained 70 min after embolization.

PEEP was then increased to 10 and 20 cmH₂O. At each level of PEEP, the transmural RVEDP was kept constant by transfusion of autologous blood; 10 minutes after transfusion, the third (P₁₀) and fourth set of measurements (P₂₀) were performed.

STATISTICAL ANALYSES

Data are reported as mean ± SD when normally distributed (hemodynamics and lung function), but otherwise (sonomicrometry), the median and Q₁/Q₃ quartiles are listed. Statistical analysis was performed using a repeated measures analysis of variance (rANOVA). If the *F* value was significant ($P < 0.05$), the following time points were compared by Bonferroni's paired *t* test (hemodynamics and lung function) or by Wilcoxon's signed rank test (sonomicrometry): eARDS versus control, P₁₀ versus eARDS, P₂₀ versus P₁₀, and P₂₀ versus eARDS. Differences were considered significant for $P < 0.05$.

TABLE 1. Effects of eARDS and PEEP on Lung Mechanics, Gas Exchange, and Intrathoracic Pressure

Variables	Control	eARDS	P ₁₀	P ₂₀
Lung mechanics				
C _{eff} (ml/cmH ₂ O)	38 ± 6	31 ± 5**	40 ± 5***	27 ± 7***
R _{exp} (cmH ₂ O · s · l ⁻¹)	10.7 ± 0.9	13.2 ± 2.3**	12.0 ± 1.9*	16.0 ± 2.6***††
Gas exchange				
Pa _{O₂} (mmHg)	562 ± 44	378 ± 127***	490 ± 81**	589 ± 43***†††
Q _s /Q _T (%)	9 ± 4	20 ± 8***	11 ± 4***	4 ± 3***†††
Intrathoracic pressure				
P _{th} (mmHg)	-3.4 ± 1.2	-2.1 ± 1.1**	0.7 ± 1.2***	3.5 ± 1.5***†††

Mean ± SD; n = 12.

The following comparisons were made: eARDS and control; P₁₀ and eARDS; P₂₀ and P₁₀ (*P < 0.05, **P < 0.01, ***P < 0.001); and P₂₀ and eARDS (††P < 0.01, ††† < 0.001).

C_{eff} = effective pulmonary compliance; R_{exp} = expiratory resistance; Pa_{O₂} = partial pressure of oxygen, Q_s/Q_T = intrapulmonary shunt; P_{th} = intrathoracic pressure.

Results

LUNG FUNCTION AND INTRATHORACIC PRESSURE

The effects of eARDS and PEEP on lung function and intrathoracic pressure are shown in table 1.

eARDS

Experimental ARDS caused a significant 18% reduction in effective pulmonary compliance (C_{eff}; P < 0.01) that was paralleled by an 23% increase in expiratory pulmonary resistance (R_{exp}; P < 0.01). Pa_{O₂} decreased from 562–378 mmHg (P < 0.001), and intrapulmonary shunt (Q_s/Q_T) more than doubled (P < 0.001). Intrathoracic pressure (P_{th}) rose by 1.3 mmHg (P < 0.01).

PEEP

At P₁₀, C_{eff} and Pa_{O₂} increased (P < 0.01), whereas R_{exp} and Q_s/Q_T decreased significantly. PEEP at 20

cmH₂O restored Pa_{O₂} and Q_s/Q_T to control levels but worsened C_{eff} and R_{exp} (P < 0.001) as compared to P₁₀. Intrathoracic pressure significantly increased by 2.8 mmHg at each level of PEEP.

CENTRAL HEMODYNAMICS AND GLOBAL RV FUNCTION

The effects of eARDS and PEEP on central hemodynamics and global RV function are shown in table 2.

eARDS

Experimental ARDS was characterized by an increase in PAP_{mea} from 14–29 mmHg and a fivefold increase in pulmonary vascular resistance (PVR; P < 0.001). Despite a significant 25% decrease in SI, CI and AOP_{mea} remained unchanged due to tachycardia. In the RV, eARDS was accompanied by an increased RVP_{mea} and RVP_{max} (P < 0.001) without a change in RV filling pressure

TABLE 2. Effects of eARDS and PEEP on Central Hemodynamics, Right Ventricular Hemodynamics, and Global Right Ventricular Contractility

Variables	Control	eARDS	P ₁₀	P ₂₀
Central hemodynamics				
HR (beats per min)	105 ± 27	126 ± 17*	137 ± 19**	140 ± 15†
AOP _{mea} (mmHg)	106 ± 15	100 ± 14	97 ± 14	76 ± 13***†††
CI (l · min ⁻¹ · kg ^{-0.75})	4.0 ± 0.6	3.7 ± 0.5	3.3 ± 0.6***	2.2 ± 0.5***†††
SI (ml/kg ^{0.75})	39 ± 9	30 ± 7***	25 ± 6***	16 ± 4***†††
PAP _{mea} (mmHg)	14 ± 3	29 ± 5***	29 ± 5	30 ± 5
PVR (dyn · s · cm ⁻⁵)	111 ± 57	539 ± 167***	645 ± 202**	1114 ± 360***†††
RV hemodynamics				
RVP _{max} (mmHg)	27 ± 4	37 ± 6***	37 ± 6	35 ± 5
RVP _{mea} (mmHg)	12 ± 3	19 ± 5***	19 ± 5	18 ± 5
RVEDP (mmHg)	7.3 ± 3.1	7.4 ± 3.0	6.3 ± 2.9	6.6 ± 2.9
RCDP (mmHg)	99 ± 15	83 ± 16**	77 ± 15	53 ± 12***†††
TTI _{RV} (mmHg · s · min ⁻¹)	914 ± 181	1674 ± 397***	2061 ± 1053	2079 ± 827
Global RV contractility				
dRVP/dt _{max} (mmHg/s)	425 ± 81	551 ± 114*	559 ± 115	494 ± 157
V _{max} (ML/s)	1.46 ± 0.32	1.60 ± 0.43	1.67 ± 0.45	1.53 ± 0.37

Mean ± SD; n = 12.

The following comparisons were made: eARDS and control; P₁₀

and eARDS; P₂₀ and P₁₀ (*P < 0.05, **P < 0.01, ***P < 0.001); and P₂₀ and eARDS (†††P < 0.001).

(RVEDP). Right coronary driving pressure (RCDP) decreased from 99–83 mmHg ($P < 0.01$), and TTI_{RV} nearly doubled ($P < 0.001$). However, global RV contractility was not compromised since V_{max} remained unchanged and the maximal rate of RV pressure rise ($dRVP/dt_{max}$) even increased ($P < 0.05$).

PEEP

During PEEP, RVEDP was kept constant by transfusion of 3.7 ± 1.9 ml/kg (P_{10}) and an additional 6.1 ± 2.0 ml/kg (P_{20}) of autologous blood. Compared to eARDS without PEEP, P_{10} caused a slight but significant reduction of CI (-11% ; $P < 0.001$) and SI (-17% ; $P < 0.001$) and caused a 9% increase in HR ($P < 0.01$), a 20% increase in PVR ($P < 0.001$), and no change in AOP_{mea} . Right ventricular hemodynamics and RV global contractility were not influenced by P_{10} .

At P_{20} , PVR more than doubled as compared to eARDS ($P < 0.001$), while AOP_{mea} , CI, and SI decreased by 24%, 40%, and 47%, respectively ($P < 0.001$). Heart rate increased by 11% ($P < 0.05$). Right ventricular pressures, TTI_{RV} , and global RV contractility were not changed significantly by P_{20} , whereas RCDP decreased to 53 mmHg ($P < 0.001$).

LOCAL RV FUNCTION

eARDS

In the RVIT, L_{dia} and L_{sys} equivalently increased subsequent to eARDS ($P < 0.05$; fig. 2); hence, systolic seg-

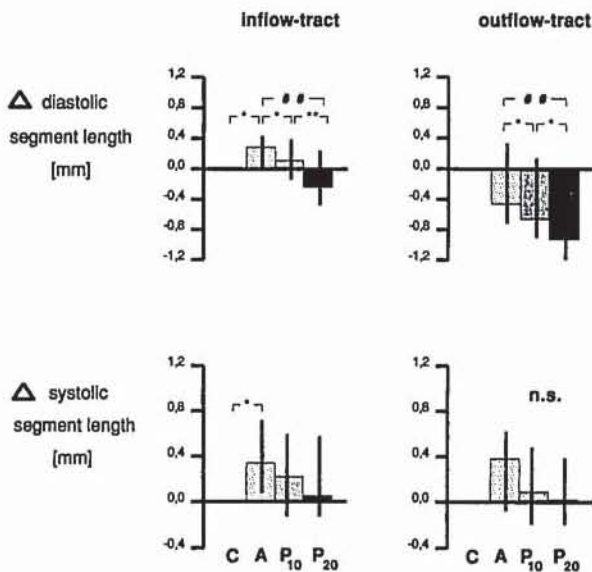


FIG. 2. Effects of eARDS and PEEP on RV segment lengths. Changes of end-diastolic and end-systolic segment lengths at eARDS (A), PEEP 10 and 20 cm H₂O (P_{10} , P_{20}) as compared to control (C) values. Data are median and Q1/Q3 quartiles; $n = 12$. (For statistics see table 1.)

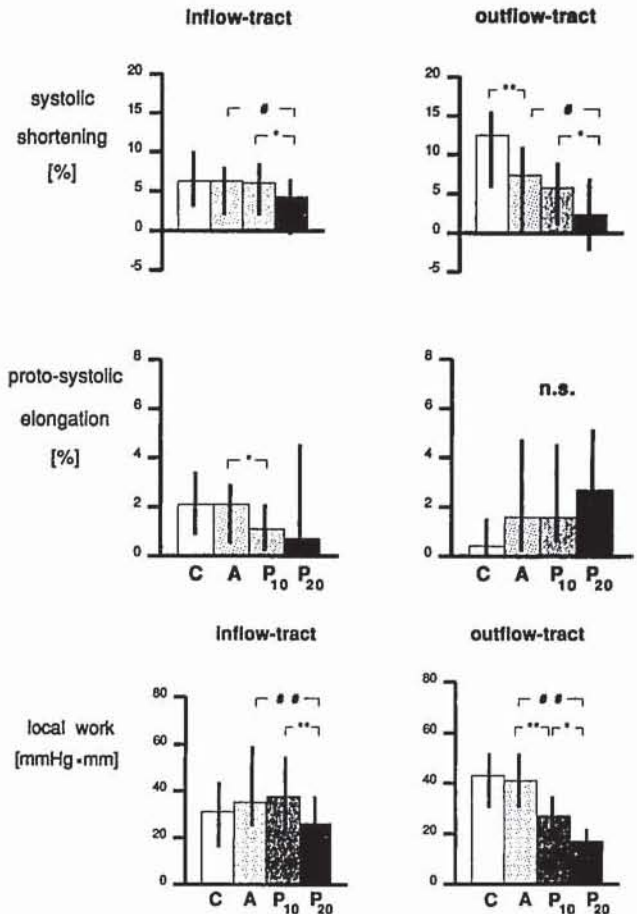


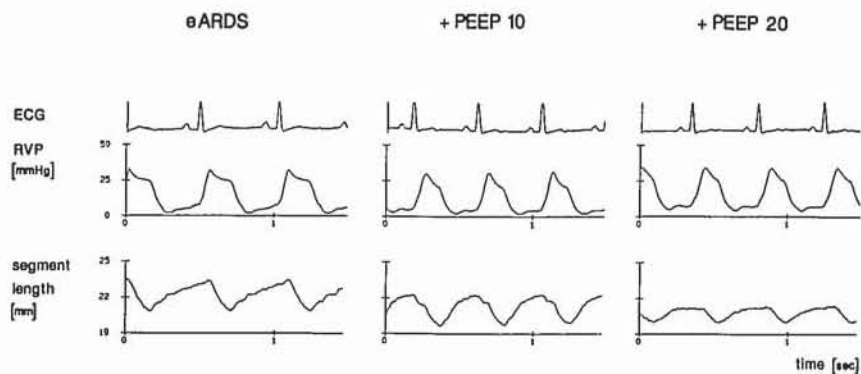
FIG. 3. Effects of eARDS and PEEP on RV segment shortening and local segmental work. C = control; A = eARDS; P_{10} = change at PEEP 10 cm H₂O; P_{20} = change at PEEP 20 cm H₂O. Data are median and Q₁/Q₃ quartiles, $n = 12$ (for statistics see table 1).

ment shortening (S_{sys}) remained unchanged (fig. 3). In contrast, S_{sys} decreased by 40% in RVOT ($P < 0.01$). Protosystolic segment elongation (E_{sys}) and local segmental work were not significantly affected by eARDS either in the RVIT or RVOT (fig. 3).

PEEP

Figure 4 shows an original tracing of phasic RV pressure and local RVIT contraction at eARDS, P_{10} , and P_{20} . While segment shortening was unchanged at P_{10} , it was severely reduced at P_{20} . Nevertheless, maximal developed RV pressure was well maintained. RV pressure-lengths loops obtained during eARDS and P_{20} in both the RVIT and RVOT are depicted in figure 5. The loops demonstrate that RVP_{max} was not affected by P_{20} although segment shortening and local segmental work declined by $\approx 40\%$ in both regions. Furthermore, the leftward shift of the loops indicates that L_{dia} , *i.e.*, local RV preload, decreased upon PEEP despite the constancy of RVEDP.

FIG. 4. Effects of PEEP on RV pressure and RV segment shortening (single experiment). Original recording of phasic RV pressure (RVP) and local RV segment length (inflow tract) during eARDS and after PEEP ventilation. Application of PEEP 20 cmH₂O, but not PEEP 10 cmH₂O, considerably reduced the amplitude of local segment shortening without affecting RV developed pressure.



The influence of PEEP on local RV segment lengths, segment shortening, and local segment work is summarized in figures 2 and 3. At P₁₀, L_{dia} and L_{sys} tended to decline in both regions of the RV free wall. In RVIT, this resulted in no change of S_{sys} and local work as compared to eARDS without PEEP. In RVOT, in contrast, a significant 35% reduction ($P < 0.01$) of local segment work was observed. Systolic segment shortening dropped from 7.4–5.8%; however, the difference was not statistically significant.

At P₂₀, L_{dia} decreased to a greater extent than L_{sys}, resulting in a substantial decline of S_{sys} in both RVIT (–32%; $P < 0.05$) and RVOT (–69%; $P < 0.05$) as compared to eARDS. Simultaneously, segmental work was reduced by 26% in the RVIT ($P < 0.01$) and 59% in the RVOT ($P < 0.01$). Protosystolic segment elongation was not significantly altered by P₂₀. Note that the drop of L_{dia}, S_{sys}, and local work was much more pronounced in RVOT than in RVIT.

Discussion

In general, a severe increase of RV pressures is needed to induce RV ischemia.^{12–14} During PEEP, however, RV ischemia has been suggested to occur at lower RV pressures, because both extracardiac compression and reflex stimulation of lung receptors, in addition to increased RV cavitory pressure and decreased RV driving pressure, may impede RV coronary blood flow in this situation.^{15,21,24,35,36}

However, whether ischemia, and consequently dysfunction, of the RV free wall, in fact, may contribute to the PEEP-induced depression of cardiac output in ARDS patients is still controversial.² Although numerous studies have addressed this topic by quantifying RV perfusion during PEEP,^{21–24,36–38} it remains unknown to what extent RV oxygen availability has met actual RV oxygen demand in these experiments.

As a new approach to this problem, we investigated local RV function and its relation to global RV contractility. Impaired fiber contraction is the final correlate of myocardial dysfunction and has been shown to reliably reflect myocardial ischemia in the RV.^{39,40} Currently, no study exists measuring the functional state of the RV free wall during ventilation with PEEP in a lung injury model.

EXPERIMENTAL MODEL

Our experimental model was designed to closely mimic the clinical setting of patients suffering from ARDS. Con-

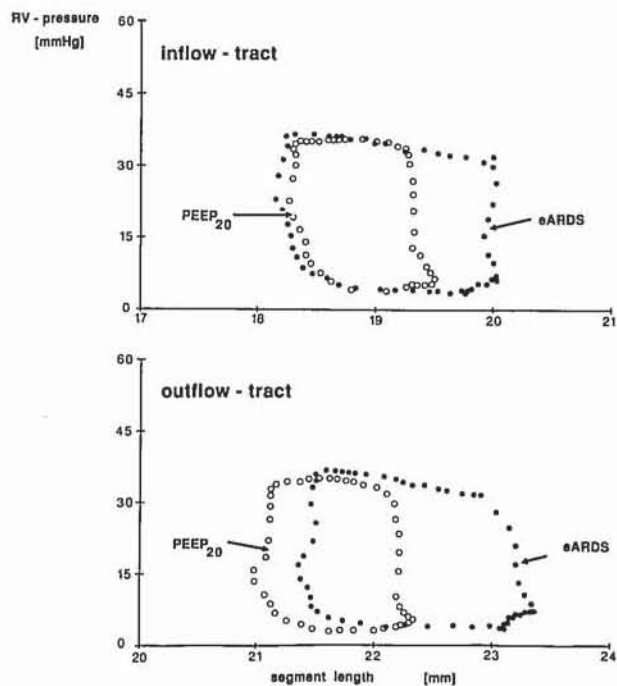


FIG. 5. RV pressure–length loops (single experiment). RV pressure–length loops from the inflow and outflow tract have been constructed at eARDS and during ventilation with PEEP 20 cmH₂O. The area within a loop is an estimate of local segment work. The loops indicate that segmental work has been reduced by PEEP 20 cmH₂O in both regions of the RV free wall.

sequently, all measurements were performed in dogs with closed pericardium and chest to rule out the side-effects of thoracotomy and pericardotomy on cardiac function. The deterioration of lung mechanics and gas exchange subsequent to pulmonary microembolization indicates the development of an ARDS-like syndrome close to that described previously.³⁴ The additional increase of PVR and PAP was intended to imitate ARDS complicated by acute pulmonary hypertension. In our model, PAP was ≈ 30 mmHg before the onset of PEEP and, hence, was similar to the PAP commonly seen in ARDS patients.⁸⁻¹¹

However, several differences between our experimental model and the clinical setting are obvious. Most patients with ARDS are not anesthetized and are not within a few hours of thoracotomy. Yet, the onset of ARDS often coincides with a trauma requiring major surgery or with other risk factors closely related to surgery. Furthermore, patients whose lungs are mechanically ventilated in the acute phase of respiratory failure most often are sedated, usually are provided with analgesia, and occasionally require paralysis. Therefore, the presence of anesthesia and surgery in our model probably did not substantially depart from the clinical setting.

Despite the lack of a time-based control, a deterioration of our animal preparation over time seems unlikely for several reasons. First, before the current experiments, we monitored the stability of our model using exactly the same regimen with respect to anesthesia, induction of eARDS, and surgery. We found that 30–70 min after pulmonary embolization, cardiorespiratory variables stabilized with no or only minimal change during the following 80 min.³⁴ No more than 80 min were needed in the current experiments to perform the measurements during PEEP. Second, hemodynamics were also obtained after removal of P_{20} in nine of 12 animals of the current study, and global cardiac performance and RV function were not significantly different from data obtained during eARDS before the onset of PEEP.[†] Third, in three pilot experiments, local RV free wall function did not change for up to 120 min after induction of eARDS.^{**} Finally, it was previously demonstrated in dogs that prolonged anesthesia, mechanical ventilation, and extensive surgery do not impair cardiorespiratory stability.⁴¹

Although our preparation probably did not deteriorate

[†] Data after removal of the PEEP of 20 cmH₂O (mean \pm SD; $n = 9$): CI $3.6 \pm 0.611 \cdot \text{min}^{-1} \cdot \text{kg}^{-0.75}$ (NS as compared to eARDS), RVP_{max} 34 ± 6 mmHg (NS); $dRVP/dt_{\text{max}}$ 449 ± 70 mmHg/s (NS), V_{max} 1.33 ± 0.17 ml/s (NS). Data not published elsewhere.

^{**} Mean systolic segment shortening in the three experiments was $6.0 \pm 3.5\%$ (RVIT) and $4.6 \pm 2.2\%$ (RVOT) at eARDS, and was $7.2 \pm 3.0\%$ (RVIT) and $5.0 \pm 3.1\%$ (RVOT) 120 min later. Data not published elsewhere.

over time, we cannot exclude that thoracotomy altered the baseline conditions in our study, *e.g.*, by decreasing overall cardiac performance.⁴² Thoracotomy, therefore, might have influenced the data of RV local and global function with respect to their absolute magnitude. However, thoracotomy is not suspected to have altered the relative changes of these variables during eARDS and PEEP. Since the amount of blood needed to maintain RVEDP at P_{20} was almost twice that needed at P_{10} , we cannot exclude that PEEP may have resulted in a progressive shift of volume into the lungs,^{43,44} thereby possibly influencing the hemodynamic stability of our model. Without doubt, this aspect is crucial in studies where the overall cost–benefit ratio of PEEP or long-term effects of PEEP are analyzed. The current experiments, however, were performed to determine the acute effect of PEEP on RV local and global function at a constant RVEDP. Since RVEDP was maintained at the very moment when measurements of RV function were performed, a gradual shift of fluid into the “leaky” lungs should not have influenced our results.

GLOBAL RV FUNCTION

As a major finding, the current study demonstrates that ventilation with PEEP up to 20 cmH₂O does not compromise global RV contractility in the dog, even if PEEP is applied in the presence of eARDS and high pulmonary artery pressure. This conclusion is based on the evaluation of both the $dRVP/dt_{\text{max}}$ and the V_{max} used as parameters of global RV contractility.

Maximal rate of ventricular pressure rise is known to sensitively measure relative changes in contractile state of both the LV and RV.⁴⁵ Our experiments revealed a 29% increase of $dRVP/dt_{\text{max}}$ at eARDS and no further change at P_{10} and P_{20} . Yet, since $dRVP/dt_{\text{max}}$ is susceptible to changes in ventricular loading conditions⁴⁶ and HR,⁴⁷⁻⁴⁹ it may overestimate ventricular contractility if preload, afterload, or HR are increased.^{45,47-50} Accordingly, the increase of $dRVP/dt_{\text{max}}$ at eARDS most likely is explained by the rise of PAP and HR at that time and probably does not reflect a true increase of global RV contractility. During PEEP, PAP_{mea} remained unchanged, while HR increased moderately (by 10 and 14 beats per min at P_{10} and P_{20} , respectively). At a constant RV preload, this increase in HR would have increased $dRVP/dt_{\text{max}}$ by $\approx 10\%$.^{48,49} The reduction of L_{dia} at P_{10} and P_{20} indicates, however, that, despite unchanged RVEDP, there actually was a decrease in effective RV preload in our experiments. A decrease in RV preload, however, is known to reduce $dRVP/dt_{\text{max}}$ ⁴⁶ and may completely offset the inotropic effects of tachycardia.⁴⁷ Hence, it seems most unlikely from our data that $dRVP/dt_{\text{max}}$ has been over-

estimated during PEEP ventilation due to changes in RV preload, afterload, or HR.

Unlike $dRVP/dt_{max}$, V_{max} (or its correlate $dRVP/dt:P$, the quotient of $dRVP/dt$ to developed RV pressure) has been shown to be relatively independent from changes of preload, afterload, and HR.^{30,45,47} Although load independency has been challenged⁵¹ and the ability of V_{max} to estimate interindividual differences in contractile state has been considered poor,⁵² V_{max} still represents an adequate parameter to assess intraindividual changes in contractility in both the LV and RV.⁵³⁻⁵⁵

In our experiments, V_{max} did not significantly change with eARDS or PEEP. While the latter finding is in accordance with the data for $dRVP/dt_{max}$, the discrepant behavior of V_{max} and $dRVP/dt_{max}$ in eARDS presumably originates from differences between these parameters with respect to their load dependency. Since V_{max} is affected less than is $dRVP/dt_{max}$ by an elevation of afterload (see above), the unchanged V_{max} at eARDS (despite elevation of $dRVP/dt_{max}$) strongly suggests unchanged global RV contractility at that time.

Our finding of an intact RV global contractility during PEEP contrasts with earlier studies that have suggested a PEEP-induced impairment of RV performance.^{15,44,56-58} It should be noted that in these studies transmural RVEDP was calculated using either pleural or esophageal pressure, both of which have been shown to underestimate the true juxtacardiac pressure and thereby RV and LV performance.^{59,60} More recently, a nonlinear systolic pressure-volume (PV) relationship during PEEP was interpreted as a decrease in global RV contractility.¹⁷ Since multiple measurements at different ventricular loading conditions were not performed, it remains questionable whether PEEP, in fact, deteriorated RV contractility in these experiments.

In contrast, an unchanged or increased RV function during PEEP was observed in various experimental and clinical studies.^{1,3,22,59,61-63} In agreement with these studies, our data indicate that PEEP may be applied to a normal myocardium before insult without compromising global RV contractility, even when RV driving pressure decreases and RV afterload is additionally increased by an ARDS-like syndrome. As pointed out recently,¹⁷ however, the influence of PEEP on the preinjured RV myocardium may be different and remains to be clarified.

LOCAL RV FUNCTION

Fiber Preload

Our finding of a decrease in L_{dia} in both the RVIT and RVOT at unchanged RVEDP during PEEP indicates a decrease of RV diastolic compliance and is compatible

with a reduction of RV filling due to increased P_{th} . In contrast to studies demonstrating unchanged or increased RV volume during PEEP,^{7,16,17,64,65} our results, which are similar to those of others,^{17,22,44,61,66,67} suggest that PEEP up to 20 cmH₂O does not cause RV dilatation, even if PVR is increased by lung injury. Consequently, and contrary to our working hypothesis, it may be concluded that RV wall stress is not increased by RV enlargement during PEEP; hence, RV ischemia, if present at all, does not originate from an increase of O₂ demand due to Laplace's law.

Our data provide the first evidence that changes of fiber preload during eARDS and PEEP may be regionally nonuniform: during eARDS, L_{dia} was elevated in the RVIT but tended to decrease in the RVOT, and during PEEP, L_{sys} decreased in both regions, with the final decrease in the RVOT, however, by far exceeding that in the RVIT.

Care has to be taken when diastolic segment lengths are interpreted in terms of local preload because a single pair of crystals (due to nonuniform fiber direction in the RV free wall⁶⁸) cannot simultaneously and accurately reflect the length of all myocardial fibers in a given region. However, since we positioned our crystals along the main axis of fiber shortening in both the RVIT and RVOT,²⁶⁻²⁸ we assume that L_{dia} as measured in the current study represents local preload of the majority of functionally active myocardial fibers. Even if we did not measure segment lengths within the main vector of fibers under all circumstances, positioning of the crystals in the circumferential direction most likely would not have changed our results.²⁷

Currently, we only can speculate on the mechanism(s) responsible for regional discrepant changes in RV wall compliance. First, RVIT and RVOT are anatomically divisible regions, with the outflow tract representing a functionally independent entity.⁶⁹ It has been suggested that in RV hypertension, the RVOT (due to predominant sympathetic innervation⁷⁰) may increase its diastolic fiber force⁷⁰ and reduce its width,⁷⁰ thereby acting as a resistive element and preventing high pressures generated in the RV sinus from affecting the pressure-sensitive pulmonary vasculature.⁷¹ The above mechanism might, in part, explain why end-diastolic segment length in RVIT, but not RVOT, increased subsequent to induction of eARDS, or why the final reduction of RVOT fiber length exceeded that of RVIT fibers during PEEP.

Second, in the RVIT, the correlation between sarcomere length and filling pressure has been shown to be considerably narrower and more reproducible than in the RVOT.⁷² Hence, changes in local intraventricular pressure may have affected diastolic lengthening of the RVIT and RVOT fibers differently.

Third, apart from increasing P_{th} , high lung volume during PEEP may result in direct mechanical cardiopulmonary interaction.^{66,73} One could imagine that regional differences in local compressive force exerted by the lungs on the RV free wall may have altered RV geometry and thereby also have been, in part, responsible for regionally nonuniform changes in local fiber preload during eARDS and PEEP.

Recently, a dissociation between fiber dimensions and global RV chamber events was observed by others,⁷⁴⁻⁷⁶ suggesting that, in the RV, fiber preload may be independent from chamber volume.⁷⁷ Accordingly, our finding of regionally different changes of RV wall compliance during eARDS and PEEP questions the validity not only of RVEDP but also of RV end-diastolic volume as an overall estimate of the functional state of RV fibers under these circumstances.

Fiber Shortening and Local Work

In the current study, P_{20} was shown to decrease systolic RV fiber shortening (S_{sys}) and local segment work. Whether this decrease of S_{sys} actually represents a deterioration of local wall function is difficult to determine, since resting fiber length was also reduced in our experiments (see above). Hence, the fall of S_{sys} at P_{20} might be caused by a leftward shift of the RV function curve in the Starling diagram, with no impairment of local contractility. This view is supported by the fact that preload reduction and the decrease of S_{sys} were most pronounced in the RVOT, while less preload reduction was paralleled by less decrease of S_{sys} in the RVIT.

Yet, fiber shortening was found to decrease at a right coronary perfusion pressure of ≈ 60 mmHg when peak RV pressure was high.³⁹ Accordingly, the fall of RCDP to 53 mmHg at P_{20} and a high RV oxygen demand (increase of RV pressures, TTI_{RV} , and PVR) might have resulted in ischemia of the RV free wall^{2,15,16,63} and impaired local wall function. However, paradoxical segment elongation in the protosystole, which was shown to be a marker of regional myocardial ischemia,⁷⁸ did not significantly increase subsequent to PEEP in our experiments. Hence, coronary vasodilatation presumably has compensated for the increased O_2 demands⁷⁹ and ischemia-induced worsening of local RV contractility probably did not occur during PEEP.

It therefore seems likely that a decrease of fiber preload was the primary mechanism for the decrease in RV wall motion in our experiments. In agreement with others,^{4,66} we therefore conclude that PEEP decreased cardiac output mainly by the Starling mechanism with no deleterious effect on either local or global RV contractility.

Since the calculation of percentage of systolic segment

shortening is based on the actual L_{dia} and thereby, to a certain extent, corrects for changes in fiber preload (*e.g.*, at increased L_{dia} , a higher absolute amplitude of contraction is needed to maintain the same level of S_{sys} , and *vice versa*), the reduction of S_{sys} in our experiments represents an overproportionate decrease of absolute fiber shortening and therefore might indicate deterioration of local contractility. Furthermore, it is uncertain, whether the Starling mechanism may fully account for a 32% (RVIT) and 69% (RVOT) decrease of S_{sys} during PEEP in the presence of a relatively small decrease in resting fiber length (fig. 2).

Although we are not able, in the absence of local ischemia, to clearly identify a mechanism other than reduced fiber preload to explain reduced wall motion, for the above reasons we cannot definitely exclude the fact that local RV contractility was compromised during eARDS and PEEP. If this latter case were true, structures other than the RV free wall (*e.g.*, the ventricular septum or the LV free wall) must have been effective to maintain RV global contractility under these circumstances.

LIMITATIONS OF THE CURRENT STUDY

Several limitations of the current study have to be considered. First, our data do not allow us to assess the contribution of lung injury to the effects of PEEP on RV function. Since both a normal⁴⁴ and decreased^{73,80} transmission of airway pressure to the heart has been observed as a result of decreased lung and microvascular compliance, both a protective or no effect of lung injury may have been present with respect to the cardiovascular side-effects of PEEP.

Second, segment lengths were measured at only two locations, which may not have been representative for the entire RV free wall. Recently, however, fiber shortening as obtained from only one segment of the RV free wall was shown to reliably reflect local events (*e.g.*, ischemia) within the RV free wall.^{39,40}

Third, geometric rearrangements of myocardial fibers within the different layers of the RV free wall (*e.g.*, due to changes in loading conditions) could have altered the main vector of fiber direction within an experiment and thereby could have affected RV fiber shortening during PEEP. However, this effect has been shown to be of negligible magnitude²⁶ and should not systematically, but rather randomly, have influenced our results.

Fourth, to avoid problems regarding the interpretation of V_{max} and $dRVP/dt_{max}$ at changing loading conditions and HR, it would have been desirable to examine the end-systolic pressure-volume relationship as a measure of contractility. However, the assessment of pressure-volume curves in the RV is critical due to the difficulty

in accurately measuring instantaneous volume in the irregular RV chamber.⁸¹ Recently, changes of single myocardial segments were suggested to accurately reflect RV volume^{32,82}; however, divergent findings were obtained by others.⁷⁴⁻⁷⁶ Hence, no satisfactory and technically applicable way of measuring instantaneous RV volume is currently available to allow us to examine pressure-volume curves.

Finally, it could be expected that RV diastolic compliance might change with lung inflation; therefore, we possibly should have kept RV diastolic volume, rather than RV diastolic pressure, constant (*e.g.*, measured by the thermodilution technique). However, in the RV, not only RVEDP but also RV filling may fail to reflect true RV preload.^{74,77} Furthermore, we anticipated that it would be difficult, if possible at all, to titrate a constant RVEDV during PEEP due to considerable inter-measurement variability inherent in the thermodilution technique and due to practical limitations with respect to the frequency of measurements. For the above reasons, we preferred to use transmural RVEDP as a measure of global RV preload while noting the problems inherent to this variable.

In an animal model closely emulating human ARDS, we showed that ventilation with up to 20 cmH₂O PEEP does not impair global RV contractility; hence, the decrease of cardiac output during PEEP cannot be attributed to global RV ischemia. Decreased RV fiber preload and fiber shortening suggest that PEEP reduced stroke volume by the Starling mechanism. Although not definitely excluded, local ischemia of the RV free wall probably did not occur during PEEP. Finally, regional differences in RV wall compliance observed during eARDS and PEEP question the validity not only of RV filling pressure but also of RV filling volume in estimating true fiber preload under these circumstances.

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