Volume Loading Reduces Pulmonary Vascular Resistance in Ventilated Animals with Acute Lung Injury: Evaluation of RV Afterload

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Abstract

During mechanical ventilation, increased pulmonary vascular resistance (PVR) may decrease RV performance. We hypothesized that volume loading, by reducing PVR, and therefore RV afterload, can limit this effect. Deep anesthesia was induced in 16 mongrel dogs (8 oleic acid-induced acute lung injury and 8 controls). We measured ventricular pressures, dimensions and stroke volumes during positive end-expiratory pressures (PEEP) of 0, 6, 12 and 18 cmH₂O at 3 LV end-diastolic pressures [(P_LVED) 5, 12 and 18 mmHg]. Oleic acid infusion (0.07 ml/kg) increased PVR and reduced respiratory system compliance (P <0.05). With PEEP, PVR was greater at a lower P_LVED. Increased PVR was associated with a decreased transseptal pressure gradient (TSG), suggesting that leftward septal shift contributed to decreased LV preload in addition to that caused by external constraint. Volume loading reduced PVR; this was associated with improved RV output and an increased TSG which suggests that rightward septal shift contributed to the increased LV preload. If PVR is used to reflect RV afterload, volume loading appeared to reduce PVR, thereby improving RV and LV performance. The improvement in cardiac output was also associated with reduced external constraint to LV filling; since calculated PVR is inversely related to cardiac output, increased LV output would reduce PVR.

Conclusion: Our results, which suggest that PVR is an independent determinant of cardiac performance but is also dependent on cardiac output, improve our understanding of the hemodynamic effects of volume loading in acute lung injury.

Keywords: volume loading, vascular resistance, acute respiratory distress syndrome
High airway pressure during mechanical ventilation can increase pulmonary vascular resistance (PVR) and can even cause acute cor pulmonale [right ventricular (RV) failure secondary to increased pulmonary artery (PA) pressure] (14; 19; 34; 39). The potential impact of increased PVR on RV function is widely recognized and its adverse effects on left ventricular (LV) preload have also been well documented (7; 16; 18; 26; 27). Volume challenges are commonly administered to hemodynamically compromised patients with acute respiratory distress syndrome (ARDS) during mechanical ventilation (32; 38). We have observed that in addition to increased intracavitary LV end-diastolic pressure (and LV area, i.e., preload), PVR is also reduced when volume is administered.

It has been taught that the RV is afterload-limited – or at least more so than the LV. Because PVR varies in response to both mechanical ventilation and volume loading, we hypothesized that RV performance improves with volume loading because its afterload (i.e., PVR) decreases. While investigators agree that “afterload” refers to the load that opposes ventricular ejection, the concept has evolved along either of two distinct lines. First, to a substantial degree, ventricular mechanics has evolved from the study of papillary muscle mechanics where afterload is the weight that isotonically contracting muscle must lift or the force that the isometrically contracting muscle develops after contraction begins. This has led to the concept that ventricular afterload should be measured as systolic force or pressure or stress. Second, the alternative line has held that resistance or “impedance” to ejection constitutes afterload. As argued in a classic paper by Milnor (25), a salient advantage of this approach is that this measure of afterload can be taken as being independent of changes in ventricular contraction and, therefore, represents more purely the load that the ventricle faces. As with other controversies in physiology, both
alternatives have their advocates. Both can be said to be intuitive and neither alternative has been substantively discredited.

Over time, the average output of one ventricle must be equal to the average output of the other, because the circulation is arranged in series and because any persistent difference would change lung blood volume intolerably. Thus, in principle, a change in preload or afterload of one ventricle could determine the output of the other ventricle indirectly. For example, a primary increase in LV preload would increase LV output, which would tend to decrease calculated PVR. Alternatively, a primary decrease in PVR (i.e., RV afterload) might increase RV output, which would tend to increase LV preload. Because PVR varies in response to both mechanical ventilation and volume loading, we tested the hypothesis that when PVR is high, the improved RV performance with volume loading is related to a decrease in PVR. We therefore assessed the effects of changes in LV filling pressure and PEEP on PVR and cardiac performance during mechanical ventilation in 8 normal dogs and in 8 with acute lung injury (ALI) induced by oleic acid (OA) infusion. A commonly used model of ALI with OA was chosen as it induces a similar inflammatory response to that found in clinical ALI (35), has been shown to minimally affect endothelium relaxation and contraction properties (21) and appears to allow both respiratory and hemodynamic stability within 60 min of administration (15).

METHODS

All experiments were approved by the institutional animal care committee whose criteria are consistent with those of the American Physiological Society.
Animal preparation

Anesthesia was induced in 16 mongrel dogs of either sex [8 control dogs (17-34 kg, mean 21 kg); 8 dogs subjected to ALI (20-30 kg, mean 24 kg)] with thiopental sodium (25 mg/kg i.v.) and midazolam (5 mg/ml bolus) and was maintained with fentanyl citrate (0.04 mg/ml i.v., initially, followed by an infusion of 4 mg/h), which was adjusted as necessary to ensure deep sedation without spontaneous respiratory effort. The animals were intubated with a cuffed endotracheal tube and ventilated with constant-volume ventilator (Harvard Apparatus, Millis, MA) with a 50% oxygen - 50% nitrous oxide mixture. Tidal volume [control dogs (16-20 ml/kg, mean 19 ml/kg); ALI dogs (14-18 ml/kg, mean 16 ml/kg)](33) and respiratory rate [control dogs (16-22 breaths/min; mean 18 breaths/min); ALI dogs (13-17 breaths/min; mean 15 breaths/min)] were adjusted to maintain physiological values of blood gases and pH. PaCO₂ was maintained between 35 and 45 mmHg.

A median sternotomy was performed and the hearts were delivered from the pericardium through a base-to-apex incision. Sonomicrometry crystals (Sonometrics, London, ONT) were implanted in the endocardium in the LV and RV and mid-wall of the septum to measure the minor-axis septum-to-LV free wall (D_{SLVFW}), septum-to-RV free wall (D_{SRVFW}) and LV anteroposterior (D_{LVAP}) dimensions (4; 11; 28). Ultrasonic flow probes (Transonic Systems, Ithaca, NY) were placed on the ascending aorta and pulmonary artery. Tracheal pressure (P_{TRACHEAL}) was measured from a side-port on the endotracheal tube with an air-filled tube connected to a pressure transducer. Catheter-tip pressure manometers (Millar Instruments, Houston, TX) were inserted into the LV (P_{LV}; retrograde through the left carotid artery), RV (P_{RV}; through the right external jugular vein), aorta (P_{AO}; retrograde through the right femoral artery), pulmonary artery
(P_{PA}; retrograde through a distal pulmonary artery branch) and left atrium (P_{LA}; through the left atrial appendage).

To create a model of ALI, a thin-walled 8-French catheter was placed directly into the right atrium (through the right atrial appendage) for OA infusion. A fluid-filled intravenous line was placed in the left external jugular vein for volume loading (Pentaspan™, 10% pentastarch in 0.9% NaCl). The right atrium was paced slightly faster than the animal’s inherent rate to maintain a constant heart rate. A left femoral arterial line was placed to obtain samples for blood-gas analysis. Body temperature was monitored with either a rectal or vaginal thermometer. After instrumentation, the heart was returned to the pericardium, which was closed with individual sutures, taking care not to compromise pericardial volume (36). The chest was closed under suction (5 mmHg) with the sternum tightly re-approximated and the animals were allowed to stabilize. The ventilator was then switched (Servo, Siemens-Elema 900C), enabling precise PEEP application while delivering 100% O₂ for the duration of the experimental protocol. Control animals were prepared similarly except no OA was given. Typical recovery time from surgery and adjustment to the second ventilator was 30 min. Recovery was defined as an adequate blood pressure (peak systolic P_{AO} > 90 mmHg) and a PaCO₂ between 35 – 45 mmHg.

**Experimental protocol**

Simultaneous pressure, dimension and hemodynamic measurements were recorded at baseline and during each intervention. After stabilization at LV end-diastolic pressure (P_{LVED}) of 5 mmHg, PEEPs of 0, 6, 12 and 18 cmH₂O were applied in random order. After hemodynamic
stabilization during each set of conditions, data were collected for 60 sec after which the animals were allowed sufficient time to recover to the baseline before the next application of PEEP. After removal of PEEP, OA (0.07 ml/kg) was infused into the right atrium over 60 sec to create ALI (2), defined by an arterial partial pressure of oxygen (PaO2)/fraction of inspired O2 (FiO2) ratio less than 200 mmHg (3). After a period of 90 min, the protocol described above was repeated at PLVED’s of 5, then 12 and finally 18 mmHg (volume was infused until the desired PLVED was achieved). The control experiments were conducted first and performed similarly except that the intermediate filling pressure was 9 mmHg instead of 12 mmHg and OA was not infused.

Data analysis

The conditioned signals (model VR 16; Electronics for Medicine/Honeywell, White Plains, NY) were amplified, passed through a low-pass filter (100 Hz), and digitized at 200 Hz. The digitized data were analyzed on a personal computer using software (CV Works, Calgary, AB) developed in our laboratory.

End-diastolic transseptal pressure gradient (TSG) was defined as PLVED – PRVED. LV area (ALVED), our index of LV end-diastolic volume, was calculated as the product of the 2 minor-axis LV dimensions (1; 37). DSRVFW was used to reflect RV end-diastolic volume (11). DSRVFW shortening (%) was calculated as [(end-diastolic DSRVFW – end-systolic DSRVFW) / end-diastolic DSRVFW] x 100 and used to reflect RV systolic performance. LV stroke work (SWLV) was calculated as LV stroke volume (SVLV) x [mean PLV (systolic) – mean PLA], where mean PLV (systolic) was calculated as PAO (diastolic) + 2/3 [PAO (systolic) – PAO (diastolic)]. Since SVRV
and SV_{LV} must be equal over an extended interval and the sensitivities of the two flowmeters were not precisely identical, SV_{RV} was adjusted to equal SV_{LV}, using mean values over a 60 sec interval while hemodynamics were stable. A beat-to-beat index of pulmonary vascular resistance (*PVR) was calculated as \([m_{PA} - m_{LA}] / SV_{RV}\); during steady-state conditions, PVR was calculated using cardiac output (CO) as the denominator. D_{SRVFW}, SV_{RV}, SW_{LV} and A_{LVED} were normalized so that the values at P_{LVED} 12 mmHg, PEEP 0 cmH_2O were set as 100%. Normalization was performed to account for different ventricular dimensions and outputs among animals. Respiratory system compliance was calculated as tidal volume / \([P_{TRACHEAL} \text{ end-inspiration} - P_{TRACHEAL} \text{ end-expiration}]\). It is unlikely that OA administration or volume loading altered chest wall compliance, which implies that changes in the respiratory system compliance were due to changes in lung compliance alone.

Statistical analysis

Repeated-measures ANOVA (Student-Newman-Keuls method) was used to test for the significance of changes at different levels of PEEP and P_{LVED}. Linear correlations were calculated for all indicated variables for changes in PEEP and filling pressures \((y = y_0 + a^*x)\). The Student’s paired \(t\)-test was used to test for the significance of changes between pre- and post-lung injury at P_{LVED} 5 mmHg; a \(P\) value <0.05 was considered statistically significant.

RESULTS

Except where otherwise noted, data are presented as mean (± SE) end-diastolic values for 5 ventilation cycles measured at end-expiration. No data are shown at P_{LVED} 5 mmHg and PEEP 18 cmH_2O because the animals became hemodynamically unstable (systolic P_{AO} < 50 mmHg).
Table 1 indicates respiratory system compliance for a given level of PEEP at baseline and after ALI. OA infusion significantly decreased respiratory system compliance for a given level of PEEP.

Table 2 lists hemodynamic parameters at baseline and after ALI at P_{LVED} 5 mmHg and PEEP 0 cmH₂O. No significant differences were observed for peak systolic aortic pressure (P_{AOPS}) and cardiac index (CI) while HR and PVR were significantly greater and SV_{LV} was significantly lower after ALI.

**PVR and P_{TRACHEAL}**

Figures 1A (normal) and 1B (ALI) show the relations between PVR and P_{TRACHEAL}. As P_{TRACHEAL} increased up to PEEP 18 cmH₂O, PVR increased at all filling pressures. The increase in PVR with higher airway pressures was greatest at the lowest LV filling pressure (P_{LVED} = 5 mmHg). In the ALI animals, volume loading to P_{LVED} 12 and 18 mmHg reduced PVR by similar amounts at each level of PEEP. However, in the normal animals, there was a significant difference in PVR at P_{LVED} 9 compared to 18 mmHg; note that the intermediate levels of P_{LVED} were different (9 and 12 mmHg respectively) in the 2 groups of animals.

**RV Function**

Figures 2A (normal) and 2B (ALI) show the relations between D_{SRVFW} and PVR. In the normal animals, as airway pressure (and PVR) increased, D_{SRVFW} decreased. However, in the ALI animals at P_{LVED} 5 mmHg, the increase in PEEP from 0 to 12 cmH₂O increased PVR but D_{SRVFW}
did not change. At $P_{\text{LVED}}$ 12 and 18 mmHg, the decrease in $D_{\text{SRVFW}}$ from PEEP 0 cmH$_2$O to the higher levels of PEEP was not statistically significant while PVR increased slightly. Volume loading decreased PVR and increased $D_{\text{SRVFW}}$ in both models.

Figures 3A (normal) and 3B (ALI) show the relations between $S_{\text{VRV}}$ and $D_{\text{SRVFW}}$. In the normal animals, both $D_{\text{SRVFW}}$ and $S_{\text{VRV}}$ decreased with increased PEEP and increased with volume loading. After ALI, when PEEP was increased from 0 to 12 cmH$_2$O at $P_{\text{LVED}}$ 5 mmHg (compare the open circle to the open square), $S_{\text{VRV}}$ decreased while $D_{\text{SRVFW}}$ did not change. At $P_{\text{LVED}}$ 12 and 18 mmHg, the changes in $D_{\text{SRVFW}}$ from PEEP 0 cmH$_2$O (grey and black circles) to the higher levels of PEEP (grey and black triangles and squares) were not statistically significant while $S_{\text{VRV}}$ decreased. Compared to $P_{\text{LVED}}$ 5 mmHg, volume loading generally increased $S_{\text{VRV}}$ and increased $D_{\text{SRVFW}}$ at each level of PEEP.

Figure 4 is a representative plot from an ALI animal in which data points were collected throughout lung inflation (as opposed to the end-expiratory data shown in all other figures). This plot illustrates the linear relation between beat-to-beat changes in % shortening $D_{\text{SRVFW}}$ (reflecting RV performance) and *PVR with increasing airway and filling pressures. As *PVR increased with PEEP and during lung inflation, % shortening $D_{\text{SRVFW}}$ decreased at all $P_{\text{LVED}}$’s. Volume loading decreased *PVR and increased % shortening $D_{\text{SRVFW}}$.

**LV Function**

Figure 5 (ALI) shows the relations between the TSG and PVR. Increased PVR was associated with a decreased TSG, which implies a leftward septal shift. At $P_{\text{LVED}}$ 5 mmHg and PEEP 6 and
12 cmH₂O, the TSG was close to 0 mmHg, which suggests that the septum shifted leftward and became flattened or even inverted (5; 18). Volume loading reduced PVR and increased the TSG, which implies a rightward septal shift.

Figure 6 shows the linear relations with 95% confidence intervals using all the raw data (pre- and post-OA) between SWLV and ALVED. The open circles indicate baseline values (r = 0.61, P < 0.001). After ALI, the SWLV – ALVED relations shifted to the right (closed circles; r = 0.66, P < 0.0001) indicating decreased contractility. LV systolic performance was closely related to LV preload throughout the experiment.

**CO and PVR**

To avoid plotting variables that are functions of each other, we plotted the pressure gradient across the lungs (mP_PA – mP_LA) as a function of CO. In the normal animals (Figure 7A), the transpulmonary pressure gradient decreased as CO increased (r = -0.95, P < 0.0001). In the ALI animals (Figure 7B), the transpulmonary pressure gradient did not change significantly as CO increased (r = -0.33, P = NS).

**DISCUSSION**

The present study demonstrates that volume loading decreases PVR when PVR is increased by high PEEP. Thus, in addition to the expected improvement in LV performance related to the increased LV preload caused by the increased filling pressure, volume loading was associated with a decreased PVR. PVR was closely related to RV and LV performance, which suggests that by reducing PVR, volume loading improved RV and therefore LV performance by series...
interaction. The TSG increased, which implies that rightward septal shift (direct ventricular interaction) also contributed to the increased LV preload, reducing the impact of external constraint. While these results support the notion that there is a direct effect of volume loading on PVR, our data suggest that the decrease in PVR with volume loading after ALI is also related to the increased CO, since the transpulmonary pressure gradient did not change significantly as CO increased (Figure 7B). The two mechanisms might have had quantitatively different effects in controls (Figure 7A), in which a prominent direct effect on PVR was more apparent (the decrease in the transpulmonary pressure gradient was significant).

Our results are consistent with a recent clinical study by Fougeres et al. (14) who assessed the hemodynamic effects of high PEEP with a subsequent increase in central blood volume in 21 mechanically ventilated ARDS patients. RV end-diastolic area (echocardiography) and PVR (flow-directed catheter) increased and cardiac index decreased with increased PEEP (5 ± 1 SD to 13 ± 4 SD cmH$_2$O), with 3 of 21 patients exhibiting acute cor pulmonale. Consistent with our observations, their findings also suggest that PEEP decreased cardiac index by increasing RV afterload rather than by decreasing RV preload; increasing central blood volume by passive leg raising decreased PVR and the right/left ventricular end-diastolic area ratio (consistent with direct ventricular interaction) and increased the cardiac index, which implies that reduced RV afterload contributed to the improved CO. Despite their use of vasopressors in a heterogeneous population of patients and their necessarily limited collection of data, our highly instrumented model of ALI yielded similar results which serve to support their interpretation that PVR is directly affected by volume loading. In addition, our observations provide a more complete synthesis of the underlying mechanisms and indicate the need to consider the potential
contribution of an increased CO to the reduced PVR. Thus, over a wide range of PEEPs and filling pressures, we provide detailed support for the notion that changes in RV afterload directly affected cardiac performance by direct as well as series ventricular interaction and that increased LV output appears to also be important. The importance of PVR is also supported by clinical studies that have shown improved cardiac function by pharmacological reduction in RV afterload (PVR) in ARDS (13; 29).

**Physiological considerations**

The mechanisms by which LV filling pressure altered PVR in the present study have not been completely clarified. The absence of a statistically significant reduction in the transpulmonary pressure gradient with volume loading at high PEEP after ALI might suggest that the reduction in calculated PVR was simply due to the increased LV output. However, after ALI, at low filling pressures, $D_{SRVF}$ (RV preload) did not decrease and may have increased when PEEP was increased but $SV_{RV}$ decreased (rather than increased). This is opposite to what would be expected if increased LV filling and output were solely responsible for the reduction in PVR. These findings suggest that increased RV afterload (PVR) directly reduced RV output and that volume loading (by either recruitment of pulmonary vessels or increased transmural pressure in the pulmonary vasculature or both) also reduced PVR directly, thereby allowing for increased RV output. This is also supported by the significant changes in the transpulmonary pressure gradient in the controls, a more homogeneous group of animals without lung injury. In keeping with the study by Fougeres et al. (14), it is unlikely that volume loading in our ALI model reduced hypoxic pulmonary vasoconstriction as oxygenation did not improve with volume loading. This observation and the lack of a significant reduction in the transpulmonary pressure gradient
suggests that the main mechanism by which PVR was reduced with volume loading was increased vascular transmural pressure and not substantially increased vessel recruitment.

Figure 7 shows the relation of the transpulmonary pressure gradient as a function of CO, for the normal and ALI animals. In the normal animals, it is noteworthy that the transpulmonary pressure gradient decreased as CO increased, indicating recruitment of new vessels and/or vasodilatation. This heretofore unreported observation represents an important adaptive pulmonary mechanism that would serve to facilitate the increase in CO that the needs of the body might require during exercise or other stress. In the ALI animals, there was no systematic change in the transpulmonary pressure gradient. Although it is difficult to make a definite conclusion because the range of CO’s in the two series of experiments was not equal, it appears that OA infusion restricts the lung’s normal ability to increase conductance (the reciprocal of PVR) – a measure of how much flow the lung can accept with a given transpulmonary pressure gradient – as CO increases.

Pulmonary vascular resistance and direct ventricular interaction

In general, high levels of PEEP increase PVR (17; 30; 31). Large tidal volumes also tend to increase PVR and, for a given tidal volume, the increase in PVR is greater with PEEP (8). Clinically, high PVR has been observed to even cause RV failure (acute cor pulmonale) during mechanical ventilation (14; 19; 34; 39). Our observations suggest that acute RV failure occurred in some animals when PVR was high. The TSG decreased which implies leftward septal shift and possible inversion of the septum, limiting LV filling and output. As shown in Figure 2B, RV diameter did not decrease with the increased PVR caused by the increase in PEEP from 0 to 12
cmH\textsubscript{2}O at P\textsubscript{LVED} = 5 mmHg. However, RV output decreased (Figure 3B) despite similar or increased RV preload.

**External Constraint**

Since the heart and lungs lie within the confines of the thoracic cage, increased intrathoracic pressure and lung volume during mechanical ventilation increases external constraint to ventricular filling (6). When intrathoracic pressure is increased, there is a similar increase in pericardial pressure, which tends to decrease LV preload (A\textsubscript{LVED}) and output (Figure 6). Our results are in keeping with the large body of literature documenting these effects (6; 12; 18; 22; 24). Volume loading offset the effects of increased external constraint as would be predicted – LV end-diastolic volume and output increased. Thus, volume loading reduced the adverse effects of increased external constraint on ventricular filling by increasing LV preload.

**Clinical Implications**

Our observations suggest that it is possible that consideration of PVR as a therapeutic target during volume loading in hemodynamically compromised, mechanically ventilated patients may help refine treatment strategies but will not be sufficient to translate such a strategy clinically without further testing in appropriate patients. These observations are in marked contrast to the opposite, deleterious responses to volume loading in situations where PVR is very high and not readily acutely reversible, such as in acute pulmonary embolism (4), chronic obstructive pulmonary disease (20) and severe congestive heart failure (28). Given the relatively infrequent use of hemodynamic monitoring with pulmonary artery catheters (10), PVR is not generally
assessed or monitored. It appears reasonable to attempt to reduce PVR when RV performance is adversely affected by increased resistance.

*Study Limitations*

The pre- and post-lung injury data could only be compared at the lowest filling pressure. Volume loading was not performed prior to lung injury to avoid the confounding effects of high-pressure pulmonary edema, the need for subsequent phlebotomy, and prolonging the experiment. It is worth noting that of 24 ALI experiments, only 8 were considered successful because many animals either died prematurely or the level of lung injury was insufficient (i.e., the PaO$_2$ / FiO$_2$ ratio exceeded 200 mmHg).

We used a constant-volume mode of ventilation and so the magnitude of changes may not be similar with other modes of ventilation. The study was not designed to address the potential of ventilator-induced lung injury with high levels of PEEP, where high airway opening pressures may exacerbate lung injury (especially at low filling pressures where PVR is high). Importantly, none of the 8 ALI dogs could withstand a PEEP of 18 cmH$_2$O at a P$_{LVED}$ of 5 mmHg. This underscores the importance of insuring adequate volume as all withstood a PEEP of 18 cmH$_2$O at the higher filling pressures. In accordance with recommended ventilation parameters for large animals (33), we used greater tidal volumes than are employed clinically – these tidal volumes have been determined to be appropriate to achieve adequate gas exchange and acid-base balance in dogs. We also did not measure alveolar pressure, thereby excluding a calculation of transpulmonary pressure limiting analysis of transmitted airway pressure to the vascular system.
We recognize that $P_{LA}$ may not always accurately reflect pulmonary outflow pressure, particularly when it was relatively low in our ALI model. Leeman et al. (23) showed that the critical closing pressure (effective pulmonary downstream pressure) was greater than $P_{LA}$ in their OA induced ALI model during mechanical ventilation with no PEEP. When CO was held constant, increases in $P_{LA}$ only increased $P_{PA}$ when $P_{LA}$ exceeded 10 mmHg. This suggests that our calculated transpulmonary pressure gradient and, therefore, PVR, may only have been problematic at the lowest filling pressure (5 mmHg) and not at mean $P_{LA}$’s of 10 and 16 mmHg (PEEP 0 cmH$_2$O). The inability to directly measure the effective upstream critical closing pressure (pulmonary capillary pressure), which could be no less than $P_{LA}$, might suggest our calculated PVR could have been overestimated at the lowest filling pressure. However, the fact that RV size either increased or remained unchanged (at low filling pressures with increased PEEP) still supports the notion that PVR increased importantly under those conditions.

We did not anticipate that PVR would be greater in the normal compared to the ALI animals. The higher PVR at the intermediate filling pressure in the normal model might be explained by the lower LV filling pressure at that point ($P_{LVED}$ 9 mmHg in the normal animals versus $P_{LVED}$ 12 mmHg in the ALI animals). The control animal experiments were conducted before those of ALI with the intention of volume loading to reach the intermediate $P_{LVED}$ 12 mmHg. However, after completion of the experiments, subsequent analysis indicated that a $P_{LVED}$ of only 9 mmHg was achieved. Importantly, the higher CO in the ALI experiments could account for the lower calculated PVR in this model. It is possible that the presence of edematous lungs required a greater volume load to maintain the predetermined filling pressures accounting for the higher CO in the ALI model (volumes administered were not recorded). It is also possible that the higher
tidal volumes in the normal animals as compared to the ALI animals (mean 19 vs 16 ml/kg respectively) may account in part for the greater PVR. It was not our intention to ventilate the normal animals with higher tidal volumes than those with ALI. In general, the intention was to ventilate the animals at the lowest possible tidal volumes while maintaining physiological blood gases.

We cannot readily explain why the transpulmonary pressure gradient displayed a more prominent negative linear relation with volume loading in the normal animals (significant at PEEP 0 cmH2O) while this was not more apparent in the ALI animals. Perhaps, heterogeneity of the ALI insult amongst animals contributed to less uniform responses. The normal animals were able to compensate for a ~2 fold increase in flow by decreasing the pressure gradient across the lungs while this was not as apparent in the ALI animals where a ~3 fold increase in flow did not result in a significant reduction in the transpulmonary pressure gradient. Thus, ALI appears to have limited the capacity of the lung to increase conductance as CO increases. However, it should be noted that the transpulmonary pressure gradient did not increase with CO (as might have been expected), because conductance increased linearly with CO in both models. We also did not anticipate the differences between the two models in the transpulmonary pressure gradient with increasing PEEP. In the ALI model, it is possible that the lower pressure pulmonary venous vasculature (left atrium) is more susceptible to the transmission of airway pressure than the higher pressure pulmonary arterial vasculature resulting in, generally, less of an increase in mP_{PA} as compared to mP_{LA} , which might be due to edematous lungs buffering airway pressure transmission.
Importantly, the main purpose of the study was to measure the hemodynamic effects of volume loading in an ALI model resembling ARDS and not to quantify the effects of lung injury per se. Inclusion of the normal animals serves to demonstrate that although not necessarily quantitatively identical, the effects of volume loading remain very similar.

Of note; the significant reduction in $SV_{LV}$ after ALI (Table 2) could be attributed to decreased LV contractility after OA infusion (Figure 6).

Conclusion

We interpret our results to suggest that at low LV end-diastolic pressure, mechanical ventilation with PEEP increased PVR resulting in impaired RV systolic function, detrimental ventricular interaction (series and direct) and reduced LV end-diastolic volume (26). Volume loading reduced PVR, which resulted in improved cardiac performance. The reduction in PVR was also closely related to improved LV performance ($SW_{LV}$). However, the independent contributions of each mechanism to these changes remain unclear. Our results, considered together with the work by Fougeres et al.(14) suggest that a direct effect on PVR is an important mechanism by which volume loading improves cardiac function in ventilated patients with ALI. However, some of our data suggest that the improved cardiac function could be partly explained by volume loading simply negating the increased external constraint, which improves LV filling. As PVR is a function of CO, any increase in CO would reduce calculated PVR. Our observations suggest that both mechanisms play a role and that one cannot eliminate either a priori.
Perspectives and Significance

During mechanical ventilation, increased PVR may decrease RV and therefore, LV performance. Although we have been unable to quantify the mechanisms underlying improved cardiac function with volume loading, the improved RV performance with volume loading is in part related to a decrease in PVR. This could have important clinical implications, especially in light of the recent Surviving Sepsis Campaign recommendations of a conservative fluid strategy for patients with established ALI/ARDS who are not in shock (10). In the present study, the differences in PVR between $P_{LVED}$ 12 and 18 mmHg tended to be small or insignificant. There is some debate over optimal fluid management in ARDS. “Wet” refers to liberal volume loading to limit adverse hemodynamic effects of mechanical ventilation, allowing a greater level of PEEP at the risk of increased pulmonary edema. “Dry” limits volume loading to maintain an adequate CO thereby minimizing pulmonary edema, but accepting a potentially greater PVR. Clinical studies have shown little difference in outcomes with the 2 strategies, with one recent study showing minor advantages to “dry” where the “wet” pulmonary capillary wedge pressures were 14 to 18 mmHg (38); our data suggest that PVR may not be reduced further at LV filling pressures above 12 mmHg (9). If so, the maximum hemodynamic benefit that may be achieved from a reduction in PVR may be at lower filling pressures than defined for the “wet” strategy (38). This does not preclude potential additional improvement in cardiac function related to greater LV preload at higher filling pressures.
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Figure Legends

Figures 1A (normal) and 1B (ALI) show the relations between PVR and $P_{\text{TRACHEAL}}$ over the range of filling pressures and PEEPs. In both normal and ALI, as $P_{\text{TRACHEAL}}$ increased with increased PEEP, PVR increased at all filling pressures with the greatest increase at $P_{LVED}$ 5 mmHg. Volume loading reduced PVR for a given level of PEEP. $P_{\text{TRACHEAL}}$, tracheal pressure (cmH2O). † = $P < 0.05$ compared to $P_{LVED}$ 5 mmHg, same PEEP.

Figures 2A (normal) and 2B (ALI) show the relations between $D_{SRVFW}$ and PVR over the range of filling pressures and PEEPs. In the normal animals, as airway pressure increased, $D_{SRVFW}$ decreased. However, in the ALI animals at $P_{LVED}$ 5 mmHg, the increase in PEEP from 0 to 12 cmH2O increased PVR but $D_{SRVFW}$ did not change. At $P_{LVED}$ 12 and 18 mmHg, the decrease in $D_{SRVFW}$ from PEEP 0 cmH2O to the higher levels of PEEP was not statistically significant while PVR increased slightly. Volume loading decreased PVR and increased $D_{SRVFW}$ in both models. $D_{SRVFW}$ was normalized so that the value at $P_{LVED}$ 12 mmHg, PEEP 0 cmH2O was set as 100%. $D_{SRVFW}$, normalized septum-to-RV free wall dimension (%).

Figures 3A (normal) and 3B (ALI) show the relations between $SV_{RV}$ and $D_{SRVFW}$ over the range of filling pressures and PEEPs. In the normal animals, both $D_{SRVFW}$ and $SV_{RV}$ decreased with increased PEEP and increased with volume loading. After ALI, when PEEP was increased from 0 to 12 cmH2O at $P_{LVED}$ 5 mmHg (compare the open circle to the open square), $SV_{RV}$ decreased while $D_{SRVFW}$ did not change. At $P_{LVED}$ 12 and 18 mmHg, the changes in $D_{SRVFW}$ from PEEP 0
cmH$_2$O (grey and black circles) to the higher levels of PEEP (grey and black triangles and squares) were not statistically significant while SV$_{RV}$ decreased. Compared to P$_{LVED}$ 5 mmHg, volume loading generally increased SV$_{RV}$ and increased D$_{SRVFW}$ at each level of PEEP. D$_{SRVFW}$ and SV$_{RV}$ were normalized so that the values at P$_{LVED}$ 12 mmHg, PEEP 0 cmH$_2$O were set as 100%. SV$_{RV}$, normalized right ventricular stroke volume (%).

Figure 4 is a representative ALI experiment including all data points during lung inflation illustrating the beat-to-beat relation between %Shortening D$_{SRVFW}$ (indicator of RV systolic function) and *PVR over the range of filling pressures and PEEPs. As *PVR increased with PEEP and during lung inflation, % shortening D$_{SRVFW}$ decreased at all P$_{LVED}$’s. Volume loading decreased *PVR and increased % shortening D$_{SRVFW}$. *PVR, index of pulmonary vascular resistance, (mmHg/ml).

Figure 5 shows the relation between the TSG and PVR over the range of filling pressures and PEEPs in the ALI animals. Increased PVR was associated with a decreased TSG. Volume loading reduced PVR and increased the TSG. TSG, end-diastolic transseptal pressure gradient (mmHg).

Figure 6 shows the relation between SW$_{LV}$ and A$_{LVED}$ over the range of filling pressures and PEEPs in the ALI animals. The open circles indicate baseline values before ALI. After ALI, the SW$_{LV}$ – A$_{LVED}$ relations shifted to the right (closed circles). LV systolic performance was closely related to LV preload throughout the experiment. SW$_{LV}$ and A$_{LVED}$ were normalized so that the
values at $P_{LVED}$ 12 mmHg and PEEP 0 cmH$_2$O were set as 100%. $SW_{LV}$, normalized left ventricular stroke work (%); $A_{LVED}$, normalized left ventricular area (%).

Figures 7A (normal) and 7B (ALI) show the relations between $mPPA - mPLA$ as a function of CO. In the normal animals, the transpulmonary pressure gradient decreased as CO increased. In the ALI animals, the transpulmonary pressure gradient did not change as CO increased. $mP_{PA}$, mean pulmonary artery pressure (mmHg); $mP_{LA}$, mean left atrial pressure (mmHg); CO, cardiac output (L/min).
Reference List


32. **Rivers EP**. Fluid-management strategies in acute lung injury--liberal, conservative, or both? 


Table 1. Respiratory system compliance (ml/cmH₂O) at baseline and after ALI at $P_{LVED}$ 5 mmHg

<table>
<thead>
<tr>
<th>PEEP (cmH₂O)</th>
<th>0</th>
<th>6</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>41±3</td>
<td>37±3</td>
<td>30±2</td>
</tr>
<tr>
<td>ALI</td>
<td>34±2*</td>
<td>30±2*</td>
<td>24±3*</td>
</tr>
</tbody>
</table>

Mean ± SE; * $P < 0.05$ compared to baseline.
Table 2. Hemodynamic parameters at baseline and after ALI at $P_{\text{LVED}}$ 5 mmHg and PEEP 0 cmH$_2$O

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>ALI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>105±3</td>
<td>113±4*</td>
</tr>
<tr>
<td>$SV_{LV}$ (ml)</td>
<td>24±3</td>
<td>17±2*</td>
</tr>
<tr>
<td>CI (ml/min/kg)</td>
<td>108±16</td>
<td>84±11</td>
</tr>
<tr>
<td>$P_{AOPS}$ (mmHg)</td>
<td>93±3</td>
<td>89±3</td>
</tr>
<tr>
<td>PVR (mmHg/L/min)</td>
<td>5±0</td>
<td>7±1*</td>
</tr>
</tbody>
</table>

CI, cardiac index; HR, heart rate; $P_{AOPS}$, peak systolic aortic pressure; PVR, pulmonary vascular resistance; $SV_{LV}$, left ventricular stroke volume. Mean ± SE; * $P < 0.05$ compared to baseline.
Figures 1A (normal) and 1B (ALI)
Figures 2A (normal) and 2B (ALI)
Figures 3A (normal) and 3B (ALI)
Figure 4
Figure 5
Figures 7A (normal) and 7B (ALI)