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# Left Ventricular Preload Determines Systolic Pressure Variation during Mechanical Ventilation in Acute Lung Injury

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## Abstract

**Background:** Systolic pressure variation (SPV) predicts responsiveness to volume loading during mechanical ventilation and may be related to changes in LV preload and the resultant changes in stroke volume (SV). We, therefore, tested the relations between LV preload, output and SPV in an acute lung injury (ALI) model during mechanical ventilation.

**Methods:** ALI was created by oleic acid infusion (0.07 ml/kg) in 8 anesthetized dogs. We measured LV, RV, aortic, left atrial (LA) and pericardial pressures, LV area ($A_{LVED}$) and SV during mechanical ventilation with positive end-expiratory pressures (PEEP) of 0, 6, 12 and 18 cmH$_2$O at LV end-diastolic pressures of 5, 12 and 18 mmHg.

**Results:** Throughout these ranges of PEEPs and filling pressures, SPV was inversely related to LV preload [$A_{LVED}$ and transmural LV end-diastolic pressure; ($P_{LVEDtm}$)] (r = −0.87 and r = −0.89, *P* <0.0001 respectively). Both preload measures were closely related to SV (both r = 0.90, *P* <0.0001). Changes in estimated $P_{LVEDtm}$ (LA end-diastolic pressure – RV end-diastolic pressure) matched changes in $P_{LVEDtm}$ (r = 0.95, *P* < 0.0001). Alternative measures of arterial pressure variation (pulse pressure variation, SV variation and delta down) behaved similarly when compared to SPV (r = 0.91, 0.97, and 0.78, *P* < 0.001, respectively).

**Conclusions:** The inverse relations between SPV and LV preload and output indicate that LV preload is a major determinant of SPV. An estimate of LV preload based on measurements from the flow-directed catheter (i.e., wedge pressure – right atrial pressure) may predict volume responsiveness in mechanically ventilated patients.

**Keywords:** Volume loading; Systolic pressure variation; Respiratory distress; Preload

Although volume is commonly administered to patients with hemodynamic compromise during mechanical ventilation to improve cardiac output, excessive amounts may precipitate or aggravate pulmonary edema, especially in patients with predisposing pulmonary or cardiac conditions. The ability to predict the hemodynamic response to a volume challenge should facilitate patient management and might help to avoid harm in those who are unlikely to benefit from volume loading.

Systolic arterial pressure variation (SPV) during mechanical ventilation is more pronounced in hypovolemic than in euvolemic patients [1-3]. Cyclical changes in left ventricular (LV) preload during mechanical ventilation and the resultant changes in stroke volume are related to complex cardiopulmonary interactions including changes in external constraint and LV afterload, as well as systemic and pulmonary venous return through series and direct ventricular interaction [4-11]. The magnitude of SPV has been shown to predict responsiveness to a volume challenge [1-3,12-16]. One might anticipate that as LV and right ventricular (RV) preload increase during volume loading, changes in intrathoracic pressure would affect ventricular filling (and output) less and thus, SPV would be less. Alternatively stated, at higher filling pressures, the ventricles are on a flatter part of the Starling curve (fiber length cannot be increased further by increasing the filling pressure further). Therefore, a given airway pressure is less likely to reduce fiber length at higher filling pressures than at lower pressures where the Starling curve is steeper.

We therefore assessed the relations between LV preload, output and SPV in an oleic acid (OA) induced acute lung injury (ALI) model

in which LV filling pressures and positive end-expiratory pressures (PEEP) were systematically varied. We also assessed the potential value of estimated transmural LV end-diastolic pressure [left atrial end-diastolic pressure ($P_{LAED}$) – RV end-diastolic pressure ($P_{RVED}$)], which reflects LV preload, in predicting volume responsiveness in our model.

## Methods

This study was approved by the institutional animal care committee whose criteria are consistent with those of the American Physiological Society.

### Animal preparation

In 8 mongrel dogs of either sex (20-30 kg, mean 24 kg), anesthesia was induced 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 (14-18 ml/kg, mean 16 ml/kg) and respiratory rate (13-17 breaths/min; mean 15 breaths/min) were adjusted to maintain physiological values of blood gases and pH in accordance with recommended ventilation parameters for large animals [17]. $PaCO_2$ 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 LV endocardium and mid-wall of the septum to measure the minor-axis septum-to-LV free wall ($D_{SLVFW}$) and LV anteroposterior ($D_{LVAP}$) dimensions [18-20]. An ultrasonic flow probe (Transonic Systems, Ithaca, NY) was placed on the ascending aorta. A flat, fluid-filled balloon transducer, connected to a pressure transducer (model P23 ID; Statham Gould, Oxnard, CA), was loosely attached to the epicardial surface on the LV free wall to measure pericardial pressure ($P_{PERI}$) [21]. 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) 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). To maintain a constant heart rate, the right atrium was paced slightly faster than the animal's inherent rate. A left femoral arterial line was placed to obtain samples for blood-gas analysis. Body temperature was monitored with a rectal thermometer. After instrumentation, the heart was returned to the pericardium, which was closed with individual sutures, taking care not to compromise pericardial volume [22]. The chest was closed under suction (5 mmHg) with the sternum tightly re-approximated and the animals were allowed to stabilize. The suction catheter was introduced via a lateral incision such that its tip was situated under the sternum, exterior to the pericardium.The ventilator was then switched (Servo, Siemens-Elema 900C) to enable precise PEEP application while delivering 100% $O_2$ for the duration of the experimental protocol. 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 $PaCO_2$ between 35 – 45 mmHg. The OA model of ALI was chosen as it induces a similar inflammatory response to that found in clinical ALI [23], has been shown to minimally affect endothelial relaxation and contraction properties [24] and appears to allow both respiratory and hemodynamic stability within 60 min of administration [25].

### Experimental protocol

Simultaneous pressure, dimension and hemodynamic measurements were recorded at baseline and during each intervention. After stabilization at an LV end-diastolic pressure ($P_{LVED}$) of 5 mmHg (5.1 ± 0.3 mmHg), PEEPs of 0, 6, 12 and 18 $cmH_2O$ were applied in random order. A saline drip of approximately 10 ml/min was given to compensate for evaporative and surgical blood losses and anesthesia-induced vasodilatation. 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 baseline before the next application of PEEP. OA (0.07 ml/kg) was then infused into the right atrium over 60 sec to create ALI [26], defined by a $PaO_2$ (arterial partial pressure of oxygen )/$FiO_2$ (fraction of inspired $O_2$) ratio less than 200 mmHg [27]. After a period of 90 min, the protocol described above was repeated at $P_{LVED}$'s of 5, then 12 and finally 18 mmHg (volume was infused until the desired $P_{LVED}$ was achieved).

### 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.

Systolic pressure variation (SPV) was calculated as a mean percentage over 3 consecutive ventilation cycles where %SPV = ($SBP_{max}$ – $SBP_{min}$)/ [($SBP_{max}$ + $SBP_{min}$)/2] x 100% where $SBP_{max}$ is maximum systolic blood pressure and $SBP_{min}$ is minimum systolic blood pressure. Pulse pressure variation (PPV) was calculated similarly by substituting pulse pressure for systolic blood pressure. $d_{Down}$ was measured as the difference between the mean value of systolic blood pressure during 5 sec of end-expiration apnea and its mean minimal value for the preceding 3 ventilation cycles, respectively. Stroke volume variation (SVV) was calculated as ($SV_{max}$ – $SV_{min}$) / mean SV x 100%. Transmural LV end-diastolic pressure ($P_{LVEDtm}$) was calculated as $P_{LVED}$ – $P_{PERI}$ while estimated $P_{LVEDtm}$ was calculated as $P_{LAED}$ – $P_{RVED}$. $A_{LVED}$, our index of LV end-diastolic volume, was calculated as the product of the 2 minor-axis LV dimensions [28,29]. SV 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 / [$P_{TRACHEAL}$ end-inspiration – $P_{TRACHEAL}$ end-expiration] which significantly decreased after induction of ALI (41 ± 3 to 34 ± 2 ml/$cmH_2O$ (mean ± SE), $P < 0.01$). 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

Statistical comparisons were performed using SigmaPlot (Systat Software, Inc. 2008). Linear correlations were calculated for all indicated variables for changes in PEEP and filling pressures (y = $y_0$+a*x); a $P$ value <0.05 was considered statistically significant.

### Results

Data are presented as mean (± SE) end-diastolic values for 3 consecutive ventilation cycles. No data are shown at $P_{LVED}$ 5 mmHg and PEEP 18 $cmH_2O$ because the animals became hemodynamically

| HR (beats/min) | 113±4 |
|---|---|
| $P_{AOPS}$ (mmHg) | 89±3 |
| $P_{LVEDtm}$ (mmHg) | 1.4±0.7 |
| SV (%) | 63±4 |
| CI (ml/min/kg) | 84±11 |
| SPV (%) | 6±1 |

CI, cardiac index; HR, heart rate; $P_{AOPS}$, peak systolic aortic pressure; $P_{LVEDtm}$, left ventricular end-diastolic transmural pressure; SV, normalized left ventricular stroke volume; SPV, systolic pressure variation. Mean ±SE

**Table 1:** Hemodynamic parameters at $P_{LVED}$ 5 mmHg and PEEP 0 $cmH_2O$.
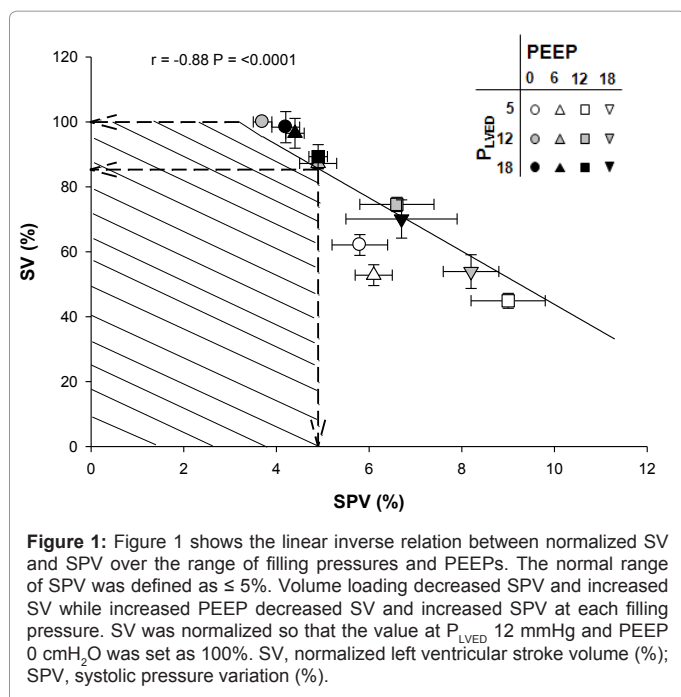
**Figure 1:** Figure 1 shows the linear inverse relation between normalized SV and SPV over the range of filling pressures and PEEPs. The normal range of SPV was defined as ≤ 5%. Volume loading decreased SPV and increased SV while increased PEEP decreased SPV and increased SPV at each filling pressure. SV was normalized so that the value at $P_{LVED}$ 12 mmHg and PEEP 0 cmH$_2$O was set as 100%. SV, normalized left ventricular stroke volume (%); SPV, systolic pressure variation (%).

unstable (systolic $P_{AO}$ < 50 mmHg) under those conditions. Table 1 lists hemodynamic parameters at $P_{LVED}$ 5 mmHg and PEEP 0 cmH$_2$O.

Figure 1 shows the linear inverse relation between normalized SV and SPV (r = −0.88, P < 0.0001). Volume loading increased SV and decreased SPV at each PEEP. Increased PEEP decreased SV and increased SPV at each filling pressure. The normal range of SPV was defined as ≤ 5% [3]. As is apparent in the figure, this defines the decrease in SV corresponding to SPV ≤ 5%, which equaled ~15% (100 − 85%). Over the full range of changes in SPV, SV decreased by up to 55%.

Figures 2A and 2B show the linear direct relations between normalized SV and normalized $A_{LVED}$ (r = 0.90, P < 0.0001) and normalized SV and $P_{LVEDtm}$ (r = 0.90, P < 0.0001) respectively. A ~55% decrease in SV was associated with a ~30% decrease in $A_{LVED}$ and a ~5 mmHg decrease in $P_{LVEDtm}$. The decrease in normalized SV corresponding to SPV ≤ 5% defined a ~10% decrease in normalized $A_{LVED}$ (from ~105 to ~95%) and a ~1.3 mmHg decrease in $P_{LVEDtm}$ (from ~4.0 to ~2.7 mmHg).

Figures 3A and 3B shows the linear inverse relations between normalized $A_{LVED}$ and SPV (r = −0.87, P < 0.0001) and $P_{LVEDtm}$ and SPV (r = −0.89, P < 0.0001) respectively. Over the range of conditions, volume loading increased $A_{LVED}$ up to ~35% and $P_{LVEDtm}$ up to ~5 mmHg as SPV decreased up to ~5%. Increased PEEP reduced both $A_{LVED}$ and $P_{LVEDtm}$ and increased SPV at each filling pressure. A SPV ≤ 5% corresponds to the ~10% decrease in $A_{LVED}$ and ~1.3 mmHg decrease in $P_{LVEDtm}$ identified in Figures 2A and 2B respectively. However, higher values of $P_{LVEDtm}$ (i.e., black circle and upright triangle) observed when $P_{LVED}$ was 18 mmHg are also included in this range, suggesting non-linearity such that there may be no further decrease in SPV, no matter how high the value of $P_{LVEDtm}$.

Figure 4 shows the relations between $P_{LVED}$, $P_{LVEDtm}$ and $A_{LVED}$. Increased PEEP decreased $A_{LVED}$ while $P_{LVED}$ did not change or even increased. At each level of PEEP, volume loading increased $A_{LVED}$, $P_{LVED}$ and $P_{LVEDtm}$. When $P_{PERI}$ was subtracted from $P_{LVED}$ to calculate $P_{LVEDtm}$, it is apparent that increased PEEP decreased $A_{LVED}$ at each

filling pressure and changed $P_{LVEDtm}$ appropriately. $P_{LVEDtm}$ was linearly correlated with $A_{LVED}$ (r = 0.99, P < 0.0001), in keeping with the similar relations between SV and both $A_{LVED}$ and $P_{LVEDtm}$ (see Figure 2A and Figure 2B)[30] .

Figure 5 shows the relation between estimated $P_{LVEDtm}$ ($P_{LAED}$ − $P_{RVED}$) and $P_{LVEDtm}$ (r = 0.95, P < 0.0001). The strong linear correlation suggests that estimated $P_{LVEDtm}$ was an accurate estimate of $P_{LVEDtm}$ over the full range of conditions.

Figure 6A, Figure 6B and Figure 6C show the relations between SPV and other measures of cyclic variation – PPV, SVV, and $d_{Down}$. Volume loading decreased and PEEP increased PPV, SVV, $d_{Down}$ and SPV. (r = 0.91, 0.97, and 0.78 and P < 0.0001, 0.0001 and 0.001, respectively).

## Discussion
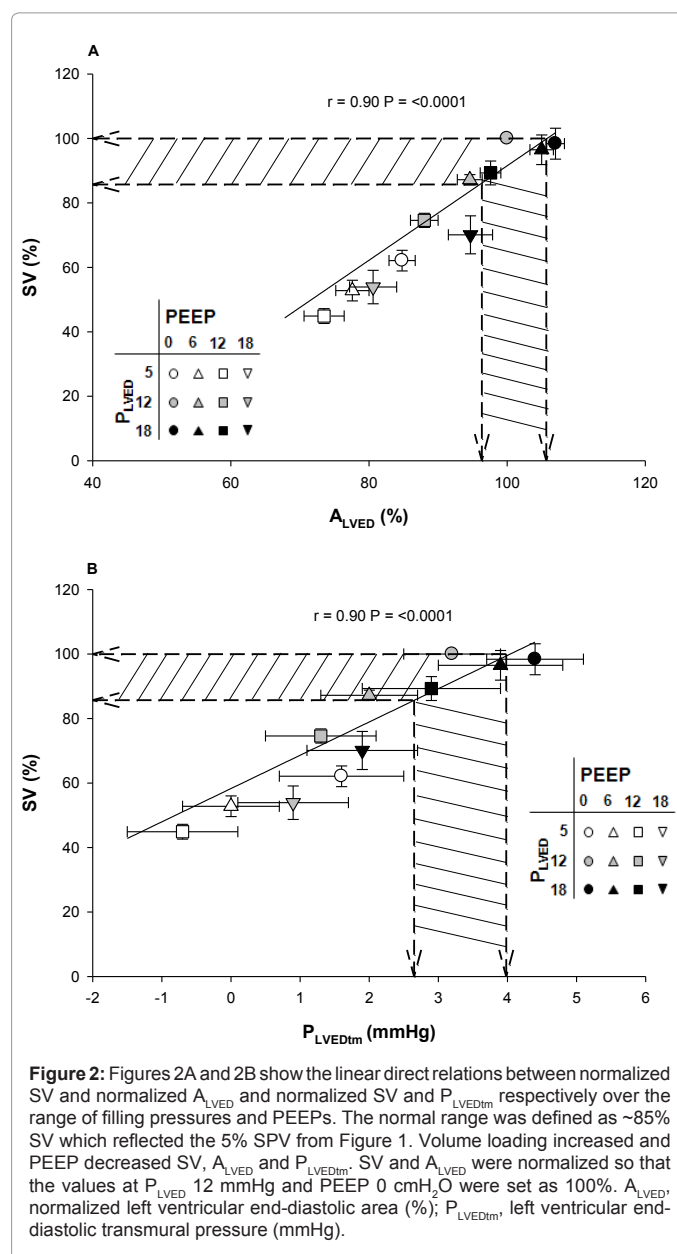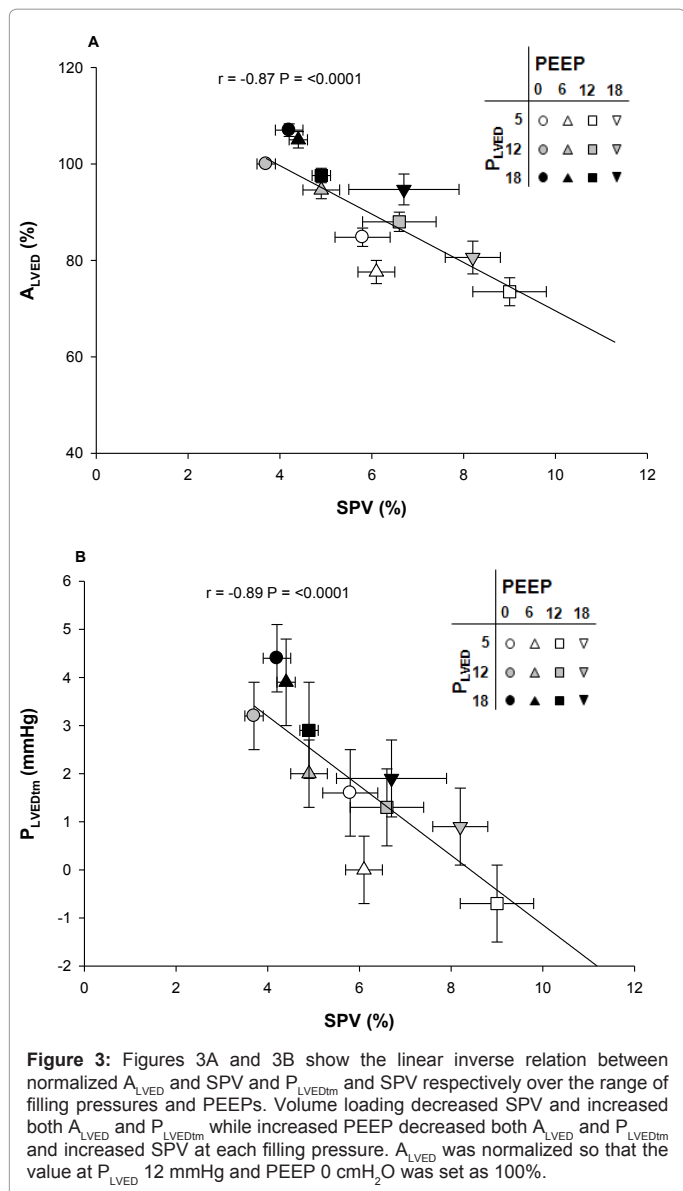
The present study, which was performed in a mechanically



**Figure 2:** Figures 2A and 2B show the linear direct relations between normalized SV and normalized $A_{LVED}$ and normalized SV and $P_{LVEDtm}$ respectively over the range of filling pressures and PEEPs. The normal range was defined as ~85% SV which reflected the 5% SPV from Figure 1. Volume loading increased and PEEP decreased SV, $A_{LVED}$ and $P_{LVEDtm}$. SV and $A_{LVED}$ were normalized so that the values at $P_{LVED}$ 12 mmHg and PEEP 0 cmH$_2$O were set as 100%. $A_{LVED}$, normalized left ventricular end-diastolic area (%); $P_{LVEDtm}$, left ventricular end-diastolic transmural pressure (mmHg).

**Figure 3:** Figures 3A and 3B show the linear inverse relation between normalized $A_{LVED}$ and SPV and $P_{LVEDtm}$ and SPV respectively over the range of filling pressures and PEEPs. Volume loading decreased SPV and increased both $A_{LVED}$ and $P_{LVEDtm}$ while increased PEEP decreased both $A_{LVED}$ and $P_{LVEDtm}$ and increased SPV at each filling pressure. $A_{LVED}$ was normalized so that the value at $P_{LVED}$ 12 mmHg and PEEP 0 cmH$_2$O was set as 100%.

ventilated canine model of ALI, shows that over a wide range of filling pressures and levels of PEEP, SPV was very closely related to LV preload during the ventilation cycle. In keeping with previous studies, SPV was also closely associated with LV output [1-3,12-16]. Despite the differences in our animal model and the patients studied by Kramer et al. [3], there was close agreement in the relative threshold in SPV that was predictive of volume responsiveness. Thus, when SPV was greater than approximately 5%, subsequent volume loading substantially increased LV preload and output. We also found that other conventional predictors of preload responsiveness (PPV, SVV and d$_{Down}$) were closely related to SPV.

The ability to predict hemodynamic responsiveness to a volume challenge has been problematic. Relying on pulmonary capillary wedge pressure to reflect ventricular volume, Perel et al. [12] and Szold et al. [15] showed that pulmonary capillary wedge pressure was related to SPV with both volume loading and phlebotomy in mechanically ventilated dogs. However, filling pressure cannot be used to reflect preload during mechanical ventilation (as is clear in Figure 4) or predict volume responsiveness [31-34]. Indeed, Denault et al. [35] found that

changes in systolic arterial pressure reflected changes in airway and intrathoracic pressure better than changes in echocardiographic end-diastolic area measurements in cardiac surgery patients. However, their study included patients with various degrees of systolic and diastolic dysfunction making comparisons to results in our animal model difficult. Importantly, our data suggest that the LV was operating on the steep portion of the cardiac function curve throughout most of the intracavitary pressures and PEEPs used with an apparent plateau only observed at $P_{LVED}$ 18 mmHg, PEEPs 0 and 6 cmH$_2$O (Figure 2A and Figure 2B).

## Assessment of LV preload

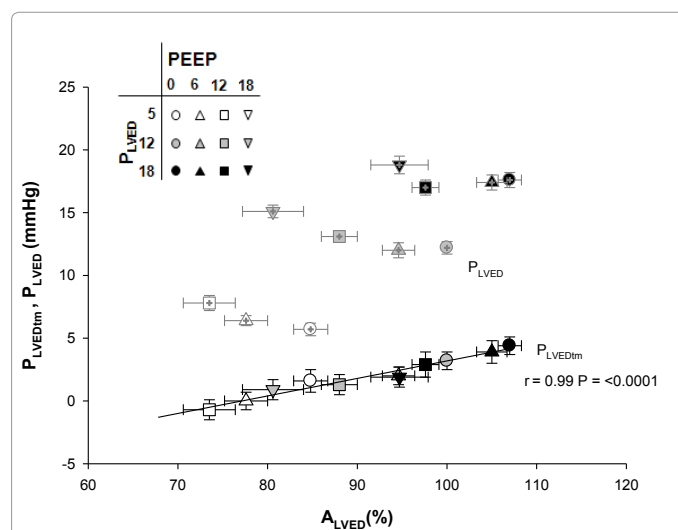Central venous and pulmonary capillary wedge pressures are poor



**Figure 4:** Figure 4 shows the relations between $P_{LVED}$, $P_{LVEDtm}$ and $A_{LVED}$ over the range of filling pressures and PEEPs. Increased PEEP decreased $A_{LVED}$ and $P_{LVEDtm}$ while $P_{LVED}$ did not change or increase. At each level of PEEP, volume loading increased $A_{LVED}$, $P_{LVED}$ and $P_{LVEDtm}$. $P_{LVED}$, left ventricular end-diastolic pressure (mmHg).
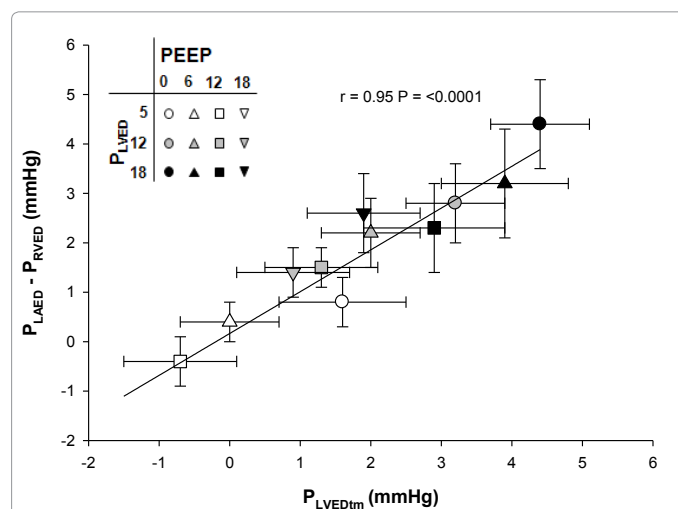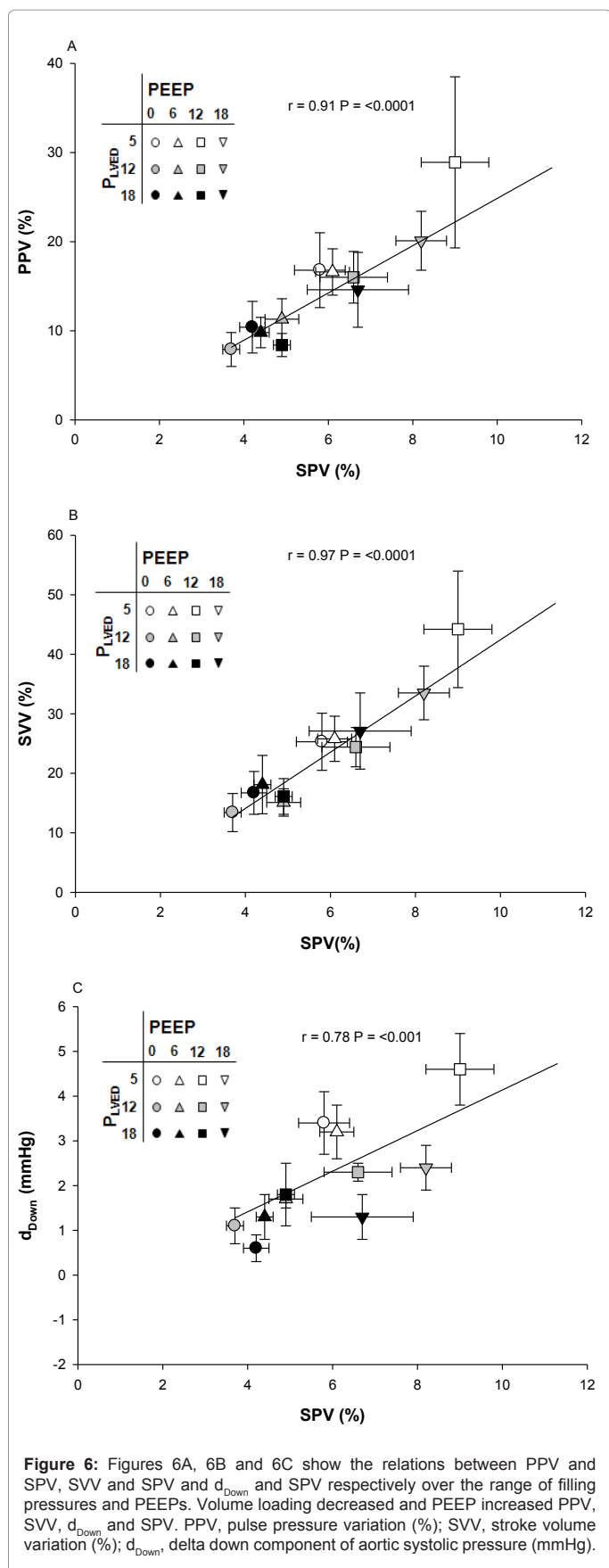


**Figure 5:** Figure 5 shows the relation between estimated $P_{LVEDtm}$ ($P_{LAED} - P_{RVED}$) and $P_{LVEDtm}$ over the range of filling pressures and PEEPs. Volume loading increased and PEEP decreased both estimated $P_{LVEDtm}$ ($P_{LAED} - P_{RVED}$) and $P_{LVEDtm}$. $P_{LAED}$, left atrial end-diastolic pressure (mmHg); $P_{RVED}$, right ventricular end-diastolic pressure (mmHg).

**Figure 6:** Figures 6A, 6B and 6C show the relations between PPV and SPV, SVV and SPV and $d_{Down}$ and SPV respectively over the range of filling pressures and PEEPs. Volume loading decreased and PEEP increased PPV, SVV, $d_{Down}$ and SPV. PPV, pulse pressure variation (%); SVV, stroke volume variation (%); $d_{Down}$, delta down component of aortic systolic pressure (mmHg).

measures of ventricular preload during mechanical ventilation and are generally believed to be unreliable in predicting the hemodynamic response to a volume challenge [36]. Previous experimental models using sonomicrometry have shown that $A_{LVED}$ reflects LV volume accurately [28,29]. Others have utilized flow-directed pulmonary artery catheters to measure pulmonary capillary wedge pressure and subtracted directly measured or estimated pericardial pressure to calculate transmural LV end-diastolic pressure; this has also been shown to be a useful estimate of LV preload in both animal and patient studies [18,37,38]. In the present study, we used two well validated measures of LV preload – LV end-diastolic dimensions [28,29] and transmural pressure [18,37,38]. Unfortunately, these measurements are not easily obtained clinically. Since pulmonary capillary wedge pressure is closely related to LV end-diastolic pressure and right atrial pressure approximates pericardial pressure, our results suggest that a flow-directed pulmonary artery catheter might be used to provide a clinical estimate of LV end-diastolic transmural pressure: pulmonary capillary wedge pressure minus right atrial pressure [37,39,40].

**Physiological considerations**

Many cardiopulmonary interactions influence LV preload and, thus, output. Opening the chest cavity greatly reduces SPV [35] which implies that these interactions are highly dependent on cyclical intrathoracic pressure changes during mechanical ventilation. During lung inflation, a transient decrease in RV inflow [4,5] and increase in RV afterload [41] contribute to a transient decrease in RV stroke volume [4,5,42]. Simultaneously, lung inflation squeezes blood out of the pulmonary circulation into the left heart [9]. Reduced RV inflow combined with increased LV inflow results in an increased transseptal pressure gradient which causes rightward septal shift (direct ventricular interaction) and increased LV preload despite the decreased sum of the ventricular diameters [4,5,42]. Although LV afterload is considered to decrease during lung inflation [10], much of the increase in systolic arterial pressure during inflation can be attributed to increased LV output because of the increased LV preload [43]. During lung deflation, increased RV inflow coupled with decreased LV inflow (partly attributed to the previously reduced RV stroke volume and transit time through the pulmonary circulation as well as increased capacity in the pulmonary circulation) result in a decreased transseptal pressure gradient, leftward septal shift and decreased LV preload and output [4,5]. The reduced SV accounts for much of the decrease in systolic arterial pressure during expiration.

Coyle et al. [44] first used the term "Positive Pressure Paradox" in mechanically ventilated intensive care patients to describe the biphasic response of systolic arterial pressure characterized by an initial increase in pressure during inspiration and subsequent drop in pressure below baseline during the expiratory phase. Their results suggested the accentuated paradox seen in hypovolemic states was reduced by a volume challenge with the reduction in the $d_{Down}$ component appearing to be of particular importance. Perel et al. [12] subsequently showed that the $d_{Down}$ component reflects volume status and is closely related to changes in CO. However, the $d_{Up}$ remained unchanged in their canine model of graded hemorrhage. These results were subsequently validated by another study which demonstrated that changes in SPV and $d_{Down}$ were related to changes in LV preload following abdominal aortic surgery [1]. In ventilated patients, Rooke et al. [14] showed that volume loading reduced while volume removal increased $d_{Down}$ and a value $\leq 2$ mmHg would predict minimal intravascular volume depletion. This corresponds well to our data – a $d_{Down}$ of $\sim \leq 2$ mmHg was associated with normal values of SPV. Moreover, our data show

that volume loading reduces SPV (and SVV) in relation to changes in LV preload which we and others [1,12] attribute mainly to a reduced expiratory decrease in $d_{Down}$ (SV). As changes in LV output are a major determinant of changes in arterial pressure, it is not surprising that previous studies have shown similar results when comparing SVV and SPV/PPV in predicting the response to a volume challenge [45,46]. Predictably, we showed strong correlations between these dynamic measurements.

### Clinical relevance

Our results suggest that estimated $P_{LVEDtm}$, using measurements obtained with a flow-directed pulmonary artery catheter, might be used to predict the hemodynamic response to volume loading during mechanical ventilation. In patients with normal hearts, a low value of estimated $P_{LVEDtm}$ may predict volume responsiveness while a high value may indicate that LV preload cannot be increased substantially. It may be appropriate to revisit the "dry vs wet" strategy that has been recently tested [47] to determine the best approach to managing patients with normal hearts and ALI in whom volume loading is to be considered. Because our data were obtained in animals with normal hearts, it is unlikely that a narrow range of estimated $P_{LVEDtm}$ would suffice to predict responsiveness in patients with abnormal hearts in whom optimal filling pressures would vary to a greater degree. Importantly, as previously indicated by Pinsky [48], patients with small and stiff LV's (e.g.'s LV concentric hypertrophy or myocardial fibrosis) could be poorly responsive while some with large LV's may still be responsive. This remains to be tested clinically.

### Study limitations

There are several limitations to the study. First, SPV is not only related to variations in SV and volume status, but also modulated by transmission of pleural pressure to the thoracic aorta. Indeed, high tidal volumes have been shown to correlate well with SPV [15] and SVV [49]. In accordance with recommended ventilation parameters for large animals [17], 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. Secondly, we used a constant volume mode of ventilation with a fixed inspiratory:expiratory ratio (1:2) making comparisons to other modes of ventilation or pressure controlled ventilation difficult. Different ventilator algorithms may alter the ratio thereby contribute differently to SPV independent of volume status. Thirdly, interpretation of results may be limited to ALI/ acute respiratory distress syndrome (ARDS) as reduced lung compliance may limit the transmission of airway pressure to the pleural space thereby limiting pleural pressure swings for a given tidal volume. However, it has been previously shown in an animal ALI model that changes in pleural pressure and $P_{PERI}$ are more dependent on tidal volume than pressure [50]. In keeping with this, there was no difference in SPV between baseline and ALI at $P_{LVED}$ 5 mmHg and PEEP 0 cmH$_2$O (5 ± 0 and 6 ± 1 % respectively $P$ = NS).

### Conclusions

The present study showed that changes in SPV were closely, inversely related to LV preload and SV, which indicates that LV preload is a major determinant of SPV. A baseline SPV of approximately ≤ 5% or $P_{LVEDtm}$ of ≥ 2.5 mmHg predicted little change in SV (<15%) with volume loading suggesting a cutoff for predicting limited versus substantial responsiveness in our model. An estimate of $P_{LVEDtm}$ based on measurements derived from a flow-directed pulmonary artery catheter may prove useful in predicting volume responsiveness in

ventilated patients. Our results highlight the need to assess LV preload accurately to predict responsiveness to volume loading.

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