Dynamic effects of positive-pressure ventilation on canine left ventricular pressure-volume relations

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Denault, Andre Y., John Gorcsan III, and Michael R. Pinsky. Dynamic effects of positive-pressure ventilation on canine left ventricular pressure-volume relations. J Appl Physiol 91: 298–308, 2001.—Positive-pressure ventilation (PPV) may affect left ventricular (LV) performance by altering both LV diastolic compliance and pericardial pressure (Ppc). We measured the effect of PPV on LV intraluminal pressure, Ppc, LV volume, and LV cross-sectional area in 17 acute anesthetized dogs. To account for changes in lung volume independent of changes in Ppc and differences in contractility, measures were made during both open- and closed-chest conditions, during closed chest with and without chest wall binding, and after propranolol-induced acute ventricular failure (AVF). Apneic end-systolic pressure-volume relations (ESPVR) were generated by inferior vena caval occlusions. With the open chest, PPV had no effects. With the chest closed, PPV inspiration decreased LV end-diastolic volume (EDV) along its diastolic compliance curve and decreased end-systolic volume (ESV) such that the end-systolic pressure-volume domain was shifted to a point left of the LV ESPVR, even when referenced to Ppc. The decrease in EDV was greater in control than in AVF conditions, whereas the shift of the ESV to the left of the ESPVR was greater with AVF than in control conditions. We conclude that the hemodynamic effects of PPV inspiration are due primarily to changes in intrathoracic pressure and that the inspiration-induced decreases of LV EDV reflect direct effects of intrathoracic pressure on LV filling. The decreases in LV ESV exceed the amount explained solely by a reduction in LV ejection pressure.

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especially when Plv is measured relative to both atmosphere and surrounding pressure. First, assessment of the instantaneous Plv-LV volume relationship allows for the characterization of LV diastolic compliance, EDV, and ejection performance. Second, the relative changes in this relation during open chest vs. closed chest during positive-pressure ventilation would separate out the selective effects of changes in lung volume from changes in ITP on LV performance. The limitation of such an analysis is the accurate measure of LV volume throughout the cardiac cycle during mechanical ventilation. Using conductance catheter technology, our laboratory has been able to circumvent this obstacle (16).

We hypothesized that positive-pressure ventilation alters LV function primarily by varying ITP, not by altering lung volume. Accordingly, first we predicted a shift in the Plv-LV volume relation to the left during inspiration, with pressure in the x-axis, to a degree proportional to the increase in ITP, such that the shift would be consistent with a positive-pressure ventilation-induced increase in ITP without a change in transmural LV ejection pressure. Second, we further hypothesized that LV EDV (preload) should also decrease with positive-pressure inspiration. However, based on the above potential interactions, it was not clear to us to what extent the decrease in EDV would be due to decreased LV filling (preceding the decrease in ESV) because of either 1) cardiac compression from the expanding lungs, 2) phasic decreases in venous return reaching the LV (not being coupled with changes in ESV), or 3) decreased LV afterload (following the decreases in ESV). Finally, based on our laboratory’s previous studies (37, 40, 41), we also predicted that, during acute ventricular failure (AVF), ESV would decrease more than EDV, thus increasing stroke volume (SV), whereas SV would fall when ventricular function was normal, because the decrease in EDV would exceed the decrease in ESV.

Accordingly, we examined the effect of positive-pressure ventilation with normal and reduced chest wall compliance in both the Plv-LV volume relationship and the ESPVR in an intact animal model during both basal (normal) and AVF conditions.

**MATERIALS AND METHODS**

After approval of our protocol by our Institutional Animal Care and Use Committee, 17 male mongrel dogs (21.5 ± 2.4 kg body wt) were anesthetized with intravenous pentobarbital sodium (30 mg/kg) after fasting for 12 h. Anesthesia was maintained during the protocol by a continuous infusion of pentobarbital (2 mg·kg⁻¹·h⁻¹), supplemented (50–75 mg iv) as necessary to prevent spontaneous movement during surgery. The trachea were intubated with a 9.0-mm-inner-diameter Hi-Lo cuffed endotracheal tube (National Catheter, Argyle, NY) with a port open at the distal end of the endotracheal tube for measuring airway pressure (Paw). IPPV during the surgical procedure and as described within the protocol was accomplished by a mechanical ventilator (Servo ventilator 900B, Siemens, Elena, Sweden) at a tidal volume of 10–13 ml/kg, constant inspiratory flow, and an inspiratory time comprising 30% of the respiratory cycle. Enriched inspired O₂ (inspired fraction of O₂ = 0.28) was given, and arterial blood gases were periodically monitored (ABL-30 Radiometer, Copenhagen, Denmark). Changes in ventilatory frequency or supplemental intravenous doses of sodium bicarbonate were given as necessary to maintain acid-base balance. A 7.5-F flow-directed, balloon-tipped pulmonary arterial thermistor catheter (American Edwards, Santa Ana, CA) was advanced into the pulmonary artery.

Saline-filled polyethylene catheters with multiple side holes (PE-90) were advanced into the right atrium and midthoracic aorta from peripheral cutdown sites. A high-fidelity pressure-tipped transducer (MPC-500, Millar, Houston, TX) was placed in the LV from a carotid artery to measure Plv. The electrocardiogram from a standard lead II was monitored.

A 10-pole dual-phase conductance catheter (7.5 Fr, Leycom, Leiden, The Netherlands) was also inserted into the LV from the other carotid artery. In four dogs, a transesophageal echocardiographic (TEE) probe (Sonos 1500, Hewlett Packard Systems, Anaheim, CA) was inserted in the esophagus and positioned in the stomach for a transgastric view of the LV function at the midpapillary level.

In 8 of the 17 dogs, a midline sternotomy was performed before the experiment was begun, and the heart was suspended in a pericardial cradle. The position of the right atrial catheter was confirmed by palpation. A hydraulic occluder was placed around the intrathoracic inferior vena cava (IVC). A lead bead was sewn into the pericardium at the apex of the LV cavity to aid in the positioning of the conductance catheter along the long axis of the LV under fluoroscopic guidance. Fluoroscopy was repeated periodically during the study to confirm the stability of the conductance catheter position and was validated during autopsy after the study was completed. A calibrated circumferential electromagnetic flow probe (Carolina Medical, King, NC) was positioned snugly around the aortic root. Flow probe signals were calibrated in vitro and found to be linear to 5% over the range of flows studied. Zero flow was taken as the diastolic plateau of the flow signals. LV SV was derived by integration of the flow signal and was itself cross-validated against thermocouple-derived SV (average of five 10-ml iced injections of 5% dextrose in water during steady-state anexa). A flat Holst-type air-filled (10 × 1.5 cm) balloon catheter was placed in the pericardium on the lateral aspect of the LV free wall and held in place by a stay suture. For measurements of pericardial pressure (Ppc), ≤0.5 ml of air was left in the balloon, as determined by inspection of the in situ balloon pressure-volume relation, as previously described by our laboratory (36, 41, 42). The pericardium was reapproximated and closed with multiple sutures. Chest tubes (20 Fr) were inserted into both pleural cavities to evacuate air and fluid from the thoracic cavity by continuous underwater seal drainage (−15 cmH₂O). The sternum was reapproximated, and the hydraulic occluder, pericardial balloon catheter, and flow probe cables were exteriorized. The fascia and skin were closed in three layers to ensure an airtight seal.

In the remaining 9 of the 17 dogs, studies were performed first before sternotomy to control for the effects that thoracotomy may have on the observed heart-lung interactions. In these animals, an intravascular hydraulic balloon catheter (Fogerty) was inserted percutaneously from the right external jugular vein and positioned under fluoroscopy in the intrathoracic IVC. Inflation of the balloon was used to rapidly and transiently reduce venous return. No measure of Ppc was attempted in these animals. After the studies described below, a sternotomy was performed, an electromagnetic flow probe was inserted around the aortic root, and the animals...
were studied again in closed-chest conditions to validate the accuracy of the LV volume signal. After the surgical procedure, which took ~2 h, the animals were observed for a 30-min period to document hemodynamic stability. Acid-base and arterial oxygenation variables were adjusted to maintain pH between 7.3 and 7.4, PCO2 between 30 and 40 Torr, and P O2 > 90 Torr. The vascular catheters were connected to low-displacement transducers (Micron MP-15, Gould, Cleveland, OH), and the Paw and Ppc catheters were connected to large diaphragm transducers (Bell and Howell 4-3271, Gould). The transducers were calibrated using a mercury manometer. The pressure, flow, and conductance catheter signals were continuously recorded on an eight-channel recorder (Gould 2800) and via an analog-to-digital board with customized software for data acquisition, at a sampling rate of 162 Hz, onto a computer (486 PC, IBM compatible).

All vascular pressures were referenced to the midthoracic plane. The zero hydrostatic pressure of all catheters was determined at autopsy by exposing the catheter opening ports to air in situ during the autopsy. At the conclusion of the experiment, the animals were killed while under general anesthesia by intravenous injection of KCl. In some of the animals, at the end of the experiment the effect of positive-pressure ventilation of Plv and LV volume was examined in the asystolic state, both before and after sternotomy.

The following variables were continuously recorded: echocardiogram, aortic flow (Qao), LV volume, Plv, aortic pressure, right atrial pressure, pulmonary arterial pressure, and Paw. In eight dogs, Ppc was also recorded. Transmural vascular pressures were calculated by referencing intrathoracic vascular pressures to Ppc.

The continuous on-line recording of electrical conductance was used as a method for measuring ventricular chamber volumes using the dual-phase method has been previously described and validated by several authors (1, 3, 24) and by us in this preparation (17). Conductance signals are digitized through a 12-bit analog-to-digital converter at a sampling rate of 50 Hz by a computer (386 PC, IBM compatible) and stored for further analysis on disk. A custom-made program (Sigma 5, Lycem) allowed for the reconstruction of the Plv-LV volume relation when the data volume are interfaced with intraluminal Plv data. These data, when calibrated by the hypertonic bolus method (0.5 ml 6% NaCl), allowed for the calculation of the excessive conductance signal due to myocardial tissue volume and mean right ventricular (RV) blood volume (parallel conductance) (25).

**Automated border detection TEE evaluation.** To further validate the observed LV volume changes from the conductance catheter during positive-pressure ventilation, in four dogs, a two-dimensional TEE probe was inserted (Sonos 1500, Hewlett Packard Systems). The TEE signals were processed by an echocardiographic automated border detection (ABD) algorithm. The image was obtained from a uniplane 5-MHz, 64-element, phased-array scanner. LV stroke area, which is the difference between the maximum end-diastolic area (EDA) and minimum end-systolic area (ESA), and the fractional area change (FAC) in percent [FAC = 100 × (1 – ESA/EDA)] were calculated for each beat. Stroke area, EDA, and ESA were taken to reflect SV, EDV, and ESV, respectively. FAC was taken to reflect LV ejection fraction. The images analyzed from the TEE ABD were obtained from a transgastric, midventricular, short-axis view by using the LV midpapillary level as an anatomic landmark. These measurements and calculations, along with the pressure measures, were stored on computer disk for subsequent analysis (model DN3550, Apollo Computer, Chelmsford, MA). The TEE technique using this border detection algorithm has been previously validated by others (34, 46) and us in this model.

**Conductance catheter validation protocol.** Our laboratory has previously shown that conductance catheter-derived and echocardiographic ABD-derived LV volumes give identical time-volume curves over a wide range of changes in RV volumes (17). Thus ventilation-induced changes in RV volumes should minimally affect sensed LV volume by conductance catheter methodologies. However, our laboratory has also shown that flooding the thoracic compartment with saline (a highly conductive medium) increases conductance catheter-sensed absolute LV volume (46). Because ventilation induces phasic changes in lung tissue density, ventilation could potentially alter conductance catheter-sensed LV volume, independent of any actual change in LV volume. To assess the potential interaction between lung volume and conductance catheter-sensed LV volume, we measured LV volume at the end of the experimental protocol in the first six animals in asystole during both closed-chest and open-chest conditions. During closed-chest conditions, potential heart-lung interactions were further accentuated by thoracoabdominal binding, as previously described (17). We reasoned that marked increases in ITP induced by positive-pressure inspiration during thoracoabdominal binding should decrease LV volume in a fashion analogous to cardiopulmonary resuscitation. However, when the increase in ITP is minimized by binder removal and then eliminated by sternotomy, similar increases in lung volume would not alter LV volume.

**Protocol.** The protocol consisted of comparing the changes from a steady-state apnea and apneic IVC occlusion of positive-pressure ventilation (tidal volume = 10 ml/kg, breathing frequency = 20 breaths/min, sine wave inspiratory flow) on the Plv-LV volume relationship under a series of conditions described below. The effects of these maneuvers on the Plv-LV volume relation were examined to define changes in LV diastolic compliance, and an apneic rapid ICC occlusion-defined LV ESPV R was examined to define changes in LV ESP-ESV domains.

The first set of experimental conditions was the stable open- or closed-chest postoperative states and is referred to as control. The second set of experimental conditions was identical to the first but was associated with the induction of AVF using a bolus propranolol infusion (1.5–2 mg/kg) with isocnductive fluid resuscitation to maintain hemodynamic stability, as described and validated by our laboratory previously (39). These studies are referred to as AVF. To further increase ITP for the same tidal volume during positive-pressure ventilation, inflatable binders (20-cm width) were placed around the thorax and upper abdomen and, when inflated, in such a fashion as to increase peak Paw by between 20 and 40 mmHg but not to increase end-expiratory Ppc, as previously described by our laboratory (39). The studies performed during the control and AVF conditions in which the binders were inflated are called control-binders and AVF-binders, respectively. Before and after IPPV runs at all conditions, an apneic steady-state Plv-LV volume relation was characterized as the average three cardiac cycles, and then a rapid ICC occlusion-induced LV ESPV R was generated to define both a stable systolic and diastolic hemodynamic condition.

To assess the effect of tidal volume on the Plv-LV volume relationship when ITP did not vary, the ventilatory maneuvers were repeated with the chest fully open but the pericar-
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Conductance catheter validation studies. In all six of the asystolic heart studies, when the chest was open and the lung inflated, there was no measurable variation in the LV volume signal. The LV volume signal did decrease slightly with lung inflation when the chest was closed in three of six animals, but this decrease in measured volume was between 1 and 2 ml for these three preparations. However, no measurable change in the Q₀ao signal was observed, as these volume changes are below the sensitivity of the flow probe. During inspiration, there was a decrease in both ESV (5.4 ± 2.5 ml) and EDV (4.1 ± 3.9 ml) and an increase in the EDP (2.4 ± 2.1 mmHg). The pressure-volume relationship shifted laterally toward the origin, such that the ESP-ESV point lay in a domain to the left of the apneic ESPVR (P < 0.05) when Plv was measured relative to atmosphere, but not when Plv was measured relative to Ppc. With thoracoabdominal binding, ESP increased more (5.4 ± 2.5 vs. 2.4 ± 2.1 mmHg, P < 0.05) than without binders, and EDP increased more than did ESP (5.4 ± 2.5 vs. 1.7 ± 5.3 mmHg, P < 0.05) relative to baseline. The end- inspiratory decreases in ESV and EDV relative to apneic values were not quantitatively different between control and control-binder conditions (Fig. 2). An example of the effect of positive-pressure inspiration of the Plv-LV volume loop during control conditions is shown in Fig. 3.

Positive-pressure ventilation during control and AVF conditions. In nine dogs, the effect of positive-pressure ventilation on LV performance was compared between control and AVF conditions. Although in both conditions there was a decrease in both the EDV and ESV in the positive-pressure inspiration (Fig. 4), the decrease in EDV during control was larger than that in the AVF condition (2.1 ± 1.8 vs. 0.2 ± 4.7 ml, P < 0.01). In addition, although positive-pressure inspiration decreased SV in control conditions, secondary to the decrease in EDV, positive-pressure ventilation did not significantly alter EDV, ESV, or SV during AVF. The increase in EDP tended to be more than the increase in ESV in the control group (2.4 ± 1.2 vs. 1.7 ± 2.7 ml, P < 0.05), but EDP and ESP increased by a similar amount in the AVF group during inspiration. An example of the effect of positive-pressure inspiration of the Plv-LV volume loop during AVF is shown in Fig. 5.

Positive-pressure ventilation during AVF with and without binders. The directional effect of positive-pressure ventilation on LV volume during AVF was not modified when binders were added, although the absolute decrease in end-inspiratory EDV and increase in EDP were greater with binders than without (n = 7) (Fig. 6). There were no significant changes in EDV, ESV, and SV. As in control conditions, binding increased both EDP and ESP (P < 0.05). However, ESP increased more with than without binding during AVF (P < 0.05), whereas EDP increased more than ESP (P < 0.05).

Positive-pressure ventilation during open-chest conditions. During open-chest conditions, either with control (n = 8) or AVF (n = 9), positive-pressure ventilation had no measurable effect on either Plv or LV volume (Fig. 7).

DISCUSSION

Positive-pressure ventilation induces significant ventilatory phase-specific changes in Plv and LV volume. The data from our study demonstrate several interrelated effects. First, baseline ventricular function has a profound effect on the subsequent impact of positive-pressure ventilation on LV performance. When ventricular function is normal, positive-pressure ventilation induces its hemodynamic effects primarily by altering ITP, not lung volume, as illustrated in Fig. 7. The result then of this effect is to decrease LV EDV.
primarily during inspiration without inducing any measurable change in systolic performance. These phenomena are clearly illustrated when $P_{lv}$ is displayed relative to $P_{pc}$ (transmural pressure) when $P_{lv}$-$LV$ volume relations during ventilation are displayed (Figs. 3 and 5).

Because the reduction in LV EDV occurs during end inspiration and is associated with an increase in trans-

![Graphs showing systole and diastole pressure-volume relations](image)

**Fig. 1.** Effect of 4 sequential positive-pressure breaths on arterial pressure ($P_a$), left ventricular (LV) pressure ($P_{lv}$), LV area ($LVA$), and LV volume ($LVV$) during controlled closed-chest conditions. Note that, with each inspiration, $LVA$ and $LVV$ decrease. For the group as a whole, $LVA$ and $LVV$ covaried (pooled data: $r = 0.7$, $P < 0.001$) with excellent individual subject covariance ($r > 0.9$ for each subject). ECG, electrocardiogram; $Paw$, airway pressure.

**Fig. 2.** Effect of positive-pressure inspiration on the change in LV end-systolic pressure (ESP) and volume (ESV) (left), and end-diastolic pressure (EDP) and volume (EDV) (right) relative to the preceding apneic interval for control conditions with (○) and without binders (●). PPV, positive-pressure ventilation. Data are means ± SD.
mural LV EDP, this preload-reducing effect of positive-pressure ventilation is due more to LV compression than ITP-induced reductions in venous return. This is because if the reductions in systemic venous return induced the fall in LV EDV, then it need not occur during end-inspiration, as the reduced flow of blood into the RV takes two to three beats to reach the left side, and, if anything, LV transmural EDP would decrease owing to the decreased flow into the RV, thus increasing LV diastolic compliance. Thus changes in LV preload, and not LV ejection or afterload, define the primary hemodynamic effects of IPPV when ventricular function is normal. These data support the long-held belief that positive-pressure inspiration reduces LV preload (13).

However, when cardiac contractility is reduced, the effects of positive-pressure ventilation are more complex and less easily explained by changes in LV EDV alone. Increases in both lung volume and ITP reduce LV EDV. Similarly, increasing ITP also induces a decrease in LV ESV during AVF conditions to a point not explained totally by a reduction in LV ejection pressure. Specifically, the LV ESP-ESV point at end inspiration is shifted upward and to the left into a domain not described by the transmural LV ESPVR (Fig. 5). The validation studies demonstrate that this shift is not due to a measurement error but reflects augmented LV ejection. These data do not allow us to identify the cause of this improvement in LV ejection efficiency during heart failure states.

Potential mechanisms for the observed increased contraction include 1) resolution of occult myocardial ischemia by afterload reduction, 2) decreased aortic input impedance by the cyclical increases in ITP, and 3) increased synchrony of contraction among regions of the heart. Decreased aortic input impedance has been
shown by our group to occur when positive-pressure ventilation is given to animals after induction of AVF induced by massive adrenergic blockade (38).

Similarly, our laboratory recently demonstrated that reduced LV ejection asynchrony shifts the LV ESP-ESV domain to the left of the baseline ESPVR (47). Although we cannot exclude the possibility of occult myocardial ischemia, the end-inspiration-only shift of the ESP-ESV domain makes this explanation unlikely. Because our laboratory previously documented that aortic input impedance changes only occur with brief and rapid increasing in ITP induced by high-frequency jet ventilation, we believe that the most likely candidate for the observed reduction in LV ESV beyond that explained by reduced ejection pressure must be improved LV ejection synchrony (37). However, specific studies addressing this issue directly need to be done to validate or refute this hypothesis.

To understand the hemodynamic effects of ventilation, it is necessary to analyze the effects of ventilation throughout the ventilatory cycle. Ventilation has profound phase-specific effects on both LV preload (EDV) and afterload.

Regarding LV preload, positive-pressure ventilation may directly and indirectly affect LV EDV (preload). Increasing lung volume above functional residual capacity will decrease alveolar but increase extra-alveolar vascular capacitance (29). The subsequent effect of this shift of pulmonary blood on pulmonary venous flow into the LV will depend on the initial state of distention of the alveolar vessels and the degree to which lung volume increases (8). This inflation-induced change in pulmonary venous flow is also coupled with a mechanical compressive effect of the increasing lung volume that impedes cardiac filling (4). Changes in intrapulmonary vascular capacitance cannot ex-
plain our data. Because AVF was associated with intravascular fluid resuscitation and an increased LV filling pressure, inspiration should have increased pulmonary venous inflow in this state. We saw LV EDV decrease in both control and AVF states.

Lung expansion compresses the heart, thus increasing both juxtacardiac pleural pressure and Ppc (36). LV EDV becomes limited during inspiration (28) by this process in a fashion analogous to cardiac tamponade, except here the lungs and not the pericardium limit absolute cardiac volumes, and both Ppc and pleural pressures increase equally. Importantly, any reduction in LV EDV would occur during inspiration and need not be associated with any change in LV diastolic compliance when it is measured as Plv relative to Ppc. Our data demonstrate that this is the most likely mechanism for the reduction in LV EDV during positive-pressure ventilation.

However, as the lungs expand during positive-pressure ventilation, ITP also increases. Increasing ITP by increasing right atrial pressure decreases the pressure gradient for systemic venous return, thus decreasing venous blood flow to the RV and reducing intrathoracic blood volume (19, 35). This will have two opposite effects on LV EDV. First, because RV EDV decreases (4), LV diastolic compliance will increase through the mechanism of ventricular interdependence, thus indirectly increasing LV EDV for a constant filling pressure (50) but in phase with positive-pressure inspiration. Second, because the two ventricles function in series through the pulmonary circulation, any inspiration-associated decrease in venous return to the RV must eventually decrease LV EDV (13). Importantly, the decrease in LV EDV need not occur during inspiration and, as was previously shown, may present as a phase lag for blood flow from the RV to LV such that LV EDV may decrease during expiration (45). Thus measures of Plv, even when referenced to Ppc, may not reflect either LV EDV or its change during ventilation because of phase-specific changes in LV diastolic compliance. Even measures of LV dimensions may be misleading, if they are examined in only one dimension, because free-wall-to-septal dimensions may vary in the opposite direction as apico-posterior dimensions during ventilation (4). Furthermore, because LV deformation of the LV short axis occurs with ventilation, models of LV volume changes from ultrasonic crystals, using orthogonal projection modeling, may not track actual LV volume changes during ventilation. Our data suggest that, although some decrease in RV inflow may occur during positive-pressure ventilation, it is not a primary cause of decreasing cardiac output in this model.

Similarly, positive-pressure ventilation alters LV afterload in a ventilatory phase-specific fashion. Positive-pressure inspiration increases ITP to the extent that lung volume increases. If arterial pressure remains, then LV ejection pressure will decrease, augmenting LV ejection to a lower ESV as defined by the LV ESPVR (9). Whenever LV contractility is reduced, this afterload reducing effect of positive-pressure ventilation becomes hemodynamically important (37, 39). Unlike ventilation-induced changes in LV EDV that can occur at any time during the ventilatory cycle, if the LV afterload-reducing effect of positive-pressure ventilation is present, it must occur during inspiration, because this is the time that ITP increases. Importantly, if positive-pressure ventilation abolishes spontaneous ventilatory negative swings in ITP, then this reduction in LV afterload can be profound (26, 43). Furthermore, LV preload and afterload are closely linked. Reducing LV preload not only decreases LV output but also decreases LV ESV, thus decreasing LV systolic wall stress.

As described above, our data directly address these complex phase-specific interactions. We found that LV developed pressure (LV ESP relative to Ppc) did not decrease between end expiration and end-inspiration. If positive-pressure inspiration only decreased preload, then LV developed pressure should also decrease by the Starling mechanism. These data are, however, consistent with previous studies (14, 39, 41) that demonstrated that increasing ITP reduces LV ejection pressure, thus maintaining LV SV, despite associated
reductions in LV EDV. The baseline contractile state has an important impact on the subsequent hemodynamic response to positive-pressure inspiration. During both control and AVF conditions, the decrease in end-inspiratory LV ESV exceeded that predicted by the associated reduction in LV ejection pressure. That is, the end-inspiratory LV ESP-ESV domain fell on a point to the left of the LV ESPVR (Fig. 5). Thus increasing ITP improved ejection performance to an extent greater than can be explained simply by a reduction in LV ejection pressure. Importantly, this also resulted in a greater end-inspiratory increase in LV SV.

Furthermore, positive-pressure inspiration reduced LV EDV less during AVF than during control conditions, whereas the percent change in end-inspiratory LV ESV was similar under all conditions (Fig. 6). These findings are consistent with the known preload dependency associated with normal cardiac function and preload independency of AVF (39), as demonstrated by Robertson et al. (44) using echocardiographic measurements of LV chambers during Val-salva maneuvers. Positive-pressure ventilation has been previously shown to increase cardiac output in animals in heart failure (39), in critically ill humans with cardiac pump failure (40), in cardiomyopathy patients before cardiac transplantation (37), and in a similar canine model of AVF and thoracoabdominal binding (41). In that model, the increase in SV was of a greater magnitude when the increase in ITP was synchronized with systole (38). These studies demonstrated that increases in pleural pressure would increase extracardiac pressure, thus selectively altering the pressure gradients for either LV ejection (38) or venous return (15, 30). Routine positive-pressure ventilation has inspiration lasting over several cardiac cycles, making cardiac cycle-specific interactions less clear. Accordingly, the present study aimed to examine a more clinically relevant scenario. Because we gave positive-pressure breaths that occurred over three to four cardiac cycles, the resulting effects could represent a combined action of the increase in ITP during both systole and diastole. This nonspecific interaction may explain why we did not observe significant increases in SV in our animals during AVF conditions. Furthermore, the absolute increases in ITP that we gave were less than in previous studies that were targeted at inducing cardiac compression as well as increasing ITP.

The increase in LV EDP during a positive-pressure inspiration could also be related to intraventricular dependence. As lung volume increases above functional residual capacity, pulmonary vascular resistance also increases. Potentially, this would impede RV ejection and may result in an increase in RV volume and pressure that could secondarily either increase intrapericardial pressure (21) or cause a shift of the intraventricular septum to the left and reduce LV diastolic compliance if RV EDV increased (7). This ventricular interdependence mechanism has been described with the use of positive end-expiratory pressure (20–23) and during ventilation of patients with acute respiratory distress syndrome (22). In normal conditions, however, positive-pressure inspiration usually decreases RV EDV by reducing preload. Thus ventricular interdependence either plays a minor role or allows the LV to accommodate more volume for the same distending pressure (5). If RV volume had increased during positive-pressure ventilation, thus limiting LV volume, we would have expected to see a predominant fall in LV EDV. Because both EDV and ESV fell much less during AVF than during normal conditions, whereas RV volumes were more likely to increase more during AVF, owing to fluid resuscitation, ventricular interdependence alone cannot explain these changes.

**Limitations of the study.** Application of conductance catheter technology to measure LV volumes throughout the cardiac cycle has been previously used and validated as reliable to estimate changes in LV volume throughout the cardiac cycle (1, 3, 10, 31). Prior analysis of heart-lung interactions using measures of LV volumes has been hampered by questions of ventilation-induced inaccuracies in the measures of these volumes. Thus we strove to validate the accuracy of our measures of LV volumes at the limits of heart-lung interactions so as to ascertain the degree to which our data could be assumed to reflect actual LV volume behavior during IPPV. The two major elements that contribute to the parallel conductance artifact are myocardial tissue conductance (6) and RV volume (25). Finally, the ESPVR has been shown, in dogs, to be influenced by the type of loading intervention (2) and to become nonlinear when the inotropic state is increased (24). However, the validation steps of our study demonstrate that these limitations are relatively small compared with the total volume changes that we saw. First, LV SV obtained from both the conductance and the Qao signals showed excellent correlation during ventilation. Second, echocardiographic and conductance catheter SVs covaried during apneic IVC occlusion and release maneuvers without any systematic bias (16). Because with IVC occlusion RV must decrease before LV volumes decrease, and during release must increase before LV volumes increase, differences in the occlusion and the relation of measured SV with independent measures of SV would identify parallel conductance artifact in the sensed LV volume signal. We were, however, unable to observe a definitive influence of the RV volume on the LV volume measured with both conductance catheter and flow probe, as our laboratory has previously described (16). The extrapolated maximal change in sensed LV volume that we could have observed, assuming that RV volume varied from 50 to 0 ml for a 20-kg dog, corresponds to <7 ml. This is comparable to data reported by Kass et al. (25) in which they noted a 5- to 7-ml decrease in EDV and ESV with the IVC occlusion, unaccompanied by any fall in SV or Plv. Parallel conductance can vary over time, making validation at one point in time less relevant later on. However, in a nonischemic heart, these changes are minimal (6) and should be insignificant over a single breath. Thus we concluded that our mea-
sures of LV volume changes during the ventilatory cycle do not reflect measurement artifact.

The inspiration-induced change in arterial pressure should mediate arterial baroreflex changes in sympathetic and parasympathetic activity. Indeed, our laboratory (41) previously showed that bilateral carotid sinus nerve sectioning induced an increase in arterial pressure that compensated for the ITP-induced reduction in afterload during large tidal volume ventilation and thoracoabdominal binding in a similar canine model. However, because vascular smooth muscle tone cannot vary as rapidly as the cycles of a normal tidal breath, changes in vasomotor tone would have to occur over the entire cardiac cycle and not just at end inspiration. Thus the changes we see in the end-inspiratory LV ESP-ESV domain during AVF conditions cannot be explained by baroreceptor-regulated changes in arterial tone.

In summary, positive-pressure inspiration decreases LV EDV and, during control and AVF, shifts the ESP-VPR to the left in a fashion that cannot be explained by changes in preload and afterload alone. The degree to which ventricular function is altered by positive-pressure ventilation will depend on the changes in ITP and baseline contractile state and are primarily determined by the changes in ITP, not lung volume. When ventricular contractile function is normal, the preload-reducing effect predominates, whereas when ventricular contractility is impaired and ventricular volumes are increased by fluid resuscitation, positive-pressure inspiration primarily decreases ESVs by reducing LV ejection pressure and improving LV ejection.

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