Peripheral Venous Pressure as an Indicator of Preload Responsiveness During Volume Resuscitation from Hemorrhage

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**BACKGROUND:** Fluid resuscitation of hypovolemia presumes that peripheral venous pressure (PVP) increases more than right atrial pressure (RAP), so the net pressure gradient for venous return (PVP-RAP) rises. However, the heart and peripheral venous system function under different compliances that could affect their respective pressures during fluid infusion. In a porcine model of hemorrhage resuscitation, we examined whether RAP increases more than PVP thereby reducing the venous return pressure gradient and blood flow.

**METHODS:** Anesthetized pigs (n = 8) were bled to a mean arterial blood pressure of 40 mm Hg and resuscitated with stored blood and albumin for pulmonary artery occlusion pressures (PAOPs) of 5, 10, 15, and 20 mm Hg. Venous pressures, inferior vena cava blood flow (ultrasonic flowprobe), and left ventricular diastolic compliance (Doppler echocardiography) were measured. Stroke volume variability was calculated.

**RESULTS:** With volume resuscitation, the slope of RAP exceeded PVP (P ≤ 0.0001) when PAOP is 10 to 20 mm Hg, causing the pressure gradient for venous return to progressively decrease. Inferior vena cava blood flow did not further increase after PAOP > 10 mm Hg. The E/e’ ratio increased (P = 0.001) during resuscitation indicating reduced diastolic compliance. A significant curvilinear relationship was found between PVP and stroke volume variability (R² = 0.62; P < 0.001), where fluid responders had PVP < 15 mm Hg.

**CONCLUSIONS:** Fluid resuscitation above a PAOP 10 mm Hg reduces myocardial compliance and reduces the venous return pressure gradient. The hemodynamic response to fluid resuscitation becomes limited by diastolic properties of the heart. PVP measurement during hemorrhage resuscitation may predict fluid responsiveness and nonresponsiveness. (Anesth Analg 2016;123:114–22)

Venous return is a function of stressed vascular volume, venous compliance and resistance, and the filling pressure gradient between the periphery (peripheral venous pressure [PVP]) and the right heart (right atrial pressure [RAP]). During volume resuscitation, the infused fluid increases stressed venous volume and pressure (PVP), which increases the venous return pressure gradient so that preload of the heart improves. Venous return is maximal when RAP equals zero and progressively decreases at higher RAP values. Schlepper demonstrated, in patients, an inverse relationship between superior vena cava blood flow and RAP, where high RAP was associated with reduced venous return.

Both the peripheral and the central venous systems have intrinsic compliances that affect the venous return pressure gradient during volume expansion. The peripheral venous system has a large vascular capacitance and a linear compliance in which an increased blood volume is associated with relatively small changes in PVP. In contrast, the diastolic compliance of the heart appears curvilinear, and, at high filling pressures, becomes governed by the pericardium, cardiac cytoskeleton, and intermyofibrillar collagen. The slope of the diastolic compliance curve of the heart is steeper with, than without, the pericardium, and the pericardium significantly affects filling pressures during volume expansion—particularly on the right side. These differences in compliance could adversely affect the venous return pressure gradient and volume resuscitation efficacy, because RAP could rise faster than PVP.

Experimental studies examining the effect of fluid expansion on the PVP-RAP pressure gradient show contradictory results. Perioperative studies in patients found that both RAP and PVP increased equally during fluid administration, so the net pressure gradient for venous return did not change. However, in those studies, filling pressures in the heart were low, indicating relatively minimal effect from pericardial restraint. In contrast, in volunteers undergoing controlled hemorrhage followed by volume infusion, Echt et al. found that the slope for RAP increased more than PVP, suggesting that the pressure gradient for venous return could decrease during volume resuscitation. Similarly, in closed-chest, anesthetized animals, Fragata and Areias found a biphasic response to...
fluid administration where small (5 mL/kg) and moderate (10 mL/kg) amounts of fluid improved early diastolic filling and cardiac output (CO), whereas a large volume load (15 mL/kg) restricted diastolic flow and reduced left ventricular (LV) compliance. Applegate et al. found that the onset of pericardial restraint occurs when RAP increases >4 to 6 mm Hg and that this progressively restricts the stroke volume (SV) response to further fluid loading. These studies indicate that the hemodynamic response to fluid administration may not represent only systolic function by the position on the Frank-Starling function curve, but rather whether the administered fluid is actually getting to the heart during diastole to increase preload.

Accordingly, in a porcine model of hemorrhage followed by blood-colloid resuscitation, the hypothesis was tested that RAP increases more than PVP, thereby reducing the venous return pressure gradient and inferior vena cava (IVC) blood flow. Because pericardial restraint during volume expansion affects both right and left sides of the heart proportionately, changes in LV diastolic compliance measured by 2D and Doppler transthoracic echocardiography were quantified during fluid resuscitation to examine potential pericardial influence.

METHODS

The animal use protocol was approved by the Institutional Animal Care and Use Committee at the University of Texas Medical Branch and was performed according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Animal Preparation

Farm-raised female Yorkshire pigs (n = 8, 22–35 kg) were sedated with an IM injection of Telazol (Zoetis Inc., Kalamazoo, MI), ketamine, xylazine, and buprenorphine. Animals were then placed prone on a heated forced air warming blanket (Bair Hugger; 3M Center, St Paul, MN) with an oxygen mask placed around the snout. Propofol (2 mg/kg) and ketamine (3 mg/kg) were administered through a 22-gauge ear vein catheter to induce general anesthesia. After orotracheal intubation, animals were mechanically ventilated (Dräger Narkomed 2c, Drägerwerk, Lübeck, Germany) with isoflurane (1%–2%), oxygen, and air (FIO2, 50%), and end-tidal carbon dioxide tension was maintained between 35 and 45 mm Hg. The animals were turned supine, and electrocardiogram leads were placed on the skin, a pulse oximeter probe placed on the ear, and a urinary catheter inserted into the bladder. Cutdown incisions on both femoral triangles were performed. The right femoral artery was catheterized for pressure monitoring. The right tibial vein was exposed, and an 18-gauge catheter was inserted into the vein. Through the center of this catheter, a transducer-tipped pressure sensor (3F Millar Mikro-Tip Pressure Catheter, Houston, TX) was placed and secured. The left femoral vein was catheterized for fluid infusion. The right neck was dissected, and a 5F single-lumen catheter was placed in the right carotid artery for subsequent hemorrhage. The right internal carotid artery was catheterized for pressure monitoring. The right tibial vein was exposed, and a 5F single-lumen catheter was placed into the vein. Through the center of this catheter, a transducer-tipped pressure sensor (3F Millar Mikro-Tip Pressure Catheter) was placed and secured via the 16-gauge catheter. The pulmonary artery catheter was floated into the pulmonary artery by transduced waveform. Via a midline laparotomy incision, the spleen was removed and its blood immediately drained into a sterile heparinized beaker. The IVC was exposed proximal to the liver and encircled with a Doppler flowprobe (size 18–20 mm; Transonic, Ithaca, NY). To ensure optimal conduction between the Doppler transducer and the IVC, 15 mL blood was allowed to clot and placed in and around the flowprobe. All surgical sites were closed in layers. Prewarmed lactated Ringer’s solution (15 mL/kg) was administered during the surgical preparation. The pig was then positioned in the right lateral decubitus position. All lines were connected to calibrated transducers and appropriately balanced at the sternal axial line. Based on this position and the healthy animal, the pulmonary artery catheter tip was likely positioned in west zone 3. The animal was then connected to a Hamilton G5 Ventilator (Hamilton Medical Inc., Reno, NV), which mandated total IV anesthesia. Isoflurane was discontinued, and a propofol infusion (125 μg/kg/min) was initiated and adjusted based on movement or signs of stimulation. Tidal volume was set at 10 mL/kg synchronized intermittent mandatory ventilation volume control mode. Positive end-expiratory pressure was not used or required. FIO2 was set to 0.4. Spo2 was maintained at 98% to 100%.

A preliminary transthoracic echocardiographic examination was performed to rule out valvular and structural cardiac abnormalities using a 3.5-MHz probe with 2D and spectral Doppler capabilities attached to an ultrasound system (Vivid 7 PRO BT04; GE Medical Systems, Milwaukee, WI).

Data Recording

Hemodynamic variables consisted of the following: mean arterial blood pressure (MAP), RAP, PVP, pulmonary arterial pressure, pulmonary arterial occlusive pressure (PAOP), CO by thermodilution, stroke volume variability (SVV) (Edwards Vigileo, Irvine, CA), pulse oximetry, capnography, heart rate, and IVC blood flow. Arterial blood gases, mixed venous oxygen saturation, electrolytes, hemoglobin, and glucose were measured using a blood gas analyzer. All pressure measurements, the electrocardiogram, pulse oximetry, IVC flow rate, Millar venous pressures (RAP, PVP), and oxygenation and ventilator indices from ventilator were electronically captured at 500 Hz and recorded using PowerLab (ADInstruments, Colorado Springs, CO). Systemic vascular resistance (SVR in dynes·s/cm5) was calculated as:

\[
SVR = \frac{(MAP-CVP)}{CO} \times 80
\]

Transthoracic echocardiography was used to measure LV end-diastolic dimension (EDD) and LV diastolic function at all measurement intervals. Diastolic assessment consisted of mitral inflow velocities (E and A waves) and mitral annular velocity using tissue Doppler (e’). EDD was determined in the parasternal LV long-axis view and provided an independent metric of LV preload. Swine were young and relatively lean, which allowed for optimal imaging of the 2- and 4-chamber apical views in the right lateral position. The same investigator, certified by the National Board of Perioperative Echocardiography, performed echocardiography examinations. Doppler echocardiography and Doppler
Peripheral venous pressure measurements were obtained over 3 to 5 cardiac cycles during a period of apnea. The pulsed Doppler sample volume was placed at the tip of the mitral valve, and peak mitral inflow velocities (E and A waves) were recorded. Tissue Doppler imaging was performed on the lateral aspect of the mitral annulus, and from these data, early (e') diastolic velocity was obtained. Ventricular compliance was assessed using the E/A ratio and the transmitral E velocity to e' ratio or E/e'. The E/e' ratio has been shown to correlate as an index of filling pressures and is a preload-independent index of LV relaxation—specifically as the E/e' ratio increases, the severity of diastolic dysfunction becomes more pronounced.19 LV diastolic dysfunction was assessed using acquired values of E/A and E/e'.

Study Protocol
After surgical preparation, the animal was allowed to stabilize for 30 minutes and baseline parameters were obtained. Next, hemorrhage was initiated from the carotid artery catheter at a rate of 1 mL/kg/min until MAP was <40 mm Hg for 3 minutes. The amount of time required for hemorrhage was 15 to 20 minutes resulting in a 15- to 20-mL/kg hemorrhage. The blood that was removed was stored in heparinized bags. Ten minutes later, measured variables were recorded. Fluid resuscitation was then initiated using either blood (hemorrhaged blood or spleen blood mixed with 5% albumin to maintain baseline hematocrit) or 5% albumin to maintain viscosity. The resuscitation fluid sequence was alternated: 500 mL blood followed by 500 mL albumin and repeated thereafter. Fluid was infused in 100-mL aliquots at a rate of 1 mL/kg/min to achieve a specified PAOP interval of 5, 10, 15, and 20 mm Hg. At each PAOP measurement interval, after 10 minutes of stabilization, parameters were recorded. Once a PAOP of 20 mm Hg was achieved and final measurements were obtained, the animal was euthanized by administering 5 mL/kg propofol followed by a supersaturated potassium chloride solution for cardiac electrical standstill.

Statistical Analysis
The sample size was based on earlier study in 8 animals, by one of our authors who demonstrated a curvilinear relationship between diastolic compliance and acute volume loading.11 We therefore studied 8 animals (n = 8).

Data are presented as mean ± standard error of the mean. Sequential adjacent intervals for each parameter were compared using analysis of variance (SAS). To compare differences in slope, a repeated measurement analysis of variance in mixed effect linear formulation (with compound symmetry covariance) was performed. Statistical significance was designated as P < 0.05. If the values were significantly different, a post hoc Bonferroni test was performed. The reported P values have each been corrected for the 4 comparisons among the 5 PAOP groups. The adjusted P value, P < 0.0125, was therefore considered statistically significant.

The Mauchly sphericity test for repeated measures showed nonsignificance (P = 0.271). The Levene test for homogeneity of variance showed equal variances among PAOP groups (P = 0.702). To test that the residuals were normally distributed, we performed the Lilliefors test statistic (P = 0.150). We concluded that we could reasonably consider the error distribution to be not statistically significantly different from normal.

Simple linear regression analysis was performed as y = P0x + P1, where P0 represents the regression coefficient for the variable x and P1 represents the intercept. Curvilinear relationships, defined using the exponential equation y = eP0x (natural log), were based on better-fitting statistics comparing Akaike information criterion and Bayesian information criterion. The log likelihood ratio test statistic was used to determine the linear relationship between different PAOP filling pressures. Receiver operating characteristic (ROC) curves were performed to assess the sensitivity, specificity, and area under the curve (AUC) for PVP and SVV based on fluid responsiveness with responders having ≥15% increase in SV and nonresponders having <15% increase in SV.

RESULTS
Baseline parameters before hemorrhage are shown in Table 1. The hemodynamic response to hemorrhage and subsequent fluid resuscitation at the 4 PAOP measurement intervals are shown in Table 2. Hemorrhage causes the predicted changes in hemodynamic variables. With fluid resuscitation, MAP is rapidly restored at a PAOP of 5 mm Hg (P < 0.0001), but thereafter undergoes little sequential change. The increases in SV and CO appear similar, with an initial increase (P < 0.0001) followed by a plateau after 10 mm Hg PAOP. Both PVP and RAP increase incrementally (P < 0.0001), reaching their highest values at a PAOP of 20 mm Hg (Table 2). The venous return pressure gradient for trends downward during volume expansion and significantly decreases between PAOP 10 and 20 mm Hg intervals (P = 0.01). IVC blood flow increases significantly after initial resuscitation (P < 0.0001) but plateaus after 10 mm Hg PAOP so that subsequent sequential measurements do not significantly differ.

Hemorrhage results in hypovolemia, and corresponding SV is very low (Fig. 1). Early fluid resuscitation significantly increases SV at PAOP 5 and 10 mm Hg (P < 0.0001). However, despite further volume loading, this relationship plateaus at PAOP 15 and 20 mm Hg. The SV-PAOP

| Table 1. Baseline Hemodynamic and Diastolic Function Data Before Hemorrhage (n = 8 animals)* |
|-----------------------------------------------|-----------------|
| Variable                                      | Baseline        |
| Heart rate (beats/min)                        | 71 ± 5          |
| Mean arterial blood pressure (mm Hg)          | 94 ± 4          |
| Cardiac output (L/min)                        | 4.5 ± 0.6       |
| Peripheral venous pressure (mm Hg)            | 9 ± 1           |
| Right atrial pressure (mm Hg)                 | 4 ± 1           |
| Mean pulmonary artery pressure (mm Hg)        | 17 ± 2          |
| Pulmonary artery occlusion pressure (mm Hg)   | 6 ± 0           |
| Inferior vena cava blood flow (L/min)         | 1.7 ± 0.3       |
| Stroke volume variability (%)                 | 10 ± 1          |
| E/A                                           | 1.3 ± 0.1       |
| E/e'                                          | 4.9 ± 0.2       |
| Systemic vascular resistance (dyne-s/cm²)     | 1600 ± 197      |

*Peripheral venous pressure measured from distal tibial vein.

E/A = ratio of peak mitral inflow velocities during rapid early diastolic filling (E) and after atrial contraction (A); e' = early diastolic mitral annular velocity by tissue Doppler.

*Data represent mean ± SEM.
relationship appears curvilinear ($R^2 = 0.73; P < 0.0001$), as volume responsiveness predominately occurs initially (Fig. 1). In contrast, the SV-EDD relationship appears linear ($R^2 = 0.81; P = 0.001$), where greater EDD causes a corresponding increase in SV in both responders and nonresponders (Fig. 2). The curvilinear diastolic PAOP-EDD relationship is shown in Figure 3 ($R^2 = 0.69; P < 0.001$), where less change in EDD occurs between PAOP 10 and 20 mm Hg compared with lower filling pressures. Of note, most fluid responders are located on the lower half of the graph in contrast to fluid nonresponders on the upper, steeper portion (Fig. 3).

Figure 4 shows the changes in PVP and RAP with hemorrhage and the various levels of resuscitation. Data were grouped from PAOP 2 to PAOP 5 (initial responder phase) and from PAOP 10 to PAOP 20 (nonresponder phase). The slope for RAP = 0.46 × PAOP + 1.1 ($R^2 = 0.64$) was statistically increased ($P < 0.0001$) compared with PVP = 0.37 × PAOP + 6.5 ($R^2 = 0.56$) during volume resuscitation of hemorrhaged animals. The slope and 95% confidence intervals were 0.46 (0.35–0.58) and 0.37 (0.26–0.47) for RAP and PVP, respectively.

Accordingly, the pressure gradient for venous return (defined as the difference between PVP and RAP) steadily decreases during resuscitation where the venous return pressure gradient = −0.15 PAOP + 5.8 ($R^2 = 0.24$; $P = 0.002$). The decrease in pressure gradient is attributable to a greater rise in RAP than PVP during volume expansion (Table 2). Our data show that LV diastolic function changes during volume resuscitation, particularly at elevated filling pressures (Table 2; Fig. 5). The $E/e'$ ratio increases with PAOP ($R^2 = 0.59; P < 0.0001$) as E/A also increases, indicating the onset of impaired relaxation and early pseudonormalization changes, particularly in nonresponders.

The relationship between PVP and SVV during hemorrhage and resuscitation is shown in Figure 6. There is a significant curvilinear relationship between the 2 variables where PVP = 17.35e−0.05 SVV ($R^2 = 0.62; P = 0.001$). Fluid was administered at 4 separate periods (PAOP 5, 10, 15, and 20 mm Hg) in animals ($n = 8$) that produced 32 data pairs, in which there were 18 responders and 14 nonresponders. All responders had PVP values <15 mm Hg.

Figure 7 shows the receiver operating curves for PVP, SVV, and PAOP. The ROC curves were generated based on the definition for responder, an increase in SV ≥15% and nonresponder, SV <15%. The AUC for PVP is 0.94 (95% confidence interval, 0.87–0.99), SVV is 0.79 (95% confidence interval, 0.62–0.96), and PAOP is 0.98 (95% confidence interval, 0.94–0.99). A significant difference is observed between PAOP versus SVV ($P = 0.01$).
Table 3 shows hemoglobin and blood chemistries during hemorrhage and resuscitation. By protocol design, serum hemoglobin remains relatively constant, and all values are within 1 g/dL of each other, although serum hemoglobin was lower at PAOP 10 versus PAOP 5 mm Hg ($P = 0.004$). Glucose concentrations during the experimental protocol did not change significantly. Venous oxygenation increased from hemorrhage to PAOP 5 ($P < 0.0005$), but thereafter did not change. Ionized calcium remains constant throughout the experimental procedure. Serum pH increased from hemorrhage to PAOP 5 ($P = 0.002$), thereafter did not change.

DISCUSSION

We found that, with progressive fluid volume administration in hemorrhaged animals, the slope of rise in RAP exceeds the slope of rise in PVP, causing the net pressure gradient for venous return to decrease. LV diastolic compliance, as reflected by mitral valve E/$e'$ and E/A ratios, changes significantly, which indicates the onset of impaired LV relaxation and reduced myocardial compliance (diastolic dysfunction) during fluid resuscitation, particularly in nonresponders. Accordingly, IVC blood flow fails to sequentially improve after PAOP 10 mm Hg. There is a significant curvilinear relationship between PVP and SVV, suggesting that the measurement of PVP may be a useful static index to predict fluid responsiveness. All fluid responders have PVP $< 15$ mm Hg.

The curvilinearity of the traditional Starling relationship comparing SV with LV end-diastolic pressure (LVEDP) has been used to define and predict a patient’s response to volume administration.21,22 Responders are thought to be functioning on the steep portion of this curve, where SV increases more than LVEDP after a fluid challenge. In contrast, nonresponders are thought to function on the flatter plateau portion of the curve, where filling pressure increases more than SV after parenteral volume expansion. Data from this study confirm this concept as seen in Figure 1.

If, however, SV is plotted against left ventricular end-diastolic volume (LVEDV) instead of LVEDP, the relationship appears linear in normal patients,23,24 as well as in patients with dilated cardiomyopathy,25,26 and may reflect recruitment of unaligned sarcomeres with greater LVEDV and stretch-induced calcium activation of myocytes.25,27 Our data support these findings with the linearity of the SV-LV EDD relationship and equal distribution of fluid...
responders and nonresponders (Fig. 2). These findings suggest that SV should improve in every patient after a fluid challenge if LVEDV increases. However, in practice, fluid responsiveness to a volume challenge is found in only 50% of patients. Consequently, other factors need to be considered to interpret these findings.

The curvilinearity of the SV-LVEDP relationship can be explained by the curvilinearity of the diastolic LVMDP-LVEDV relationship, which indicates that myocardial diastolic compliance may be instrumental in determining fluid responsiveness. The lower flat portion of the diastolic compliance curve represents sarcomere stretch with filling, whereas the steep upper portion reflects imposed restraining influences from the pericardium, cardiac cytoskeleton, and intramyocardial collagen. Because of this configuration, filling pressure in the heart during fluid resuscitation could rise more than PVP, thereby decreasing the pressure gradient for venous return. Data from the current study confirm this concept, as the position on the diastolic compliance curve shifts rightward with fluid resuscitation (Fig. 3) with progressively impaired relaxation causing the pressure gradient for venous return to decrease (Fig. 4). Most fluid responders are located on the lower portion of the diastolic compliance curve, whereas nonresponders are centered on the steep upper portion of the curve (Fig. 3). Furthermore, our results agree with other studies in which large amounts of infused fluid restricted diastolic filling of the heart and reduced LV compliance. Consequently, the hemodynamic response to volume administration not only represents systolic function, as determined by the position on the traditional Starling function curve (Fig. 1), but also whether the administered fluid is actually translocated to the heart during diastole to increase end-diastolic volume.

These data are consistent with the concept of imposed pericardial restraint during fluid administration. It is known that the pericardium causes an upward shift in the diastolic compliance curve of the heart and, with volume expansion, the pericardium contributes to elevated diastolic pressures and limits cardiac filling of both ventricles. Our measurements of E/A and E/e’ during fluid resuscitation indicate that the onset of impaired LV relaxation with pseudonormalization and reduced diastolic compliance occurs during fluid resuscitation from hemorrhagic shock within clinically accepted end points of therapy. Consequently, the slope of RAP change is greater than the slope of PVP change with higher filling pressures. Furthermore, our data are compatible with and help interpret the reported findings of Kumar...
et al.,29,30 where normovolemic volunteers received 3 L of IV saline. In those studies, SV increased not by an increase in LVEDV but from hypervolemic hemodilution with an accompanying reduction in left ventricular end-systolic volume. The crystalloid infusion caused significant reductions in hematocrit, viscosity, and SVR but failed to increase cardiac filling, presumably because of a reduction in diastolic ventricular compliance. Although our data support the concept of progressive pericardial restraint during fluid resuscitation, a definitive study will require direct measurement of pericardial pressure.

After a significant increase in heart rate with hemorrhage, heart rate remained stable throughout the resuscitation period (Table 2). Because heart rate inversely affects right ventricular filling,5 any confounding effect from tachycardia on SV was minimized. Despite a progressive reduction in the venous return filling pressure gradient with fluid volume expansion, IVC blood flow continues a trend to increase, which may represent a progressive reduction in the resistance to venous return throughout volume resuscitation. Multiple factors affect venous return other than the filling pressure gradient, including sympathetic activation which, although not directly affecting venous compliance, may reduce the unstressed venous capacitance causing an increase in blood volume.2,35 During resuscitation, part of the administered fluid may redistribute within the splanchnic venous bed from the stressed volume to replenish the unstressed volume. Last, blood viscosity can affect venous resistance.3 In our study, we minimized any effect of hemodilution and reduced viscosity by alternating albumin with whole blood or albumin mixed with high-hematocrit blood collected from spleen.

In laboratory and clinical studies, dynamic indices have repeatedly proven to be better predictors of fluid volume responsiveness than static indices, such as filling pressures.24 Static central filling pressures such as RAP and PAOP reflect end-diastolic volumes of the heart, as well as unquantifiable influences from myocardial compliance. However, dynamic indices reflect the heart-lung interactions occurring during positive pressure ventilation, causing preload-afterload mismatch in the right ventricle. Our data indicate that PVP may represent a sensitive static index of preload responsiveness during fluid resuscitation of hemorrhagic shock. With the inherent limitations imposed on the acquisition and interpretation of dynamic indices,32 the measurement of PVP may be simpler and applicable in other cases where the use of dynamic indices is limited such as during spontaneous ventilation.

There are several limitations to the present study that require further discussion. Strictly speaking, the net pressure gradient for venous return equals RAP – mean circulatory filling pressure (MCFP), where the latter is the pressure in the venous system during circulatory standstill at zero blood flow and determined by the stressed venous volume. Because of inherent complexities obtaining the MCFP measurement at repeated intervals in an intact animal, we substituted PVP for MCFP, and baseline values of PVP in our animals appear comparable with the MCFP values reported in other studies.1,3,33 Next, we did not directly measure pericardial pressure, and a definitive study would require this measurement in addition to opening the chest and pericardium after fluid resuscitation to conclusively demonstrate pericardial restraint. However, the steep portion of the diastolic compliance curve has already been shown to be significantly influenced by an intact pericardium,11 and all fluid nonresponders in this study were located on this steep portion (Fig. 3). This was a carefully conducted, well-controlled, study in healthy normal animals with normal diastolic compliance, which could explain the high AUC obtained by our ROC curves for PVP, SV, and PAOP. Our data need to be validated in patients with and without diastolic dysfunction. The presence of diastolic dysfunction may cause greater filling pressures in response to fluid infusions than normal patients,34 which could significantly affect the patient’s response to fluid administration. We also measured left- and right-sided pressures and LV diameters but did not quantify intracardiac volumes. Although LVEDV can accurately approximate LVEDV assessed by more invasive means,35 we used transthoracic echocardiography so as not to alter chest wall or pericardial integrity. Volumetric studies of the heart at elevated pericardial pressures show that the atria increase in size more than the ventricles during fluid administration,36 which could account for a further increase in end-diastolic pressure without an increase in LVEDV and SV. Finally, we did not examine the venous pressure waveform during the venous filling phase, such as venous pulse pressure and slope, which could provide further insight into venous capacitance and compliance.37

In conclusion, with progressive fluid resuscitation in hemorrhaged animals, the slope of rise in RAP exceeds the slope of rise in PVP causing the venous return pressure gradient to decrease. Accordingly, IVC blood flow increases with the initial fluid bolus after hemorrhage but fails to sequentially improve when PAOP exceeds 10 mm Hg. There is a significant curvilinear relationship between

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### Table 3. Blood Analysis and Hemoglobin After Hemorrhage and During Varying Levels of Volume Resuscitation (n = 8 Animals)2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hemorrhage (−2 mm Hg)</th>
<th>5 mm Hg</th>
<th>10 mm Hg</th>
<th>15 mm Hg</th>
<th>20 mm Hg</th>
<th>ANOVA (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.0 ± 0.2</td>
<td>9.5 ± 0.3</td>
<td>8.6 ± 0.2</td>
<td>8.4 ± 0.2</td>
<td>8.2 ± 0.2</td>
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<tr>
<td>pH (units)</td>
<td>7.38 ± 0.01</td>
<td>7.31 ± 0.02</td>
<td>7.31 ± 0.01</td>
<td>7.33 ± 0.01</td>
<td>7.36 ± 0.01</td>
<td>0.002</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>125 ± 21</td>
<td>130 ± 19</td>
<td>109 ± 15</td>
<td>88 ± 12</td>
<td>82 ± 10</td>
<td>0.21</td>
</tr>
<tr>
<td>Ionized calcium (mg/dL)</td>
<td>1.3 ± 0</td>
<td>1.3 ± 0</td>
<td>1.2 ± 0</td>
<td>1.2 ± 0</td>
<td>1.3 ± 0</td>
<td>0.77</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation (%)</td>
<td>60 ± 3</td>
<td>77 ± 3</td>
<td>84 ± 3</td>
<td>85 ± 3</td>
<td>86 ± 3</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

ANOVA = analysis of variance

*Data represent mean ± SEM.

Statistically significant difference, PAOP value versus previous value (sequential comparison).

Statistically significant difference, PAOP 10 versus PAOP 20.
PVP and SVV, suggesting that the measurement of PVP may be a useful static index to predict fluid responsiveness. Significant changes in LV diastolic compliance, as reflected by mitral valve E/e′ and E/A ratios, indicate the onset of impaired relaxation and pseudonormalization during fluid resuscitation. These data indicate that the hemodynamic response to fluid administration during resuscitation from hemorrhagic shock can be significantly influenced by the diastolic properties of the heart and whether the fluid is actually translocated from the periphery to increase end-diastolic volume. Diastolic properties of the heart may limit the systolic response to fluid administration during fluid resuscitation. These data indicate that the hemodynamic response to fluid administration during resuscitation from hemorrhagic shock can be significantly influenced by the diastolic properties of the heart and whether the fluid is actually translocated from the periphery to increase end-diastolic volume. Diastolic properties of the heart may limit the systolic response to fluid administration after hypovolemic shock, and greater emphasis should be placed on the clinical assessment of diastolic function during resuscitation.

DISCLOSURES
Name: Michael Kinsky, MD.
Contribution: This author helped design, develop, and conduct the study; acquire, collect, and analyze the data; and prepare the manuscript.
Attestation: Michael Kinsky attests to having approved the final manuscript and level of participation and also attests to having reviewed the original study data and data analysis, and attests to the integrity of the original data and the analysis reported in this manuscript.
Name: Nicole Ribeiro, MD.
Contribution: This author participated in the study and analyzed the data.
Attestation: Nicole Ribeiro attests to this level of participation.
Name: Maxime Cannesson, MD, PhD.
Contribution: This author analyzed and interpreted the data.
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Name: William E. Johnston, MD.
Contribution: This author helped design and develop the study; analyze and interpret the data; and prepare the manuscript.
Attestation: William E. Johnston attests to having approved the final manuscript and level of participation, also attests to having reviewed the original study data, data analysis, and attests to the integrity of the original data and the analysis reported in this manuscript.

REFERENCES
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