Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects

Anand Kumar, MD; Ramon Anel, MD; Eugene Bunnell, MD; Kalim Habet, MD, MD; Sergio Zanotti, MD; Stephanie Marshall, RN; Alex Neumann, MS; Amjad Ali, MD; Mary Cheang, MS; Clifford Kavinsky, MD, PhD; Joseph E. Parrillo, MD

Objective: **Pulmonary artery occlusion pressure and central venous pressure have been considered to be reliable measures of left and right ventricular preload in patients requiring invasive hemodynamic monitoring. Studies in recent years have questioned the correlation between these estimates of ventricular filling pressures and ventricular end-diastolic volumes/cardiac performance variables in specific patient groups, but clinicians have continued to consider the relationship valid in the broader context. The objective of this study was to assess the relationship between pressure estimates of ventricular preload (pulmonary artery occlusion pressure, central venous pressure) and end-diastolic ventricular volumes/cardiac performance in healthy volunteers.**

Design: **Prospective, nonrandomized, nonblinded interventional study.**

Setting: **Cardiac catheterization and echocardiography laboratories.**

Subjects: **Normal healthy volunteers (n = 12 group 1, n = 32 group 2).**

Interventions: **Pulmonary catheterization and radionuclide cineangiography (group 1) and volumetric echocardiography (group 2) during 3 L of normal saline infusion over 3 hrs.**

Measurements and Main Results: **In group 1, the initial pulmonary artery occlusion pressure and central venous pressure did not correlate significantly with initial end-diastolic ventricular volume indexes or cardiac performance (cardiac index and stroke volume index). Changes in pulmonary artery occlusion pressure and central venous pressure following saline infusion also did not correlate with changes in end-diastolic ventricular volume indexes or cardiac performance. In contrast, initial end-diastolic ventricular volume indexes and changes in these ventricular volume indexes in response to 3 L of normal saline loading correlated well with initial stroke volume index and changes in stroke volume index, respectively. The relationship between left ventricular end-diastolic volume index and stroke volume index was confirmed in group 2 subjects using mathematically independent techniques to measure these variables. In addition, initial central venous pressure, right ventricular end-diastolic volume index, pulmonary artery occlusion pressure, and left ventricular end-diastolic volume index failed to correlate significantly with changes in cardiac performance in response to saline infusion in group 1 subjects.**

Conclusions: **Normal healthy volunteers demonstrate a lack of correlation between initial central venous pressure/pulmonary artery occlusion pressure and both end-diastolic ventricular volume indexes and stroke volume index. Similar results are found with respect to changes in these variables following volume infusion. In contrast, initial end-diastolic ventricular volume indexes and changes in end-diastolic ventricular volume indexes in response to saline loading correlate strongly with initial and postsaline loading changes in cardiac performance as measured by stroke volume index. These data suggest that the lack of correlation of these variables in specific patient groups described in other studies represents a more universal phenomenon that includes normal subjects. Neither central venous pressure nor pulmonary artery occlusion pressure appears to be a useful predictor of ventricular preload with respect to optimizing cardiac performance. (Crit Care Med 2004; 32:691–699)**

KEY WORDS: volunteers; saline; heart; cardiac output; stroke volume; ventricular volume; cardiac compliance; pulmonary artery occlusion pressure; central venous pressure; preload

The thermodilution-capable, balloon-tipped pulmonary artery catheter (PAC) has been a mainstay in the management of the hemodynamically unstable patient in the intensive care unit for the last 30 yrs. In recent years, the therapeutic utility of the PAC has been challenged based on studies suggesting an unfavorable balance of risk and benefit. Sandham et al. (1) demonstrated that preoperative pulmonary artery catheterization fails to improve mortality rate in high-risk, elderly surgical patients, whereas Connors et al. (2) demonstrated that pulmonary artery catheterization may increase mortality rate in critically ill intensive care patients. Despite these questions regarding therapeutic utility, the underlying theoretical foundation which suggests that these devices provide accurate data regarding key hemodynamic variables has remained well accepted in the broader clinical context. Nonetheless, more than a dozen studies performed over the last 2 decades have challenged that assumption

From the Division of Cardiovascular Disease and Critical Care Medicine (AK, RA, EB, KH, SZ, SM, AN, CK) and Section of Nuclear Medicine (AA), Rush-Presbyterian–St. Luke's Medical Center, Chicago, IL; Biostatistical Consulting Unit (MC), Department of Community Health Sciences, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada; and Division of Cardiovascular Disease and Critical Care Medicine (JEP), Cooper Hospital/University Medical Center, Robert Wood Johnson Medical School, Camden, NJ.

DOI: 10.1097/01.CCM.0000114996.68110.C9

with respect to specific patient groups. These studies, performed in patients with sepsis (3–6), trauma (7), burn injury (8), acute respiratory failure (9), perioperative major cardiovascular surgery requiring cardiopulmonary bypass (10–18), and other critical illness (5, 6, 19), suggest that, contrary to expectations, PAC-derived central venous pressure and pulmonary artery occlusion pressure (PAOP) fail to correlate with either ventricular end-diastolic volume (EDV) or stroke volume (SV). In addition, these studies suggest that alterations in central venous pressure and PAOP associated with changes in circulating volumes do not correlate significantly with changes in EDV and SV (3, 6, 7, 9, 10, 15–19). This lack of correlation between pressure and volume indexes of preload has been ascribed to several causes, including, most prominently, variations in ventricular compliance specific to the patient groups studied (20). Despite the fact that none of these studies involving specific groups of critically ill patients employed a control group of healthy subjects as controls, the underlying assumption has been that these relationships would hold in most other patient groups and certainly in those without significant cardiopulmonary disease.

This study represents the first and only effort to examine the relationship between PAC-determined pressure estimates of ventricular preload (central venous pressure and PAOP), right and left EDV, and cardiac performance (stroke volume index [SVI] and cardiac index [CI]) both at baseline and following infusion of a large volume (3 L) of saline in normal healthy volunteers. Biventricular radionuclide cineangiography (RNCA) and invasive hemodynamic techniques (PAC and arterial catheter) were used for initial studies. Volumetric echocardiography was used to confirm results in a second subject population. The object was to determine whether PAOP and central venous pressure could predict adequacy of ventricular filling and the response to volume infusion in a healthy population.

METHODS

This study received Institutional Review Board approval. Informed consent was obtained from all subjects before enrollment.

Twelve subjects (mixed gender, ages 18–40) volunteered and gave informed consent for the first phase of this study involving the placement of a thermodilution-capable balloon-tipped pulmonary artery catheter (group 1). Thirty-two males were recruited for the echocardiographic portion of this study (group 2). Subjects were within 15% of their ideal body weight as determined by the Metropolitan Life Tables. Complete history, physical exam, and electrocardiogram as well as laboratory values that included plasma electrolytes, complete blood count, prothrombin time, partial thromboplastin time, human immunodeficiency virus, hepatitis B surface antigen, hepatitis C antibody, urinalysis, urine drug screen, and serum immunoglobulins were obtained to determine the fitness of these individuals for the study.

Subjects were studied after an overnight fast in the supine position. The individuals had an 18-gauge peripheral intravenous catheter placed in each arm. In group 1, a pulmonary artery catheter and radial arterial catheter were placed (described subsequently), after which the subject rested for 1 hr. At the end of the hour, baseline vital signs (temperature, blood pressure, heart rate [HR], and respiratory rate) and invasive hemodynamics/RNCA were obtained. In group 2, baseline vital signs were obtained immediately before echocardiography. In both groups, after completion of baseline measurements, normal saline was intravenously infused at a rate of 1 L/hr for 3 hrs. All subjects were monitored with electrocardiogram, pulse oximetry, and radial arterial catheter or Dynamap. Vital signs were obtained every 15 mins for the 4- to 6-hr duration of the study and were monitored under the supervision of a physician. RNCA/invasive hemodynamic or echocardiographic data were again obtained following 3 L of saline infusion.

Pulmonary Artery and Radial Artery Catheterization

A percutaneous introducer (Percutaneous Sheath Introducer, Arrow, 9-Fr) was placed in the right femoral vein under ultrasound guidance using minimal local anesthesia (lidocaine 2%). A PAC (VIP pulmonary artery flotation catheter, PA-Edwards Life Sciences, 7.5-Fr, 110 cm) was then passed through to the pulmonary artery using brief fluoroscopic guidance. Radial artery catheters (QuickFlash Radial Artery Catheter, Arrow, 20 g, 1.5 inches) were placed in either the right or left radial artery. Placement of all invasive devices was performed by an experienced invasive cardiologist.

Thermodilution cardiac outputs were measured by three successive injections of 10 mL of cold (6–10°C) dextrose 5% in water at end-expiration as per standard protocol. The recorded value was the mean of the three individual values. Recorded values for pulmonary artery pressure (PAP), PAOP, and right atrial pressure were also obtained at end-expiration from graphic recordings examined by a single trained observer blinded to the patient and condition (pre or post saline infusion). The systolic, diastolic, and mean pressures from the transduced arterial catheter were recorded at the same time as the PAP pressures.

Radionuclide Cineangiography

Sequential measurement of biventricular ejection fraction (EF) in group 1 subjects was performed by repeat first-pass RNCA using technetium ^{99}-DPTA. Tc ^{99}-DPTA was injected as a tight bolus into the central veins using the pulmonary artery catheter introducer. In this study, the baseline radionuclide tracer dose was 3 mCi, whereas the follow-up was 7 mCi. The study was performed in a 30° right anterior oblique projection with a slant hole collimator fitted on to a small field gamma camera interfaced with a dedicated computer system (ICON, Siemens, Gammasonic). The data were acquired in frame mode with 440 frames, each of 60 msecs duration. The first transit cardiac data were reformatted into a multiple-gated study using the subject's electrocardiogram recorded with the first pass data. This method provides independent cinematic display of the right as well as left ventricle. EFs are calculated from the reformatted gated first pass studies using standard dual region of interest and background correction (21, 22).

SV was derived by dividing thermodilution cardiac output by the concomitant HR. EDV was obtained by dividing SV by EF, and end-systolic volume was calculated as EDV − SV. Systemic vascular resistance index was calculated as 79.9(MAP − right atrial pressure)/CI and pulmonary vascular resistance index as 79.9(mPAP − PAOP)/CI, where MAP is mean arterial pressure and mPAP is mean pulmonary artery pressure.

PACs and arterial catheters were removed immediately following the study, and all subjects were discharged 1–2 hrs after the final assessment.

Echocardiography

In group 2, simultaneously acquired left ventricular echocardiograms, phonocardiograms, electrocardiograms, and noninvasively determined systolic/diastolic blood pressures were used to determine cardiac volumetric and performance indexes before and after 3 L of saline infusion. Standard views including parasternal long and short axis as well as apical four- and two-chamber views were obtained using a Hewlett Packard 5500 ultrasound machine. SV was determined from the mean of five consecutive beats using the measured left ventricular outflow (aortic valve) diameter from the parasternal long axis view and an outflow tract velocity measured at the aortic valve with a Doppler probe (23, 24). Cardiac output was cal-

culated with this SV multiplied by the simultaneous HR. Left ventricular volumes were independently obtained by Simpson's rule (method of disks) using the average of volumes from apical four- and two-chamber views (25). These volumes were measured at end-diastole (defined as the Q wave of the electrocardiogram) and end-systole (defined as the first high-frequency component of the aortic second heart sound) in five cardiac cycles. EF was obtained by subtracting end-systolic volume from EDV and dividing by EDV. The total peripheral resistance was determined using the calculated cardiac output and the measured MAP from the Dynamap using the formula total peripheral resistance (dyne/secs·cm^{-5}) = (MAP)(79.9)/cardiac output. The right atrial pressure was omitted in this calculation because of the negligible effect that the right atrial pressure exerts on this calculation in these normal volunteers. Echocardiograms were performed and read by a single, highly experienced echocardiographer who was blinded to the patient and experimental condition.

Statistical Analysis

Hemodynamic values at baseline and at completion of the 3-hr saline infusion were pooled to derive means and standard errors of the mean. Hemodynamic values postsaline infusion were compared with baseline values using two-tailed paired Student's *t*-test analysis. Correlation analysis using the Pearson correlation coefficient was employed to examine the relationship between variables of interest. We considered $p < .05$ to be significant for all univariate analyses. Stepwise, discriminant, multivariate regression analysis was used to examine the potential contribution of hemodynamic constituent variables to SVI.

RESULTS

RCNA/PAC Study Group 1. Twelve subjects (eight male, four female) were recruited for the invasive monitoring portion of this study. Mean ± SE age, height, and weight were 30.9 ± 2.8 yrs, 173.3 ± 2.5 cm, and 86.3 ± 5.1 kg, respectively.

Cardiovascular variables including ventricular volumes in group 1 subjects are shown in Table 1. Infusion of 3 L of normal saline over 3 hrs resulted in an increase of CI of almost 30%, most of which was generated by a 23% increase in SVI. The remainder of the increase in CI was accounted for by the modest and nonsignificant increase in HR. All subjects demonstrated an increase in both SVI and CI. PAOP almost doubled (78% increase), whereas central venous pressure increased 42%. All subjects demonstrated an increase in PAOP, whereas nine of 12 subjects showed an increase in central venous pressure (two did not change) with 3 L of saline infusion. A small increase in MAP (8%) was also noted. Systemic vascular resistance index and pulmonary vascular resistance index both decreased significantly (approximately 17% and 28%, respectively). After volume infusion, mean left ventricular end-diastolic volume (LVEDVI) increased approximately 11%, but the response was inconsistent (eight of 12 subjects) and there was wide variability among subjects (Table 1). Mean right ventricular end-diastolic volume index (RVEDVI) also increased approximately 10% with saline infusion, but again only eight of 12 subjects exhibited this increase in RVEDVI.

Relationships of Presaline Infusion Estimates of End-Diastolic Ventricular Pressures, End-Diastolic Volumes, and Cardiac Performance Indexes. Regression analysis (Table 2) indicated that initial central venous pressure did not correlate with initial RVEDVI (Fig. 1*A*), SVI (Fig. 2*A*), or CI. Similarly, PAOP, before fluid loading, had no significant correlation with LVEDVI (Fig. 1*C*), SVI (Fig. 2*C*), or CI. A highly significant correlation existed between SVI (but not CI) and both RVEDVI (Fig. 3*A*) and LVEDVI (Fig. 3*C*). Since a fast heart rate might be expected to decrease SVI and decrease end-diastolic volume (as a function of decreased filling time), a correlation between these variables was also assessed. A significant negative correlation between HR and RVEDVI ($r = .5970$, $p = .0403$) existed, and a trend toward a negative relationship between HR and both LVEDVI ($r = .4683$, $p = .1246$) and SVI ($r = .4575$, $p = .1347$) was also noted. Strong positive correlations were also found to exist between initial RVEDVI and LVEDVI but not between initial central venous pressure and PAOP (although there was a modest trend in that direction; Fig. 4*A*). When patients were assessed following volume loading with 3 L of saline over 3 hrs, the same relationships held (data not shown).

Relationships of Postsaline Infusion Changes in Estimates of End-Diastolic Ventricular Pressures, End-Diastolic Volumes, and Cardiac Performance Indexes. For the most part, changes in these variables from initial values in response to volume loading were similar to those found before saline infusion (Table 3). Changes in both central venous pressure and PAOP failed to correlate significantly with changes in RVEDVI (Fig. 1*B*) or LVEDVI (Fig. 1*D*), respectively. In addition, neither central venous pressure (Fig. 2*B*) nor PAOP (Fig. 2*D*) changes correlated with SVI responses to saline infusion. In contrast, changes in RVEDVI (Fig. 3*B*) and LVEDVI (Fig. 3*D*) were paralleled by consistent increases in SVI. In addition, there were trends toward a correlation with increases in CI ($p < .2$ for each). In contrast to presaline infusion (baseline), there was no relationship between changes in HR and either ventricular volumes or SVI (HR vs. RVEDVI, $r = .2195$, $p = .4931$; HR vs. LVEDVI, $r = .1057$, $p = .7437$; HR vs. SVI, $r = .0824$, $p = .8979$). As found under baseline conditions, a strong relationship existed between changes in RVEDVI and LVEDVI, but unlike the prefluid infusion state, there was also a modest but significant relationship between changes in central venous pressure and PAOP (Fig. 4*B*) in response to fluid infusion.

Relationship Between End-Diastolic Volumes and Cardiac Performance Indexes in Echocardiographic Study Group 2

Echocardiographic studies (group 2) were used to confirm and extend the PAC/

Table 1. Mean (±SE) values for cardiovascular variables before and after 3 L of saline infusion

	Presaline Infusion	Postsaline Infusion	Percentage Change	*p* Value
HR, min^{-1}	68.4 ± 3.4	72.2 ± 4.1	5.7 ± 3.5	NS
MAP, mm Hg	88.1 ± 3.3	94.6 ± 3.0	7.8 ± 2.2	.004
CVP, mm Hg	9.4 ± 0.7	12.4 ± 0.9	41.5 ± 15.2	.028
PAOP, mm Hg	9.7 ± 0.9	15.3 ± 0.8	77.8 ± 26.4	.0128
CI, L·min^{-1}·m^{-2}	2.96 ± 0.12	3.87 ± 0.29	30.0 ± 6.5	.0006
SVI, mL/m^2	44.0 ± 1.9	54.1 ± 3.0	23.1 ± 4.7	.0005
LVEDVI, mL/m^2	70.6 ± 2.2	78.3 ± 4.0	10.7 ± 3.7	.0138
RVEDVI, mL/m^2	81.8 ± 4.2	89.6 ± 5.8	9.5 ± 3.5	.019

HR, heart rate; NS, not significant; MAP, mean arterial pressure; CVP, central venous pressure; PAOP, pulmonary artery occlusion pressure; CI, cardiac index; SVI, stroke volume index; LVEDVI, left ventricular end-diastolic volume index, RVEDVI; right ventricular end-diastolic volume index.

Table 2. Correlation coefficients between initial measures of cardiac preload and cardiac performance variables

	CVP	PAOP	RVEDVI	LVEDVI	SVI
PAOP	.4794				
	.1148				
RVEDVI	.0305	.5277			
	.9251	.0778			
LVEDVI	.4309	.0492	.7159		
	.1619	.8794	.0088		
SVI	.3223	.0903	.8222	.9613	
	.3069	.7802	.0010	<.0001	
CI	.3207	.4103	.2092	.4252	.4857
	.3094	.1852	.5142	.1682	.1094

CVP, central venous pressure; PAOP, pulmonary artery occlusion pressure; RVEDVI, right ventricular end-diastolic volume index; LVEDVI, left ventricular end-diastolic volume index; SVI, stroke volume index; CI, cardiac index. Top row in each cell indicates the Pearson correlation coefficient; the bottom row indicates the corresponding *p* value.

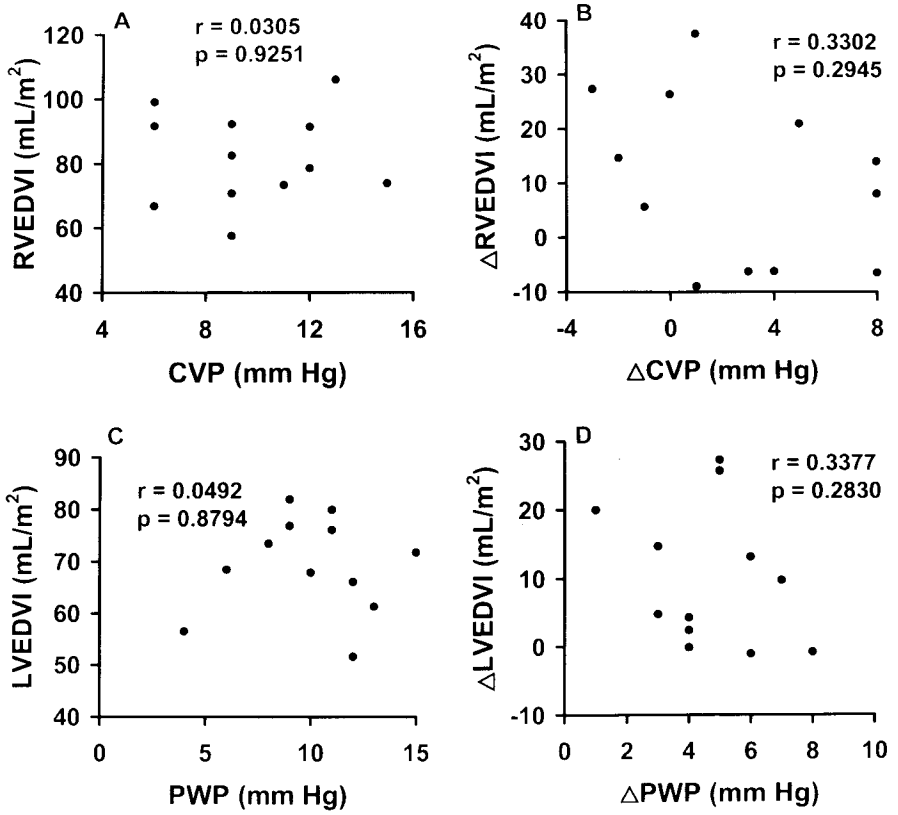

Figure 1. Relationship between *A*, initial central venous pressure (*CVP*) and right ventricular end-diastolic volume index (*RVEDVI*); *B*, changes in central venous pressure and RVEDVI in response to saline; *C*, initial pulmonary artery occlusion pressure (*PWP*) and left ventricular end-diastolic volume index (*LVEDVI*); and *D*, changes in PWP and LVEDVI in response to saline in group 1 subjects. No significant relationship was found between initial values for central venous pressure and RVEDVI or changes in these variables following 3 L of saline infusion. Similar negative results were found for the relationship between PWP and LVEDVI.

RNCA-derived data (group 1). All subjects in this study group were male. Mean and SE for age, weight, height, and body surface area were 28.5 ± 1.3 yrs, 77.2 ± 1.9 kg, 172.9 ± 1.8 cm, and 1.94 ± 0.02 m^2, respectively. As noted in Figure 5*A*, a significant correlation continued to exist between presaline infusion LVEDVI and SVI. In addition, the increase in SVI following volume infusion was highly correlated with the increase in LVEDVI (Fig. 5*B*). Analysis of this second group also confirms a significant negative correlation between baseline HR and LVEDVI ($r = .5157$, $p = .0025$) but not between the changes in these same variables following volume infusion ($r = .0342$, $p = .8522$).

Multivariate Analysis of Hemodynamic Contributors to Stroke Volume Index in Group 1 Subjects. To confirm that central venous pressure and PAOP possess no independent predictive power with respect to SVI (either at baseline or in response to volume loading), stepwise, discriminant multivariate analysis was performed to examine potential constituent variables to SVI in group 1 subjects. When LVEDVI, left ventricular ejection fraction (LVEF), HR, and PAOP were included in the model, only the first three contributed to initial SVI. When LVEDVI was dropped from the model, only LVEF remained predictive. PAOP made no contribution in either case. Parallel results were found with respect to right heart variables (RVEDVI, right ventricular ejection fraction, and central venous pressure with HR). Similarly, changes in LVEDVI and LVEF independently predicted alterations in SVI following volume loading when LVEDVI, LVEF, PAOP, and HR changes were included. Again, parallel findings were demonstrated when SVI response was modeled using changes in RVEDVI, right ventricular ejection fraction, central venous pressure, and HR. SVI was also modeled in group 2 subjects using LVEDVI, LVEF, and HR both at baseline and with respect to changes in response to saline loading. In both cases, LVEDVI and LVEF demonstrated independent predictive power. A trend toward independent predictive power for HR did not quite reach significance in both cases.

Relationship Between Initial Pressure and Volumetric Preload Estimates and Cardiac Performance Response to Saline Infusion. Because it has been suggested that lower initial preload may be associated with the ability of volume infusion to augment cardiac performance, the relationship between initial variables of right and left ventricular preload (LVEDVI, RVEDVI, PAOP, central venous pressure) with both SVI and CI in response to 3 L of saline loading over 3 hrs was also examined. No relationship between any initial variable of preload and the increase in SVI or CI associated with volume loading was noted (Table 4).

DISCUSSION

One of the most common uses of the PAC is to optimize ventricular filling

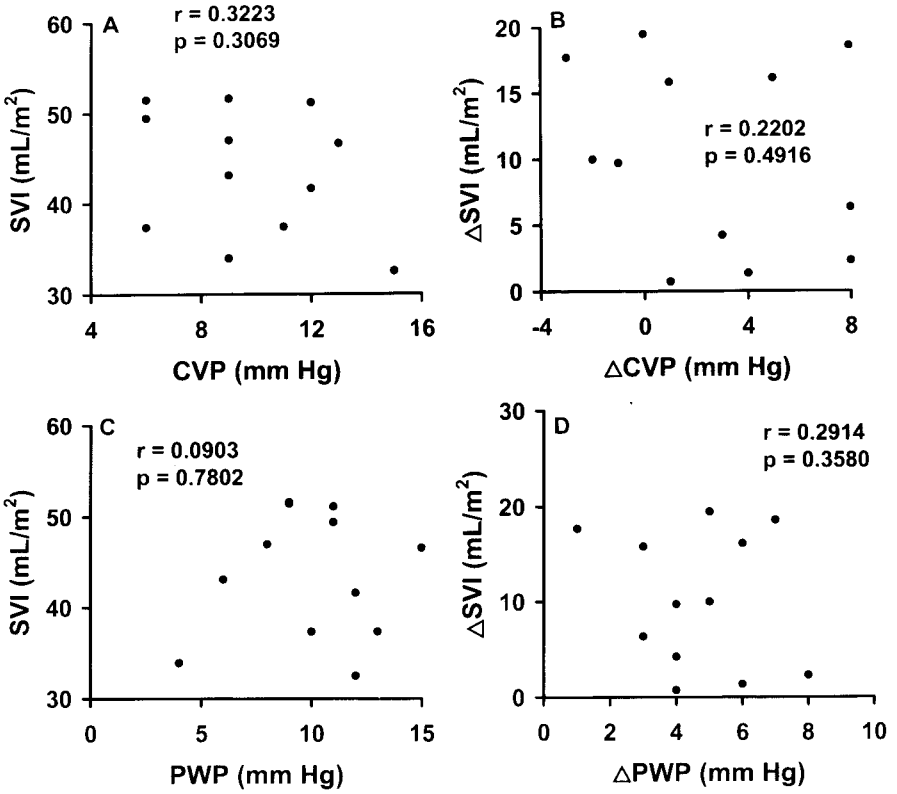

Figure 2. Relationship between *A*, initial central venous pressure (*CVP*) and stroke volume index (*SVI*); *B*, changes in central venous pressure and SVI in response to saline; *C*, initial pulmonary artery occlusion pressure (*PWP*) and SVI; and *D*, changes in PWP and SVI in response to saline in group 1 subjects. No significant relationship was found between initial values for either central venous pressure or PWP and SVI or changes in these variables following 3 L of saline infusion.

pressures (estimated by PAOP and central venous pressure) as an approximation of true ventricular preload (LVEDVI, RVEDVI) for purposes of maximizing cardiac performance indexes (CI, SVI) during critical illness. This approach is predicated on the assumption that PACs, at a minimum, deliver reliable, clinically relevant information about true ventricular preload. Although several studies have, in recent years, undermined this assumption in respect to specific patient groups (3–19), this study provides the first evidence that awake, healthy subjects without cardiopulmonary disease exhibit no predictable relationship between static measurements of pressure-based preload indexes (central venous pressure, PAOP) and volumetric preload indexes (RVEDVI, Fig. 1*A*; LVEDVI, Fig. 1*C*) or cardiac performance variables (SVI, Fig. 2*A* and 2*C*; CI). In addition, neither the end-diastolic volume (Fig. 1*B* and 1*D*) nor the SVI (Fig. 2*B* and 2*D*) response to fluid loading (3 L of saline infused over 3 hrs) in normal volunteers is predicted by the concomitant increase in either PAOP or central venous pressure. These findings are confirmed in stepwise, discriminant multivariate analysis of the relationship between key potential contributory hemodynamic variables to initial SVI and to changes in SVI following 3 L of saline infusion. No combination of variables yielded a model in which either central venous pressure or PAOP made a significant contribution to SVI (even if end-diastolic volumes were excluded). This finding applied to both the initial presaline infusion state and to changes in variables following 3 L of saline infusion.

In contrast, a strong relationship between both initial RVEDVI or LVEDVI and SVI (but not CI) existed (Fig. 3*A* and 3*C*). A consistent, predictable SVI (but not CI) response to saline infusion-generated increases in end-diastolic ventricular volumes was also found (Figs. 3*B* and 3*D*). Despite this strong correlation between ventricular volumes and SVI, the relationship between these variables (based on these data) would be uncertain in group 1 subjects. The nature of the derivation of end-diastolic ventricular volume from RCNA-derived ejection fraction and PAC-derived SVI results in mathematical coupling of the constitutive and derived variables (EDVI = SVI × EF). This same problem exists in several previous studies in which end-diastolic volume was calculated directly or indirectly from stroke volume (5, 6, 12, 15, 26). In addition, the fast response thermistor-equipped PAC with right ejection fraction capability may also engender mathematical coupling between SVI and RVEDVI in several relevant studies (7, 8, 16, 18, 19, 27). To ensure that the observed relationship between end-diastolic volume and SVI exists independent of mathematical coupling, data from an additional group of healthy volunteers who underwent identical volume loading under noninvasive echocardiographic monitoring were examined. Stroke volume and left ventricular end-diastolic volume were measured before and after saline infusion using unrelated echocardiographic techniques. Because mathematically independent techniques were used for measurement, the strong correlation between initial LVEDVI and SVI and the change in these variables following saline loading in group 2 subjects represent an accurate representation of their relationship (Fig. 5*A* and 5*B*).

In relation to the issue of hypovolemia, studies have suggested that initial estimates of preload (both pressure and volume) can predict ventricular performance response to fluid infusion (7, 10, 12, 19, 26–28). These data suggest that lower ventricular volumes and filling pressure estimates are associated with more robust cardiac performance responses to fluid infusion. To assess this issue, the relationship between initial PAOP, LVEDVI, central venous pressure or RVEDVI, and SVI/CI response to volume loading was assessed using correlation analysis. No significant relationship was found (Table 4).

The present study shows that among the healthy subjects, there is an extremely wide variability in ventricular filling volumes for values of PAOP and central venous pressure that would be considered to lie within the normal range. Even though ventricular volumes were indexed for body surface area, a central venous pressure of 9 mm Hg could represent a RVEDVI that measured between 50 and 90 mL/m^2 (Fig. 1*A*). Similarly, a PAOP of 11 mm Hg could represent an LVEDVI of anywhere between 50 and 80 mL/m^2 (Fig. 1*C*). These data demonstrate that the adequacy of ventricular filling cannot be inferred from static

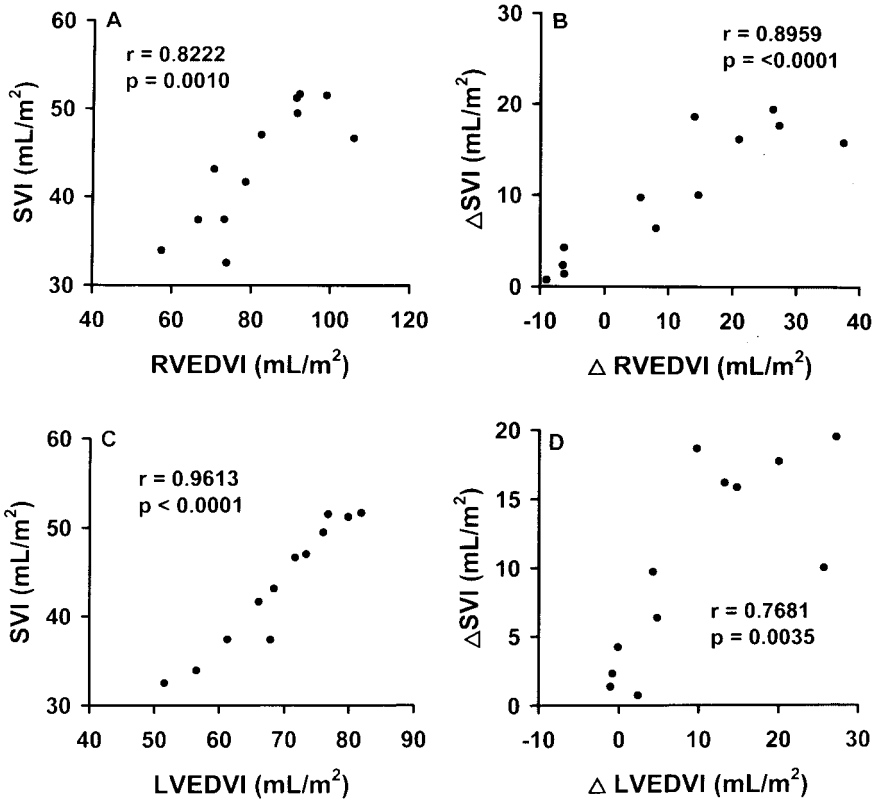

Figure 3. Relationship between *A*, initial right ventricular end-diastolic volume index (*RVEDVI*) and stroke volume index (*SVI*); *B*, changes in RVEDVI and SVI in response to saline; *C*, initial left ventricular end-diastolic volume index (*LVEDVI*) and SVI; and *D*, changes in LVEDVI and SVI in response to saline in group 1 subjects. A highly significant relationship was found between both initial values for RVEDVI or LVEDVI and SVI or changes in these variables following 3 L of saline.

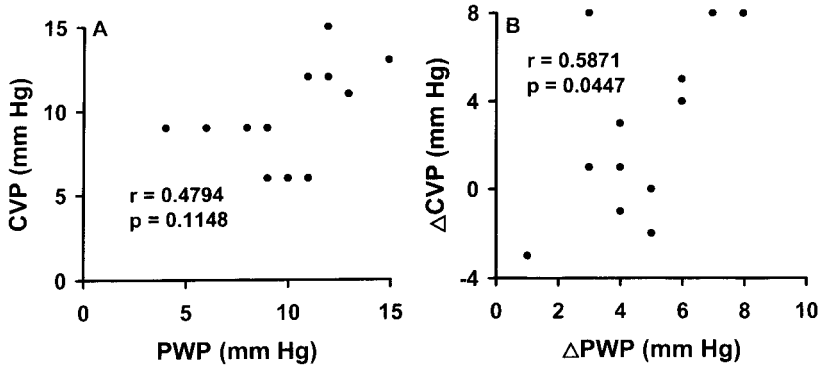

Figure 4. Relationship between *A*, initial pulmonary artery occlusion pressure (*PWP*) and central venous pressure (*CVP*); and *B*, changes in PWP and central venous pressure in response to saline in group 1 subjects. No change in initial PWP and central venous pressure was found. However, a significant relationship between changes in PWP and central venous pressure in response to 3 L of saline infusion was noted.

measures of central venous pressure and PAOP in normal subjects.

Augmentation of preload through fluid infusion has become the key initial element in the resuscitation of shock. Optimally, direct measurement of the ventricular end-diastolic volumes allows for the most accurate assessment of preload. The application of this approach in the clinical context has been difficult due to logistic and technical problems. For that reason, end-diastolic pressures as estimated by central venous pressure and PAOP have been used as substitute end points. Implicit in their widespread use is the belief that central venous pressure and PAOP represent an acceptable substitute for ventricular volume as an indicator of preload. For this approach to be valid, however, cardiac compliance must be relatively consistent across different patients and stable within a given patient.

Studies of critically ill intensive care patients and perioperative major cardiovascular surgery patients using a variety of imaging/measurement techniques over the last 25 yrs have demonstrated that pressure estimates of preload (PAOP, central venous pressure) fail to predict either ventricular end-diastolic volumes or cardiac performance (SVI or CI) (3–19). In addition, ventricular volumes and performance in these patient groups fail to respond in a consistent and predictable manner to changes in preload as measured by PAOP or central venous pressure (3, 6, 7, 9, 10, 15–19). In contrast, volumetric estimates of preload (LVEDVI, RVEDVI) have, for the most part, been found to be much more strongly predictive of cardiac performance both at baseline and following acute changes in circulating volume (5–7, 10, 11, 15, 16, 18, 19).

Within the groups of patients who have consistently failed to demonstrate statistical coupling between standard pressure estimates of ventricular preload (PAOP, central venous pressure) and direct volumetric measures of preload as well as measures of cardiac performance (SVI, CI), several contributory mechanisms have been postulated. A strong correlation between PAOP and left ventricular end-diastolic pressure exists in most patients (29–34). However, this relationship may become distorted in specific circumstances including postcoronary artery bypass surgery (14, 29, 35). Evidence of uncoupling between PAOP and left atrial pressure or left ventricular end-diastolic pressure as a consequence of elevated pulmonary vascular resistance (36) and pulmonary venous constriction has been described (37). Patients may also demonstrate significant reductions in total transmural cardiac compliance so that increases of ventricular filling pressure are poorly reflected by cardiac volume (20). Mechanisms that may account for such decreases in cardiac compliance include myocardial edema due to trauma, infarction, or sepsis (38–40); increased juxta-cardiac pressure due to mechanical ventilation, positive end-expiratory pressure, septal shift, or pericardial effusion/tamponade (7, 8, 41, 42); impaired diastolic relaxation due to ischemia or

Table 3. Correlation coefficients between changes in measures of cardiac preload and cardiac performance variables following volume infusion

	CVP	PAOP	RVEDVI	LVEDVI	SVI
PAOP	.5871				
	.0447				
RVEDVI	.3302	.4128			
	.2945	.1823			
LVEDVI	.5590	.3377	.8018		
	.0586	.2830	.0017		
SVI	.2202	.2914	.8959	.7681	
	.4916	.3580	<.0001	.0035	
CI	.1309	.1695	.4573	.4008	.7263
	.6851	.5984	.1350	.1966	.0074

CVP, central venous pressure; PAOP, pulmonary artery occlusion pressure; RVEDVI, right ventricular end-diastolic volume index; LVEDVI, left ventricular end- diastolic volume index; SVI, stroke volume index; CI, cardiac index. Top row in each cell indicates the Pearson correlation coefficient; the bottom row indicates the corresponding *p* value.

Neither central venous pressure nor pulmonary artery occlusion pressure appears to be a useful predictor of ventricular preload with respect to optimizing cardiac performance.

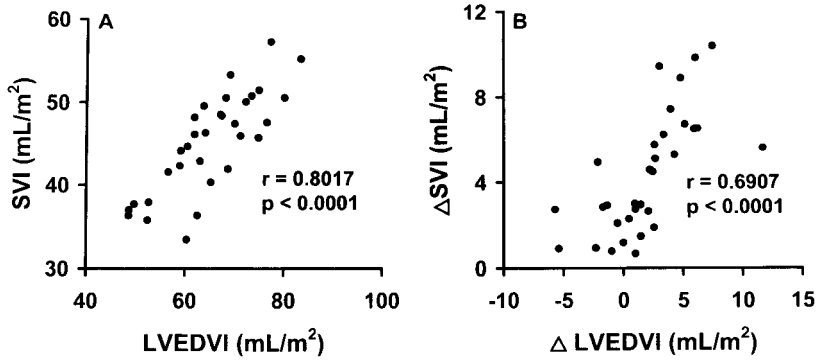

Figure 5. Relationship between *A*, initial volumetric echocardiography-derived left ventricular end-diastolic volume index (*LVEDVI*) and Doppler-echocardiography-derived stroke volume index (*SVI*); and *B*, changes in volumetric echocardiography-derived LVEDVI and Doppler echocardiography-derived SVI in response to saline in group 2 subjects. Highly significant relationships existed between both initial LVEDVI and SVI and changes in these variables following 3 L of saline infusion in group 2 subjects in whom mathematically independent techniques were used to derive the values.

Table 4. Correlation coefficients between changes in cardiac performance in response to volume infusion as a function of initial cardiac preload measures

	PAOP	LVEDVI	CVP	RVEDVI
ΔSVI	.0857	.1580	.3280	.0991
	.7910	.6239	.2979	.7592
ΔCI	.0014	.2767	.3407	.3459
	.9964	.3839	.2785	.2708

PAOP, pulmonary artery occlusion pressure; LVEDVI, left ventricular end- diastolic volume index; CVP, central venous pressure; RVEDVI, right ventricular end-diastolic volume index; ΔSVI, change in stroke volume index; ΔCI, change in cardiac index. Top row in each cell indicates the Pearson correlation coefficient; the bottom row indicates the corresponding *p* value.

cardiopulmonary bypass (14, 32, 43, 44); myocardial hypertrophy due to hypertension or hypertropic cardiomyopathy (29); or pharmacologic effects of myocardial depressants such as inhaled anesthetics (45). Others have suggested that an intact pericardium may be important in maintenance of the "normal" relationship between end-diastolic pressures and volumes (12, 46, 47).

None of these potential mechanisms can play a role in the healthy subjects of this study. The lack of correlation between initial and postvolume infusion changes in central venous pressure/PAOP and end-diastolic volumes and cardiac performance indexes appears to be primarily attributable to a greater and more dynamic intrinsic variability in diastolic ventricular compliance among and within healthy individuals than has been understood. Given that the findings of this study mirror the lack of correlation found in studies of patients with critical illness, trauma, or perioperative cardiac surgery, these data suggest that the lack of a statistical relationship between ventricular filling pressure estimates and ventricular volumes/cardiac performance represents a universal phenomenon that extends to normal subjects. Measurement of central venous pressure or PAOP may continue to be useful for titration of therapy in specific patient groups (e.g., cardiomyopathy, congestive heart failure, and hypovolemia/hypovolemic shock) in whom correlations between volumetric and pressure estimates of preload have been found (15, 28, 48). However, the high degree of variability of cardiac compliance in normal hearts limits the utility of these variables as predictors of ventricular preload/cardiac performance to a much greater extent than has been appreciated. In addition, our data may yield some insight as to the underlying reasons for the apparent therapeutic futility of PAC use in critically ill patients (1, 2).

In the intensive care unit, the balloon-tipped, thermodilution-capable PAC has been a central diagnostic modality. Among its important uses are management of fluid resuscitation with respect to adequacy of ventricular filling and avoidance of pulmonary edema, assessment of global oxygen supply/consumption match as indicated by mixed venous oxygen saturation, and determination of total cardiac output with titration of vasopressor and inotrope support as related to cardiovascular function. Our data, in combination with other studies citing the lack of correlation between estimates of ventricular filling pressures with end-

diastolic volumes and cardiac performance, argue against the routine use of central venous pressure and PAOP for estimation of preload except in specific conditions at the extremes of intravascular volume status (hypovolemia and severe heart failure). This study demonstrates that cardiac compliance is highly variable in normal subjects. As a consequence, end-diastolic cardiac pressure estimates (PAOP and central venous pressure) do not reliably reflect preload in most subjects. This dynamic physiologic variation in diastolic cardiac compliance must be factored into the evaluation of all patients in whom invasive cardiovascular evaluation is used.

ACKNOWLEDGMENTS

We gratefully thank Steve Mink, MD (Health Sciences Centre, University of Manitoba, Winnipeg, Canada) for his insightful commentary following review of the manuscript.

REFERENCES

1. Sandham JD, Hull RD, Brant RF, et al: A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med* 2003; 348:5–14
2. Connors AF Jr, Speroff T, Dawson NV, et al: The effectiveness of right heart catheterization in the initial care of critically ill patients. *JAMA* 1996; 276:889–897
3. Sakka SG, Reinhart K, Meier-Hellmann A: Comparison of pulmonary artery and arterial thermodilution cardiac output in critically ill patients. *Intensive Care Med* 1999; 25: 843–846
4. Jardin F, Valtier B, Beauchet A, et al: Invasive monitoring combined with two-dimensional echocardiographic study in septic shock. *Intensive Care Med* 1994; 20:550–554
5. Calvin JE, Driedger AA, Sibbald WJ: Does the pulmonary wedge pressure predict left ventricular preload in critically ill patients? *Crit Care Med* 1981; 9:437–443
6. Calvin JE, Driedger AA, Sibbald WJ: The hemodynamic effect of rapid fluid infusion in critically ill patients. *Surgery* 1981; 90:61–76
7. Diebel L, Wilson RF, Heins J, et al: End-diastolic volume versus pulmonary artery wedge pressure in evaluating cardiac preload in trauma patients. *J Trauma* 1994; 37: 950–955
8. Martyn JA, Snider MT, Farago LF, et al: Thermodilution right ventricular volume: A novel and better predictor of volume replacement in acute thermal injury. *J Trauma* 1981; 21: 619–626
9. Lichtwarck-Aschoff M, Zeravik J, Pfeiffer UJ: Intrathoracic blood volume accurately reflects circulatory volume status in critically ill patients with mechanical ventilation. *Intensive Care Med* 1992; 18:142–147
10. Tousignant CP, Walsh F, Mazer CD: The use of transesophageal echocardiography for preload assessment in critically ill patients. *Anesth Analg* 2000; 90:351–355
11. Thys DM, Hillel Z, Goldman ME, et al: A comparison of hemodynamic indices derived by invasive monitoring and two-dimensional echocardiography. *Anesthesiology* 1987; 67: 630–634
12. Ellis RJ, Mangano DT, VanDyke DC: Relationship of wedge pressure to end-diastolic volume in patients undergoing myocardial revascularization. *J Thorac Cardiovasc Surg* 1979; 78:605–613
13. Hoeft A, Schorn B, Weyland A, et al: Bedside assessment of intravascular volume status in patients undergoing coronary bypass surgery. *Anesthesiology* 1994; 81:76–86
14. Douglas PS, Edmunds LH, Sutton MS, et al: Unreliability of hemodynamic indexes of left ventricular size during cardiac surgery. *Ann Thorac Surg* 1987; 44:31–34
15. Hansen RM, Viquerat CE, Matthay MA, et al: Poor correlation between pulmonary arterial wedge pressure and left ventricular end-diastolic volume after coronary artery bypass graft surgery. *Anesthesiology* 1986; 64: 764–770
16. Tuman KJ, McCarthy RJ, March RJ, et al: Effects of phenylephrine or volume loading on right ventricular function in patients undergoing myocardial revascularization. *J Cardiothorac Vasc Anesth* 1995; 9:2–8
17. Buhre W, Weyland A, Schorn B, et al: Changes in central venous pressure and pulmonary capillary wedge pressure do not indicate changes in right and left heart volume in patients undergoing coronary artery bypass surgery. *Eur J Anaesthesiol* 1999; 16: 11–17
18. Dennis JW, Menawat SS, Sobowale OO, et al: Superiority of end-diastolic volume and ejection fraction measurements over wedge pressures in evaluating cardiac function during aortic reconstruction. *J Vasc Surg* 1992; 16: 372–377
19. Diebel LN, Wilson RF, Tagett MG, et al: End-diastolic volume. A better indicator of preload in the critically ill. *Arch Surg* 1992; 127:817–821
20. Raper R, Sibbald WJ: Misled by the wedge? The Swan-Ganz catheter and left ventricular preload. *Chest* 1986; 89:427–434
21. Morrison DA, Turgeon J, Ovitt T: Right ventricular ejection fraction measurement: Contrast ventriculography versus gated blood pool and gated first-pass radionuclide methods. *Am J Cardiol* 1984; 54:651–653
22. Port SC: Recent advances in first-pass radionuclide angiography. *Cardiol Clin N Am* 1994; 12:359–372
23. Huntsman LL, Stewart DK, Barnes SR, et al: Noninvasive Doppler determination of cardiac output in man. Clinical validation. *Circulation* 1983; 67:593–601
24. Lewis JF, Kuo LC, Nelson JG, et al: Pulsed Doppler echocardiographic determination of stroke volume and cardiac output: Clinical validation of two new methods using the apical window. *Circulation* 1984; 70:425–531
25. Takenaka A, Iwase M, Sobue T, et al: The discrepancy between echocardiography, cineventriculography and thermodilution. Evaluation of left ventricular volume and ejection fraction. *Int J Cardiac Imag* 1995; 11:255–262
26. Mangano DT, Van Dyke DC, Ellis RJ: The effect of increasing preload on ventricular output and ejection in man: Limitations of the Frank-Starling mechanism. *Circulation* 1980; 62:535–541
27. Wagner JG, Leatherman JW: Right ventricular end-diastolic volume as a predictor of the hemodynamic response to a fluid challenge. *Chest* 1998; 113:1048–1054
28. Cheung AT, Savino JS, Weiss SJ, et al: Echocardiographic and hemodynamic indexes of left ventricular preload in patients with normal and abnormal ventricular function. *Anesthesiology* 1994; 81:376–387
29. Flores ED, Lange RA, Hillis LD: Relation of mean pulmonary arterial wedge pressure and left ventricular end-diastolic pressure. *Am J Cardiol* 1990; 66:1532–1533
30. Swan HJ, Ganz W, Forrester J, et al: Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. *N Engl J Med* 1970; 283:447–451
31. Buchbinder N, Ganz W: Hemodynamic monitoring: Invasive techniques. *Anesthesiology* 1976; 45:146–155
32. Rahimtoola SH, Loeb HS, Ehsani A, et al: Relationship of pulmonary artery to left ventricular diastolic pressures in acute myocardial infarction. *Circulation* 1972; 46:283–290
33. Braunwald E, Rahimtoola SH, Loeb HS, et al: Left atrial and left ventricular pressure in subjects without cardiovascular disease. *Circulation* 1961; 24:267–274
34. Lizman J, Powers S, Older J: Correlation of pulmonary wedge and left atrial pressures. *Arch Surg* 1974; 109:270–277
35. Mammana RB, Hiro S, Levitsky S, et al: Inaccuracy of pulmonary capillary wedge pressure when compared to left atrial pressure in the early postsurgical period. *J Thorac Cardiovasc Surg* 1982; 84:420–425
36. Entress JJ, Dhamee MS, Olund T, et al: Pulmonary artery occlusion pressure is not accurate immediately after cardiopulmonary bypass. *J Cardiothorac Anesth* 1990; 4:558–563
37. Krahmer RL, Fang HK, Vitello J, et al: Pulmonary capillary wedge pressure estimates of left ventricular preload are inaccurate in endotoxin shock: Contribution of Starling resistor forces to septic pulmonary hypertension. *Shock* 1994; 2:344–350
38. Yu P, Boughner DR, Sibbald WJ, et al: Myocardial collagen changes and edema in rats with hyperdynamic sepsis. *Crit Care Med* 1997; 25:657–662
39. Munt B, Jue J, Gin K, et al: Diastolic filling in

human severe sepsis: An echocardiographic study. *Crit Care Med* 1998; 26:1829–1833
40. Poelaert J, Declerck C, Vogelaers D, et al: Left ventricular systolic and diastolic function in septic shock. *Intensive Care Med* 1997; 23: 553–560
41. Taylor RR, Covell JW, Sonnenblick EH, et al: Dependence of ventricular distensibility on filling of the opposite ventricle. *Am J Physiol* 1967; 213:711–718
42. Ludbrook PA, Byrne JD, McKnight RC: Influence of right ventricular hemodynamics on left ventricular diastolic pressure-volume relations in man. *Circulation* 1979; 59:21–31
43. Mann T, Brodie BR, Grossman W, et al: Effect of angina on the left ventricular diastolic pressure-volume relationship. *Circulation* 1977; 55:761–766
44. Bristow JD, Van Zee BE, Judkins MP: Systolic and diastolic abnormalities of the left ventricle in coronary artery disease. Studies in patients with little or no enlargement of ventricular volume. *Circulation* 1970; 42: 219–228
45. Hamilton WK, Larson CP, Bristow JD, et al: Effect of cyclopropane and halothane on ventricular mechanics: A change in ventricular diastolic pressure-volume relationships. *J Pharmacol Exp Ther* 1966; 154:566–574
46. Glantz SA, Misbach GA, Moores WY, et al: The pericardium substantially affects the left ventricular diastolic pressure-volume relationship in the dog. *Circ Res* 1978; 42: 433–441
47. Sarnoff SJ, Berglund E: Ventricular function: Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog. *Circulation* 1954; 9:706–718
48. Firth BG, Dehmer GJ, Markham RV Jr, et al: Assessment of vasodilator therapy in patients with severe congestive heart failure: Limitations of measurements of left ventricular ejection fraction and volumes. *Am J Cardiol* 1982; 50:954–959