Mean systemic filling pressure : from Guyton to the ICU

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Chapter 7

Bedside assessment of total systemic vascular compliance, stressed volume and cardiac function curves in ICU patients

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Abstract

Mean systemic filling pressure (Pmsf) can be measured at the bedside with minimally-invasive monitoring in ventilator-dependent patients using inspiratory hold maneuvers ($Pmsf_{hold}$) as the zero flow intercept of cardiac output (CO) to central venous pressure (Pcv) relation. We compared $Pmsf_{hold}$ to arm vascular equilibrium pressure during vascular occlusion ($Pmsf_{arm}$) and their ability to assess systemic vascular compliance (Csys) and stressed volume by intravascular fluid administration. In 15 mechanically ventilated postoperative cardiac surgery patients inspiratory holds at varying airway pressures and arm stop-flow maneuvers were performed during normovolemia and after each of 10 sequential 50 ml bolus colloid infusions. We measured Pcv, $Pmsf_{arm}$, stroke volume and CO during fluid administration steps to construct Pcv to CO (cardiac function) curves and Δvolume/ΔPmsf (compliance) curves. $Pmsf_{hold}$ was measured before and after fluid administration. Stressed volume was determined by extrapolating the Pmsf-volume curve to zero pressure intercept.

$Pmsf_{hold}$ and $Pmsf_{arm}$ were closely correlated. Csys was linear (64.3 ± 32.7 $ml \cdot mmHg^{-1}$, 0.97 ± 0.49 $ml \cdot mmHg^{-1} \cdot kg^{-1}$ predicted body weight). Stressed volume was estimated to be 1265 ± 541 ml (28.5 ± 15 % predicted total blood volume). Cardiac function curves of patients with an increase of > 12% to 500 ml volume extension (volume responsive) were steep, while the cardiac function curves of the remaining patients were flat. In conclusion, systemic vascular compliance, stressed volume and cardiac function curves can be determined at the bedside and can be used to characterize patients' hemodynamic status.

Introduction

The accurate assessment of the volume status of a hemodynamically unstable patient at the bedside is challenging but, if available, would be important in assessing the determinants of cardiovascular insufficiency and response to therapy. Intravascular volume can be divided into unstressed volume (Vu, the volume that is needed to fill the blood vessels, without creating a distending pressure) and stressed volume (Vs, the volume that stresses the vascular walls, resulting in a distending pressure). This distending pressure is referred to as mean systemic filling pressure (Pmsf). Vs is an important cardiovascular variable, because along with the systemic vascular compliance (Csys), Vs determines Pmsf.[1] Pmsf is the pressure to which all intravascular pressures equilibrate during cardiac arrest, and is the pressure which is determined by both Csys and Vs. Pmsf itself is a major determinant of venous return, because it defines the upstream pressure and, relative to central venous pressure (Pcv), is the driving pressure for venous return and thus cardiac output (CO). Vs can be considered as reflecting the effective intravascular blood volume, a primary determinant of circulatory status. Thus, estimates of Vs and its change in response to disease or therapy can help the clinician in the decision of whether to choose volume resuscitation, diuresis, inotropic agents, or vasoactive medication in critically ill patients. In combination with a cardiac function curve, measuring Pmsf and Vs should provide a powerful tool to characterize the hemodynamic status of patients.

Under most conditions the primary method by which CO increases is an increase in Pmsf causing venous return to increase. Increasing contractility in this context is primarily important for keeping Pcv, the back pressure for venous return, as low as possible and also keeping left atrial pressure low to minimize pulmonary edema formation. Operationally, the circulation can rapidly increase Pmsf by increasing Vs, decreasing Csys, or both. Accordingly, if routine bedside Pmsf measures were possible, then both Vs and Csys could be determined during fluid administration or removal. When Pmsf is measured before and after fluid administration, a pressure-volume relationship can be constructed, in which Csys is the slope of the relation (Δvolume/ΔPmsf) (figure 7.1). When Csys is constant, the curve is linear. Extrapolation of this relationship to a point where pressure equals zero, i.e. subtracting the amount volume that causes Pmsf, results in an estimation of Vs.

Magder and DeVarennes[2] estimated Vs in humans as the volume of blood drained into a reservoir in five subjects during hypothermic circulatory arrest for vascular surgery. Although an elegant validation of the concept of Vs, this technique is not suitable for usual clinical care. We documented that Pmsf can be measured in ventilator-dependent patients at the bedside using a series of inspiratory hold maneuvers ($Pmsf_{hold}$).[3] $Pmsf_{hold}$ accurately followed changes in volume status induced by anti-Trendelenburg positioning and fluid administration. However, the estimation of $Pmsf_{hold}$ requires at

least 3 minutes to perform the 4 inspiratory hold maneuvers. Thus, it does not lend itself to repeat measures at short intervals or when Pmsf is rapidly changing. We therefore sought a faster bedside method for determining Pmsf and found a useful proposal by Anderson.[4] He hypothesized that the circulation of the arm behaves similar to the total systemic circulation and suggested that Pmsf could be measured in the arm during by instantaneously interrupting arterial inflow to the arm and venous outflow from the arm. Although different vascular beds when viewed in isolation have different vascular compliances and resistances, which can vary independent of each other, during steady-state conditions, all vascular beds drain to a common downstream pressure and must reflect a common upstream pressure driving that flow. For practical reasons, we thus opted for measures of vascular pressures in the forearm. Accordingly, we measured forearm arterial and venous equilibrium pressure induced by transient stop-flow, referred to as arm equilibrium pressure ($Pmsf_{arm}$) and compared its values to $Pmsf_{hold}$ values obtained with the inspiratory hold technique.[3] Recently, we[5] showed that stop-flow pressure in the arm predicted fluid responsiveness as well as stroke volume variation (SVV) and pulse pressure variation (PPV). However, this stop-flow pressure has not been published as a measure of Pmsf.

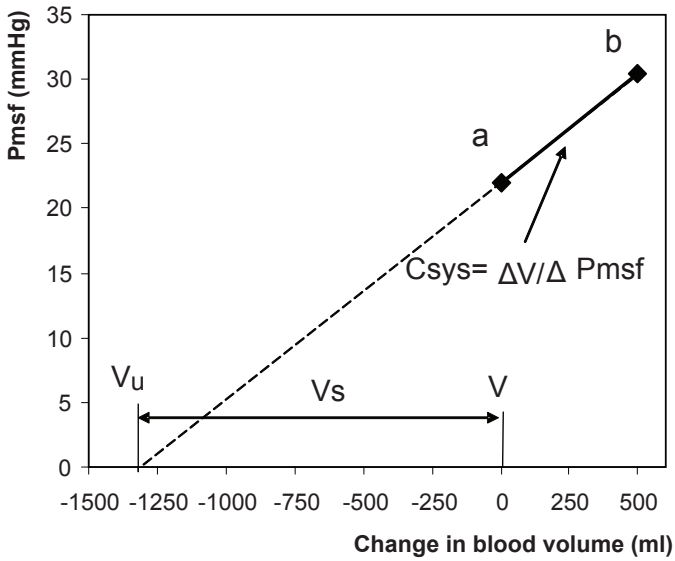

Figure 7.1 Schematic diagram of the determination of systemic compliance and stressed volume
Relationship between change in blood volume and mean systemic filling pressure (Pmsf) for normovolemia (a) and after intravascular volume administration with 500 ml (b). In the figure, systemic compliance (Csys) , stressed volume (Vs) and unstressed volume (Vu) are indicated. The value of Csys can be found by dividing the administered volume of 500 ml by the change in Pmsf (from point a to point b). In this example, removal of 1270 ml blood will lead to a Pmsf of 0 mmHg, with all the remaining blood within the system resting in the unstressed volume and with zero blood flow.

The aim of the study was to assess the ability of $Pmsf_{arm}$ to track $Pmsf_{hold}$ and to assess Csys and Vs in ventilated patients by measuring $Pmsf_{arm}$ during stepwise fluid

administration. We further hypothesized that patients who could not increase CO with fluid administration would have an expanded Vs and operate on the flat part of the heart function curve whereas patients who increase CO would have a lower Vs and operate on the steep part of the heart function curve. Accordingly, we constructed cardiac function curves (Pcv and CO) and estimated Csys and Vs in postoperative cardiac surgery patients during graded volume resuscitation. Because fluid administration was needed to determine Pmsf, Csys and Vs, the study was not designed to study the predictive value of fluid responsiveness of the variables.

Methods and materials

Patients. The study was approved by the hospital ethics committee of Leiden University Medical Center and was carried out in Leiden. The institutional review board of University of Pittsburgh approved review and analysis of the data. We included 15 patients planned for elective coronary artery bypass surgery or valvular surgery. Written informed consent was obtained from all subjects on the day before surgery. Patients with congestive heart failure (New York Heart Association class 4), aortic aneurysm, or extensive peripheral arterial occlusive disease were not considered for the study. The protocol was started during the first postoperative hour after admission to the intensive care unit (ICU). All patient's lungs were mechanically ventilated with volume-controlled ventilation adjusted to achieve normocapnia, with tidal volumes of 7 to 12 $ml \cdot kg^{-1}$ and 5 cm H_2O positive end-expiratory pressure (Evita 4, Dräger AG, Lübeck, Germany). All patients were in sinus rhythm. Sedation was maintained with propofol (2.5 $mg \cdot kg^{-1} \cdot h^{-1}$) and sufentanil (0.06-0.20 $\mu g \cdot kg^{-1} \cdot h^{-1}$). During the study interval no changes were made in vasoactive drug therapy and no interventions other than the described below volume challenges were given to these otherwise hemodynamically stable patients.

Physiological monitoring. Arterial blood pressure was measured with a radial artery catheter and Pcv was measured with a MultiCath 3 venous catheter (Vigon GmbH & Co, Aachen, Germany) inserted in the right internal jugular vein. Both catheters were connected to a pressure transducer (PX600F, Edwards Lifesciences). Zero levels of blood pressures were referenced to the intersection of the anterior axillar line and the fifth intercostal space. Airway pressure (Paw) was measured at the proximal end of the endotracheal tube with an air-filled catheter connected to a transducer, balanced at zero level against ambient air. Pressures were recorded online using a data acquisition program on a personal computer. Pulse contour analysis (Modelflow pulse contour method) was used to determine CO and stroke volume as we have previously described and validated.[6-9]

Determination of $Pmsf_{hold}$. The determination of $Pmsf_{hold}$ has been previous described in detail.[3] Briefly, four inspiratory holds of 12 seconds are applied, under control of a computer, at pressure levels of 5, 15, 25 and 35 cm H_2O, respectively, and the resulting

mean Pcv and mean CO were measured during the plateau phase (between 7 and 12 seconds into the inspiratory hold maneuver). A venous return curve is constructed by plotting the values of the four pairs of Pcv and CO against each other. $Pmsf_{hold}$ is defined as the Pcv at zero CO.

Determination of $Pmsf_{arm}$ by the arm stop-flow procedure. With a rapid cuff inflator (Hokanson E20, Bellevue, Washington) connected to compressed air and a cuff around the upper arm blood stop-flow is created with a cuff pressure 50 mmHg above systolic blood pressure and continued for 35 seconds. Arterial pressure (Pa) and venous pressure (Pv) were monitored via catheters in the radial artery and in a vein in the same hand. $Pmsf_{arm}$ was defined as the average radial artery pressure for one second at 30 seconds after induction of stop-flow (figure 7.2). As validation, we compared $Pmsf_{hold}$ with $Pmsf_{arm}$ before and after 500 ml fluid administration.

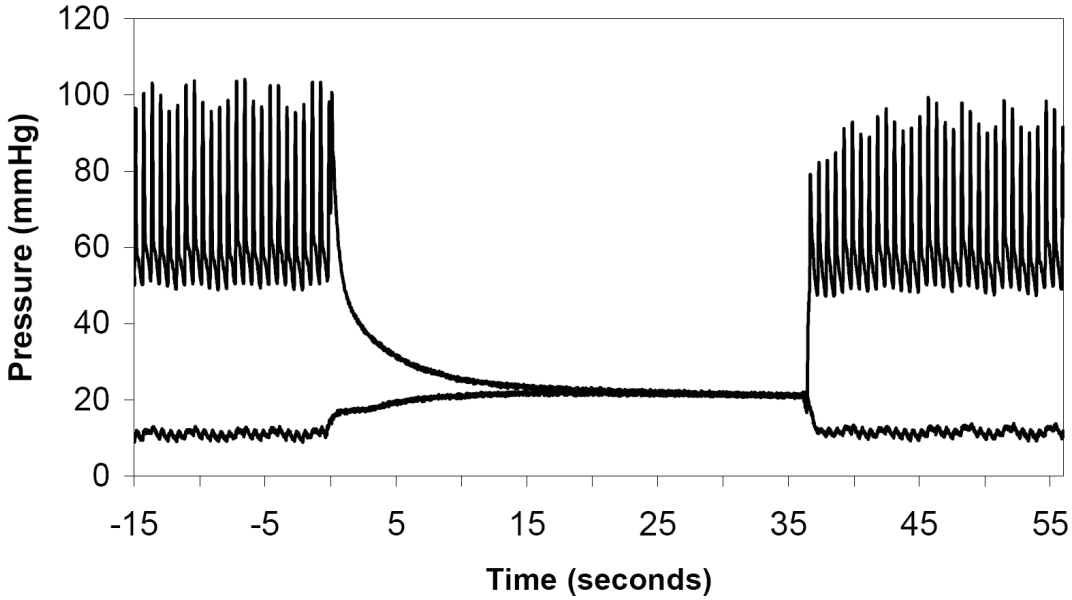

Figure 7.2 Arm occlusion procedure
Representative registration of radial artery pressure and venous pressure before (–15 to 0 seconds), during (0 to 36 seconds) and after the occlusion of the upper arm of a patient. $Pmsf_{arm}$ is the mean arterial pressure 30 seconds after stop-flow. Note the influence of mechanical ventilation on arterial and venous pressure before and after occlusion.

Compliance, stressed volume and cardiac function curves. Fluid administration was performed in 10 steps, each lasting 2 minutes. During each step 50 ml Hydroxyethyl Starch (HES 130/0.4) was administered over 1 minute. $Pmsf_{arm}$, Pcv and CO were measured one minute after the infusion. Pcv and CO after each fluid administration step were taken to reflect a right-sided cardiac function curve. The slope of the $Pmsf_{arm}$-volume infused curve ($\Delta volume/\Delta Pmsf_{arm}$) was taken to reflect Csys. Because Csys was linear over the range of volume and Pmsf measured, we extrapolated the ($\Delta volume/\Delta Pmsf_{arm}$) curve to zero $Pmsf_{arm}$ to estimate Vs. Both Vs and Csys were indexed to

predicted body weight to be able to calculate Vs as the proportion of predicted total blood volume. Predicted total blood volume was calculated as 69 ml·kg^{-1} predicted body weight for men and 65 ml· kg^{-1} predicted body weight for women.[10] The predicted body weight of male patients was calculated as equal to 50 + 0.91 · (centimeters of height – 152.4); that of female patients was calculated as equal to 45.5 + 0.91 · (centimeters of height – 152.4).

Statistical analysis. The Liliefors method confirmed that data were normally distributed; data are presented as mean ± SD. For the comparison of $Pmsf_{arm}$ and $Pmsf_{hold}$ values (combined before and after fluid administration) Pearson correlation was used. Linear regressions were fitted using a least-squares method. Paired t-tests were used to test the changes in parameters before and after 500 ml fluid administration. Concordance for changes in $Pmsf_{arm}$ and $Pmsf_{hold}$ was calculated by cross-tabulation and expressed in percentage. Independent sample two-tailed t-test was used to test for differences between patients with < 12% or > 12% change in CO after fluid administration. A p-value < 0.05 was considered significant.

Results

Fifteen patients were included in the study. Patient clinical characteristics are shown in table 7.1. In all patients, arm Pa and Pv equilibrated after 20 to 30 seconds stop-flow. In figure 7.2 the Pa and Pv in the arm during stop-flow for one patient are shown.

Comparison of $Pmsf_{hold}$ and $Pmsf_{arm}$. In 3 patients $Pmsf_{hold}$ was not assessable because of technical problems in the software control of the ventilator. In 12 remaining, patients measurements of $Pmsf_{hold}$ and $Pmsf_{arm}$ were obtained in supine position before and after 500 ml intravascular fluid administration. $Pmsf_{arm}$ and $Pmsf_{hold}$ values before and after fluid administration for every patient are depicted in figure 7.3. Pearson correlation coefficient was 0.905 ($p < 0.001$). Concordance for changes in $Pmsf_{arm}$ and $Pmsf_{hold}$ with fluid administration was 100%.

Cardiac function curve. In all 15 patients averaged $Pmsf_{arm}$ at baseline was 21.0 ± 6.8 mmHg and increased significantly to 27.7 ± 7.4 mmHg after the 10 fluid administration steps of 50 ml ($p = 0.001$). During the fluid administration steps, Pcv increased (table 7.2). We separated the patients in two groups. One group of 9 patients had a CO increase > 12% and were in the steep part of the heart function curve (figure 7.4) whereas the other group of 6 patients operated in the flat part of the curve. Three data points in one patient were not included because of technical problems. Patients with a CO increase < 12% on 500 ml fluid administration had significantly higher $Pmsf_{arm}$ values at baseline than patients with a > 12% increase (26.4 versus 17.3 mmHg, $p = 0.006$). There were no significant differences in baseline values of Pcv, Pa, SVV, PPV, or CO between the 2 groups.

Table 7.1 Patient and baseline hemodynamic characteristics

Characteristics		Mean	SD
Age (years)		64	11
Weight (kg)		81	14
Surgery			
	CABG	9	
	Valve	5	
	CABG+valve	1	
Pa (mmHg)		80.7	18.2
Pcv (mmHg)		7.9	3.0
HR (min^{-1})		86.5	15.7
CO ($l \cdot min^{-1}$)		5.4	1.2
Temperature start of study (˚C)		36.8	0.7
Temperature end of study (˚C)		36.9	0.8
pH		7.36	0.07
pCO2 (kPa)		5.2	0.7
pO2 (kPa)		17.7	4.7
		Number of patients	**Mean dose** ($\mu g \cdot kg^{-1} \cdot min^{-1}$)
Vasoactive medication			
	Dobutamine	8	5
	Enoximone	1	2
	Norepinephrine	7	0.09
	Epinephrine	1	0.09
	Sodium nitroprusside	1	0.5

CABG, coronary artery bypass grafting; Valve, valve repair or replacement; Pa, mean arterial blood pressure; Pcv, central venous pressure; HR, heart rate; CO, cardiac output; SD, standard deviation.

Compliance and stressed volume. Fluid administration resulted in an increase in $Pmsf_{hold}$ and $Pmsf_{arm}$ of 8.4 ± 4.2 mmHg (p = 0.0001) and 7.7 ± 6.6 mmHg (p = 0.005), respectively (table 7.2). The mean slope of the curve was 0.97 ± 0.47, not significantly different from 1 (p = 0.84). The $Pmsf_{arm}$-volume relationships (compliance curves) were linear for all patients (figure 7.5), with an average slope (i.e. mean Csys) of 64.3 ± 32.7 $ml \cdot mmHg^{-1}$ (0.97 ± 0.49 $ml \cdot mmHg^{-1} \cdot kg^{-1}$ predicted body weight) (table 7.3). Extrapolation of the $Pmsf_{arm}$-volume curve to a $Pmsf_{arm}$ of zero resulted in an estimated Vs of 1265 ± 541 ml which equated to 28.5 ± 15% of predicted total blood volume. There were no significant differences in Vs and Csys between the patients with and without > 12% increase in CO to fluid administration.

Discussion

This study demonstrates that using 50 ml rapid fluid administration steps and estimating Pmsf by the arm stop-flow Pa-Pv equilibrium method allows for bedside estimates of Pmsf, Csys and Vs, as well as the construction of more traditional cardiac function curves (CO to Pcv). Furthermore, we found that the relationship between $Pmsf_{arm}$ and volume, i.e. intravascular compliance curve, is linear. This linearity allows for the

bedside assessment of total Csys and estimates of Vs. We were able to distinguish patients who operated on the steeper portion of the cardiac function curve and were thus volume responsive from patients that operated on the flat part of the curve (figure 7.4). Because fluid administration was needed to determine compliance and Vs, we did not study fluid responsiveness from these variables.

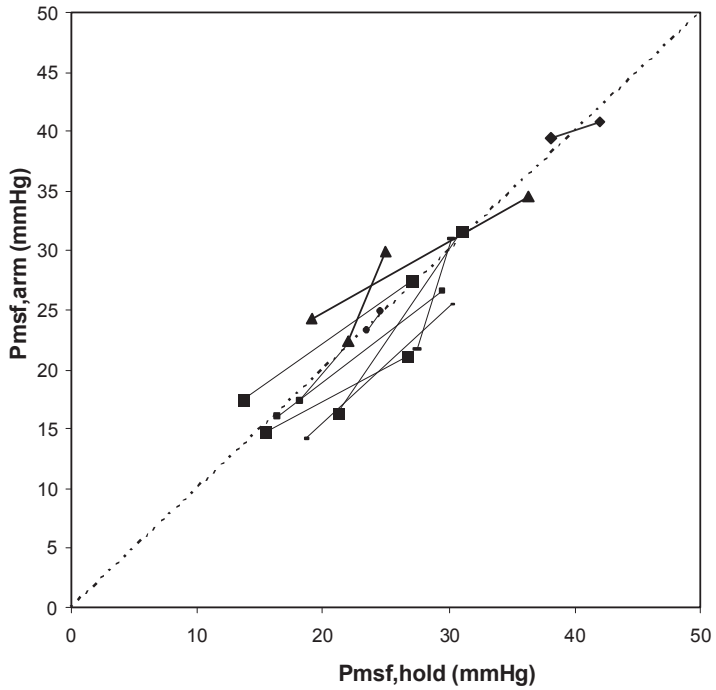

Figure 7.3 Mean systemic filling pressure determined with inspiratory holds and during arm occlusion

Plot of $Pmsf_{hold}$ and $Pmsf_{arm}$ for every patient at baseline and after 500 ml fluid administration. Every patient has his/her own symbol (squares, triangles, etc.) and the values at baseline and after fluid loading are connected by a line. Mean slope of the curve was 0.97 ± 0.47. $Pmsf_{hold}$ is mean systemic filling pressure measured with the inspiratory hold technique (see text); $Pmsf_{arm}$ is mean systemic filling pressure measured with the stop-flow procedure in the arm (see figure 7.2).

Table 7.2 Changes in hemodynamic variables after 500 ml fluid administration

	Baseline		+ 500ml		
	Mean	SD	Mean	SD	p
$Pmsf_{arm}$ (mmHg)	21.0	6.8	27.7	7.4	< 0.0001
Pcv (mmHg)	7.9	3.0	10.6	3.5	< 0.0001
Pa (mmHg)	80.7	18.2	89.1	18.3	< 0.0001
PPV (%)	10.1	6.6	5.5	3.6	0.003
SVV (%)	14.6	11.0	7.6	5.5	0.002
CO ($l \bullet min^{-1}$)	5.4	1.2	6.0	1.4	< 0.0001
HR (min^{-1})	86.5	15.7	87.0	14.1	0.56
Pvr (mmHg)	13.0	6.0	17.1	6.6	< 0.0001

$Pmsf_{arm}$, mean systemic filling pressure measured during stop-flow in the arm; Pcv, central venous pressure; Pa, mean arterial radial pressure; PPV, pulse pressure variation; SVV, stroke volume variation; CO, cardiac output; HR, heart rate; Pvr, pressure gradient for venous return ($Pmsf_{arm}$ – Pcv).

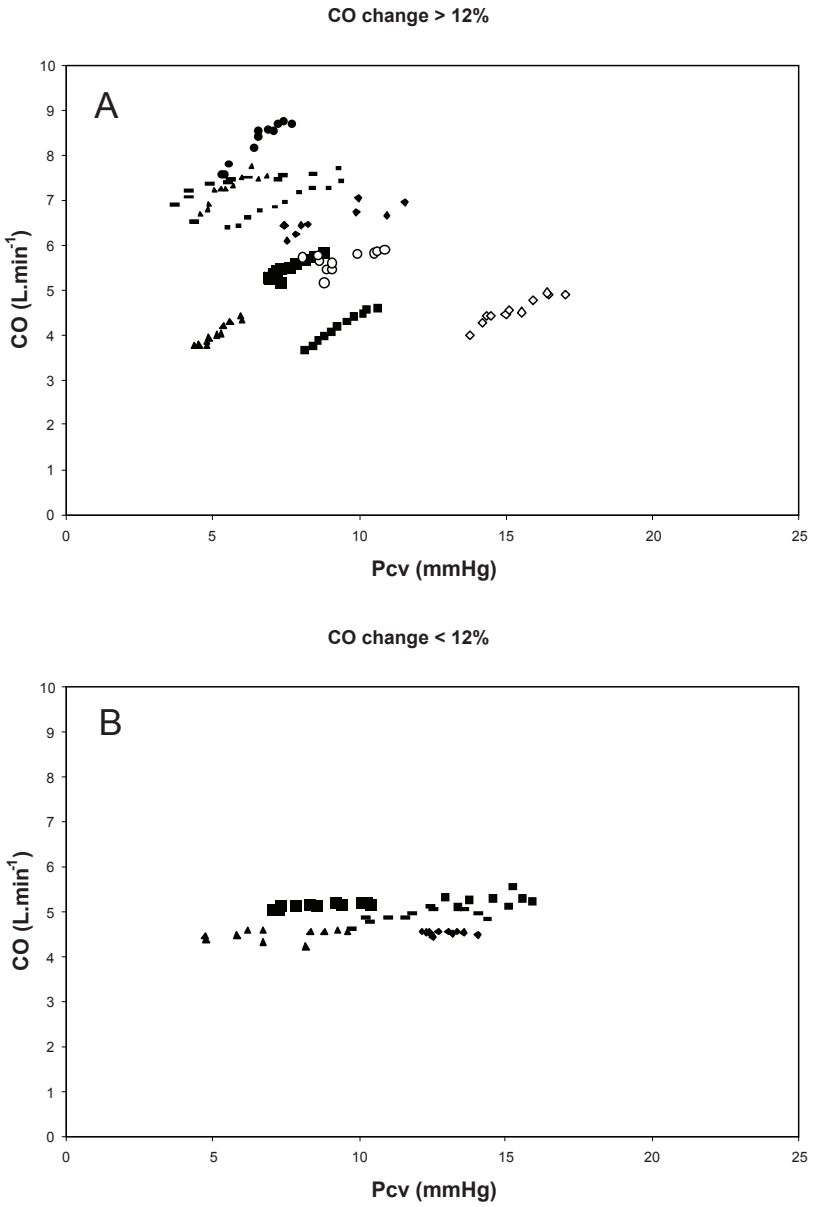

Figure 7.4 Individual cardiac function curves
Individual cardiac function curves for patients with (A) and without (B) a >12% increase in cardiac output (CO) after 500 ml fluid administration. Fluid administration was performed in 10 steps of 50 ml and central venous pressure (Pcv) and CO were measured at baseline and after each volume step. Every patient has his/her own symbol (squares, triangles, dashes, etc). Note that the patients with >12% increase in CO on 500 ml fluid administration were on the steep part and the remaining patients were on the flat part of the curve.

Cardiac function curves. Recent interest in functional hemodynamic monitoring variables, such as PPV and SVV during positive-pressure ventilation, presumes that those subjects who will respond to fluids by increasing their CO are operating on the steep portion of their ventricular function curve. Although intuitively obvious, this presumption has never been validated. For this study we used the cardiac function curve as substitute for a Frank-Starling curve, with Pcv as input and CO as output variable. Our data confirm this assumption. Although, Versprille and Jansen[11] studying pigs and Pinsky[12] studying dogs plotted similar cardiac function curves for the right ventricle

using variations in right ventricular power and Pcv during the ventilatory cycle in different volume states, to our knowledge, the construction of a cardiac function curve and the calculation of Vs by using small additions of fluid in ICU patients has not yet been published.

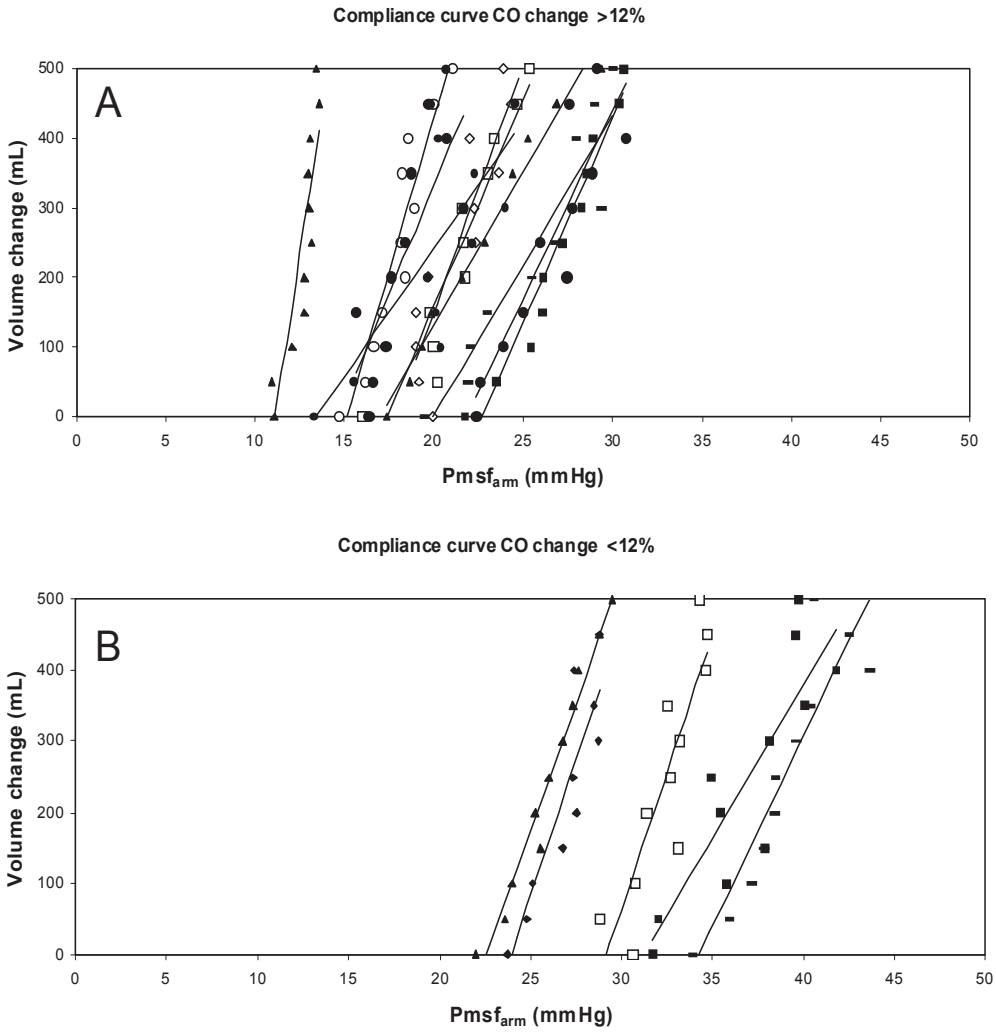

Figure 7.5 Individual volume-pressure curves
Individual volume-pressure curves patients with (A) and without (B) >12% increase in cardiac output (CO) on 500 ml fluid administration. Fluid administration was performed in 10 fluid administration steps of 50 ml and mean systemic filling pressure was measured with the arm occlusion method ($Pmsf_{arm}$, see figure 7.2) after each fluid administration step. Systemic vascular compliance (Csys) is defined as $\Delta volume/\Delta Pmsf_{arm}$, which is the reciprocal of the slope of the curve. Note that $Pmsf_{arm}$ is significantly lower in group A compared to group B ($p = 0.006$) and that the slope of the curve (Csys) is similar in both groups.

Arm equilibrium pressure as measure of Pmsf. Because the execution of the $Pmsf_{hold}$ technique requires 3 minutes, it was not suitable to following Pmsf changes during the 10 rapid fluid administration steps of 50 ml performed at intervals of 2 minutes. Theoretically, Pmsf can be measured anywhere in the circulation under the condition of stop-flow if regional vascular compliance does not change during the stop-flow maneuver. In a pilot study with stop-flow by upper arm occlusion during 60 seconds,

we observed that a plateau pressure developed in both Pa and Pv after 20 to 30 seconds of stop-flow. Therefore, we defined mean arterial pressure between 29 and 30 seconds as $Pmsf_{arm}$. The rapid cuff inflator (Hokanson E20, Bellevue, Washington) inflates in less than 0.3 seconds.[13] In this time, venous return stops before arterial stop-flow, limiting the inflow of blood in the arm to maximal 1 heartbeat. We expect that the resulting overestimation of $Pmsf_{arm}$ is negligible because the amount of inflow over one heartbeat is small compared to the total amount of blood in the arm. It is important to note that we did not observe any complications from the arm occlusion procedure in our patients. In this study, changes in volume status assessed by $Pmsf_{hold}$ were faithfully tracked by $Pmsf_{arm}$ (figure 7.3). Therefore, we considered $Pmsf_{arm}$ as a valid substitute for $Pmsf_{hold}$ in estimating Pmsf. $Pmsf_{arm}$ has the potential to be used in clinical practice in the operating room and ICU, because only an arterial catheter is required and $Pmsf_{arm}$ can be measured in all patients, including spontaneously breathing patients and patients with arrhythmias.

Table 7.3 Hemodynamic data for individual patients

No	$Pmsf_{arm}$ (mmHg)	Compliance (ml•mmHg^{-1})	Vs (ml)	CO (l•min^{-1})	Pcv (mmHg)	Pa (mmHg)	Change in CO (%)
1	20.0	70.8	1264	4.0	13.8	65.6	22.5
2	23.7	77.4	1856	4.4	12.5	63.7	1.4
3	31.7	29.7	876	6.4	12.0	114.5	-4.7
4	22.0	71.9	1623	4.2	8.2	71.5	8.2
5	21.8	59.2	1346	3.7	9.7	78.2	25.5
6	11.1	163.7	1815	6.7	4.6	75.9	12.6
7	33.9	54.0	1853	4.6	8.1	68.3	4.0
8	16.0	59.9	1044	5.2	7.3	72.0	12.8
9	22.4	54.3	1187	7.6	5.3	79.3	14.7
10	14.8	88.6	1343	5.2	8.8	87.0	14.1
11	16.4	33.3	403	6.4	7.4	124.7	9.4
12	17.4	44.1	750	3.8	4.4	55.7	17.4
13	13.3	36.6	490	6.4	5.4	85.7	20.6
14	19.4	43.2	863	6.6	4.4	82.9	16.0
15	30.6	77.4	2259	5.1	7.0	85.9	2.3
mean	21.0	64.3	1265	5.4	7.9	80.7	11.8
SD	6.8	32.7	541	1.2	3.0	18.2	8.4

$Pmsf_{arm}$, mean systemic filling pressure at baseline; compliance, the slope of the volume-pressure curve; Vs, stressed volume estimated by extrapolation of the volume pressure curve; CO, cardiac output; Pa, mean arterial blood pressure; change in CO, percentage of change in CO after 500 ml fluid administration.

Total systemic vascular compliance. Csys has been mainly measured in dogs in three ways: 1. measuring Pmsf during total stop-flow before and after fluid administration; 2. using a right heart bypass and changing right atrial pressure; and 3. measuring instantaneous right ventricular stroke volume to Pcv during positive-pressure inspiration (instantaneous venous return curve). With the total stop-flow method values of vascular compliance between 1.8 and 2.0 ml·mmHg^{-1}·kg^{-1} body weight were

found.[14-16] Using the bypass method and instantaneous venous return curve method, values between 1.3 and 2.5 ml·mmHg^{-1}·kg^{-1} body weight were obtained.[12,17-21] The mean Csys of 0.97 ± 0.49 ml·mmHg^{-1}·kg^{-1} predicted body weight we found in ICU patients is lower than these values, which can be species related. However, it can also be explained by a lower volume status of the animals as is reflected in lower Pmsf values reported in animals.[12,16,17,19,22] Pmsf can be increased up to 25 mmHg with both fluid administration and the administration of norepinephrine.[23] The influence of medication in our study and in the animal studies is another possible explanation for differences in estimated Csys. In dogs, Csys decreased when beta-2 stimulation[16], epinephrine[20] or norepinephrine[24] was given. The majority of our patients (10 of 15) were treated with vasopressor drugs and only one patient was treated with a vasodilator to restore mean arterial pressure to a normal range. Fluid loss by capillary leakage, diuresis and blood loss during the study period, leading to a smaller volume increase, could also lead to an underestimation of compliance. Measurements were performed in a period of 25 minutes to limit this leakage factor. We monitored chest tube drainage during the volume challenge interval and in none of the subjects did this drainage exceed 50 ml, nor was diuresis pronounced during the study period. Furthermore, care was taken that insensible fluid loss was compensated for with a 60 ml·hr^{-1} infusion of crystalloid.
London *et al*. estimated human systemic vascular compliance by measuring the change in Pcv in response to fluid administration.[25,26] This vascular compliance, called total effective vascular compliance, was 2.08-2.55 ml·mmHg^{-1}·kg^{-1} body weight in young healthy subjects and substantially lower (1.49-1.55 ml·mmHg^{-1}·kg^{-1} body weight) in hypertensive patients.[25,26] In both studies Pcv was used because Pmsf could not be obtained. However, it is doubtful if Pmsf can be exchanged for Pcv, because Pcv is also affected by the surrounding pressure and by changes in both ventricular function and venous return and thus CO due to intravascular volume expansion. The Pcv-based total effective compliance is therefore theoretically not comparable to our Pmsf-based determination of Csys.

Stressed volume. Stressed volume (Vs) is only one component of the systemic vascular compartment. If starting from zero blood volume one were to start to fill the vasculature, the initial volume entering the intravascular space would not create a measurable distending pressure or Pmsf, because the vasculature can accommodate initial volume by conformational changes in the vessels as they start to engorge. At some minimal circulating blood volume subsequent volume infusion causes Pmsf to become positive relative to surrounding pressure. The volume in the vasculature below this level is called the unstressed volume (Vu) and is influenced by Csys. If Csys increased, then Vu would also increase and vice versa. Because only Vs and Csys determine Pmsf, if Vu were to change and total blood volume would remain unchanged, then Vs would vary reciprocally.
The pressure gradient between Pmsf and central venous pressure (Pcv) is the driving

force for venous return and thus for steady-state CO as well. Vs is a primary determinant of Pmsf and is therefore a major determinant of venous return and CO. We determined Vs by extrapolation of the $Pmsf_{arm}$-volume curve to the zero pressure intercept presuming that the reduction in volume needed to achieve a zero Pmsf is equal to Vs. We chose this extrapolation method to determine Vs because only two parameters are needed: changes in volume and Pmsf. For this extrapolation method to be accurate, however, the Pmsf-volume change relationship (compliance) must be linear. Linear Pmsf-volume relationships have been described in several animal studies[13,17,23,25-27], thus indicating a stable compliance. A constant compliance of the total vasculature was also found by Drees and Rothe[23], while Pmsf was varied in the range from 5 to 25 mm Hg. Lee *et al*.[28] also described a linear relationship between Pmsf and volume for Pmsf above 5 mmHg, however below 5 mmHg the curve deviated slightly from linear.
The average Vs in our patients was 19.6 $ml \cdot kg^{-1}$ predicted body weight. This value is very close to the value of 20.2 $ml \cdot kg^{-1}$ found in 5 patients on cardiopulmonary bypass during hypothermic circulatory arrest for major vascular surgery.[2] Mean Vs was 29 % of predicted total blood volume, again, similar to the 30% Magder and DeVarennes[2] found and in the estimated range of 20-30% given by Jacobsohn *et al*.[29] The wide variation in values of Vs can be explained by several factors. First, we included fluid responsive and nonresponsive patients and thus variation in Vs can be expected. Second, although we had 11 points on the pressure-volume curve, because of the 10 volume administration steps and 1 baseline measurement for each patient, a slight change in slope has a large effect on the value of Vs due to the extrapolation outside of the range of the measurements. Third, we linearly extrapolated the $Pmsf_{arm}$-volume curve. Because we could not measure in the lower pressure range, we cannot comment on the characteristics of the curve in that range. In case of nonlinearity in this lower pressure range, we expect Vs would be underestimated.

Limitations. Although we report on a relatively small number of patients (n = 15) our results were highly significant. Thus, we do not expect that increasing the number of patients will alter these conclusions. We studied a highly instrumented uniform patient population following cardiac surgery in whom baseline vasomotor tone, vascular permeability and cardiac performance were similar and unaffected by extraneous disease. Vasomotor tone can be influenced by temperature and metabolic acidosis. After surgery, the temperature can increase decreasing vasomotor tone and metabolic acidosis can induce vasodilation or hyporesponsiveness to vasoconstrictors. However, our patients were normothermic and their core temperatures were unchanged during the study and metabolic acidosis was absent or mild. In our study, vasoactive medication was not changed. Changing vasomotor tone will alter Vu, Vs and Csys. Therefore, conclusions about the use of this technique during changes in external pharmacologic support should be made with caution and need to be independently validated. It is not clear whether similar findings and accuracy would be seen in septic patients with

combined loss of vasomotor tone and capillary leak. Still, Pinsky *et al*.[17] examined Csys and Pmsf before and after the induction of acute endotoxic shock in a canine model; they found similar Csys values before and during endotoxemia although Vu increased markedly during endotoxemia, and during endotoxemia, all animals were hypotensive.

It would be interesting to see the cardiac function curves and Pmsf-volume plots in different patient groups (such as sepsis, cardiac failure, trauma and ARDS) and with different vasoactive medication. Because total blood volume was not measured in our study, though it was in other studies[12,17], Vu could not be determined and needed to be estimated from previously validated nomograms. When combined with measurements of total blood volume the proportion of Vs/Vu could be readily studied for a variety of diseases and medications.

Conclusions

Total Csys, Vs and cardiac function curves can be determined at the bedside using stop-flow forearm pressure equalization and might be used to characterize patients' hemodynamic status. We predict that in the future, cardiovascular therapy will be based on assumptions derived by venous return physiology because it will be possible to directly measure Pmsf, Vs, and Csys at the bedside, allowing construction of venous return curves and cardiac function curves during stepwise fluid administration.

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