Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients*

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Objective: **To measure the relationship between blood flow and central venous pressure (P_{cv}) and to estimate mean systemic filling pressure (P_{msf}), circulatory compliance, and stressed volume in patients in the intensive care unit.**

Design: **Intervention study.**

Setting: **Intensive care unit of a university hospital.**

Patients: **Twelve mechanically ventilated postoperative cardiac surgery patients.**

Interventions: **Inspiratory holds were performed during normovolemia in supine position (baseline), relative hypovolemia by placing the patients in 30 degree head-up position (hypo), and relative hypervolemia by volume loading with 0.5 L colloid (hyper).**

Measurements and Main Results: **We measured the relationship between blood flow and P_{cv} using 12-second inspiratory-hold maneuvers transiently increasing P_{cv} to three different steady-state levels and monitored the resultant blood flow via the pulse contour method during the last 3 seconds. The P_{cv} to blood flow relation was linear for all measurements with a slope unaltered by relative volume status. P_{msf} decreased with hypo and increased with hyper (18.8 ± 4.5 mm Hg, to 14.5 ± 3.0 mm Hg, to 29.1 ± 5.2 mm Hg [baseline, hypo, hyper, respectively, $p < 0.05$]). Baseline total circulatory compliance was 0.98 mL·mm Hg^{-1}·kg^{-1} and stressed volume was 1677 mL.**

Conclusions: **P_{msf} can be determined in intensive care patients with an intact circulation with use of inspiratory pause procedures, making serial measures of circulatory compliance and circulatory stressed volume feasible. (Crit Care Med 2009; 37:912–918)**

KEY WORDS: mean systemic filling pressure; circulatory compliance; stressed volume; mechanical ventilation; cardiac output; cardiac surgery

The cardiovascular system is a closed circuit with varying blood flow out of the heart into the arterial system (cardiac output [CO]) and flow back to the heart from the venous system (venous return [VR]), which may not be equal at any point in time owing to ventilation-induced changes in VR, but which over time must be equal (1, 2). Thus, under steady-state apneic conditions CO and VR become equal. Guyton et al (3, 4) showed that the relationship between stepwise changes in right atrial pressure (P_{ra}) and the resulting changes in VR describes a VR curve, which itself is a function of the circulating blood volume, vasomotor tone, and blood flow distribution. Importantly, P_{ra} at the extrapolated zero-flow pressure intercept reflects mean systemic filling pressure (P_{msf}), and the slope of this relation describes the resistance for venous return (R_{vr}) (3, 5). This relationship between P_{ra} and VR was well described in animal models with an artificial circulation (4), in patients during stop-flow conditions (6), and in animals with an intact circulation using invasive hemodynamic monitoring (7–10). However, it has never been evaluated in humans with an intact circulation. If such VR curves could be easily constructed at the bedside, then complex cardiovascular analysis would be feasible, thereby, augmenting greatly our understanding of the dynamic determinants of circulatory insufficiency states and their responses to therapies. Intravascular blood volume can be divided into unstressed volume (the blood volume necessary to fill the blood vessels without generating an intravascular pressure) and stressed volume (the blood volume that generates the intravascular pressure, which is P_{msf} in no-flow conditions).

Previously, Pinsky (7) constructed instantaneous VR curves based on the beat-to-beat changes in P_{ra} and simultaneously measured right ventricular output during a single mechanical breath, neglecting possible transient effects of increasing P_{ra} on VR (1, 2). Versprille and Jansen (8) prevented these transient changes by measuring P_{ra} and right ventricular output during steady-state conditions generated by ventilator-applied inspiratory pause periods at different inflation volumes. Unfortunately, it is difficult to measure pulmonary blood flow on a beat-to-beat basis at the bedside. We hypothesized that if inspiratory-hold maneuvers that increase P_{ra} create a new steady state, then VR and CO would again be equal and direct measures of left-sided CO could be used to estimate steady-state VR.

Thus, we studied the effect of 12-second inspiratory-hold maneuvers on the relation between central venous pressure (P_{cv}), as a surrogate for P_{ra}, and arterial pulse contour-derived cardiac output (COmf), as a surrogate for VR, as P_{cv} was varied by inspiratory-hold maneuvers and intravascular volume status altered by a head-up tilt body position (relative hypovolemia) and intravascular volume loading (hypervolemia).

*See also p. 1143.

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MATERIALS AND METHODS

Patients. Twelve postoperative patients after elective coronary artery bypass surgery or aortic valve replacement were included in the study after approval by the university medical ethics committee and patient's informed consent was obtained. All patients had symptomatic coronary artery disease without previous myocardial infarction and were on beta-adrenergic blocking medication. Patients with congestive heart failure (New York Heart Association class 4), aortic aneurysm, extensive peripheral arterial occlusive disease, or postoperative valvular insufficiency were not considered for this study. Patients with postoperative arrhythmia, those with the necessity for artificial pacing, or the use of a cardiac assist device were also excluded.

Anesthesia during surgery was maintained with sufentanil and propofol and patients were ventilated in synchronize intermittent mandatory ventilation mode (Evita4 servo ventilator Draeger, Lubeck, Germany) adjusted to achieve normocapnia (arterial P_{CO_2} between 40 and 45 mm Hg) with tidal volumes of 6–8 $mL \cdot kg^{-1}$ and a respiratory rate of 12–14 $breaths \cdot min^{-1}$. Fraction of inspired oxygen (F_{IO_2}) was 0.4 and a positive end-expiratory pressure of 5 cm H_2O was applied. A hemodynamic stability was achieved using fluids and catecholamines. During the study interval, all subjects were hemodynamically stable and no changes were made in their vasoactive drug therapy. Every patient experienced full recovery from anesthesia within 8 hours after surgery and was discharged from intensive care unit on the first postoperative day.

Measurements. Arterial blood pressure (P_a) was monitored via a 20-G, 3.8-cm long radial arterial catheter inserted by Seldinger technique and connected to a pressure transducer (PX600F, Edwards Lifesciences). P_{cv} was measured with a central venous catheter inserted through the right internal jugular vein (MultiCath 3 venous catheter, Vigon GmbH & Co, Aachen, Germany) and connected to a pressure transducer (PX600F, Edwards Lifesciences). Both P_a and P_{cv} transducers were referenced to the intersection of the anterior axillary line and the fifth intercostal space. Airway pressure (P_{vent}) was measured at the entrance of the endotracheal tube. P_{vent} was balanced at zero level against ambient air. Standard electrocardiogram leads were used to monitor heart rate. Beat-to-beat CO was obtained by modelflow (COmf) pulse contour analysis as previously described by us (11–13). We calibrated the pulse contour CO measurements with three thermodilution CO measurements equally spread over the ventilatory cycle (12).

Experimental Protocol. Before starting the protocol, the mechanical ventilation mode was switched to airway pressure release ventilation release ventilation with the same rate, F_{IO_2}, and positive end-expiratory pressure level. Inspiration pressure was adapted to have the same gas exchange as in SIMV mode. This change in ventilation mode allowed external control of the ventilatory process. We developed a computer program to drive the ventilator. During the observation period, ventilator settings, sedation, and vasoactive medications remained unchanged. No spontaneous breathing movements were observed during the study. P_a, P_{cv}, and P_{vent} were recorded on computer disk for offline data analysis at a sample frequency of 100 Hz and 0.2 mm Hg resolution.

We constructed VR curves by measuring steady-state P_a, P_{cv}, and COmf over the final 3 seconds for a set of four 12-second inspiratory-hold maneuvers at P_{vent} plateau pressures of 5, 15, 25, 35 cm H_2O. The inspiratory-hold maneuvers were separated by 1-minute intervals to reestablish the initial hemodynamic steady state. An example of the hemodynamic changes during an inspiratory hold is shown in Figure 1. When P_{vent} increases, P_{cv} increases concomitantly, whereas COmf and P_a decrease with a delay of three-four beats, reaching a steady state between 7 and 12 seconds after start of inflation. From the steady-state values of P_{cv} and COmf during the four inspiratory pause periods, a VR curve was constructed by fitting a linear regression line through these data points (Fig. 2).

The four inspiratory-hold maneuvers were performed under three sequential volumetric

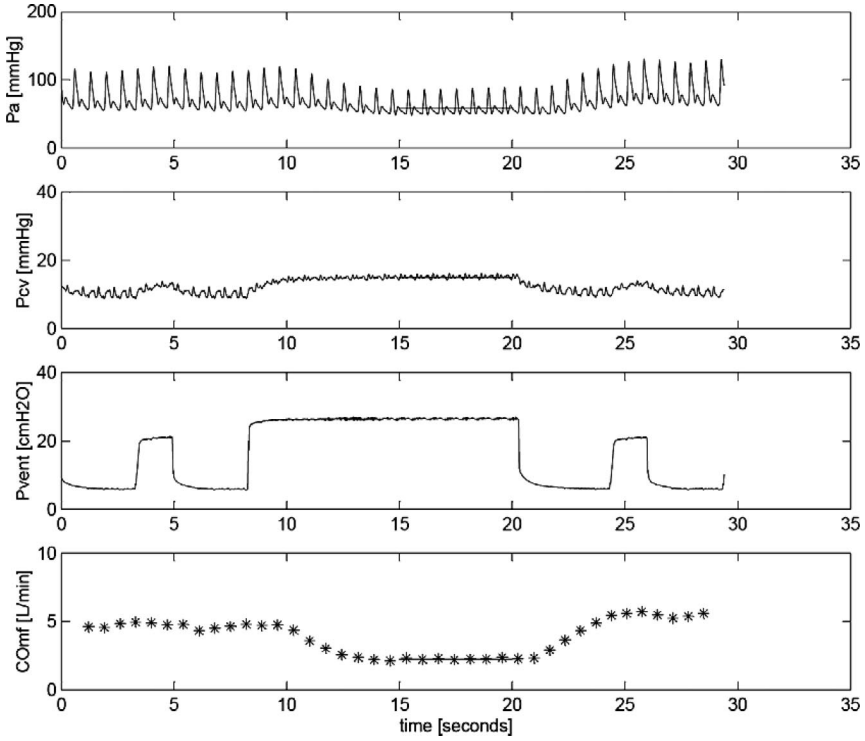

Figure 1. Effects of an inspiratory-hold maneuver on arterial pressure (P_a), central venous pressure (P_{cv}), airway pressure (P_{vent}), and beat-to-beat cardiac output (*COmf*). Preceding the hold maneuver, the effects of a normal ventilatory cycle are plotted.

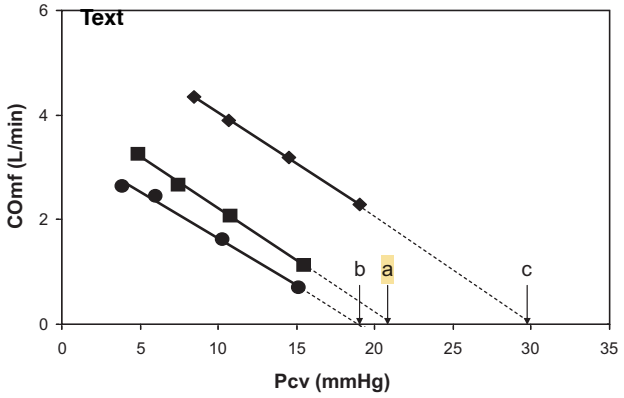

Figure 2. Relationship between venous return (*COmf*) and central venous pressure (P_{cv}) for an individual patient. Venous return curves are plotted for three conditions: baseline (*a*), hypovolemia (*b*), and hypervolemia (*c*).

conditions: initial baseline conditions (baseline) with the subject lying supine, relative hypovolemia by rotating the bed to a 30 degree head-up (anti-Trendelenburg) position (hypo), and after administration of 500 mL hydroxyethyl starch (130/0.4) in supine position (hyper). Measurements were done 2 minutes after head-up tilt and 2–5 minutes after the fluid bolus, which was given in 15–20 minutes.

Data Analysis and Statistics. We fitted the set of four data points of P_{cv} and COmf by linear regression for each volume state to define the VR curve. We defined P_{msf} as the extrapolation of this linear regression to zero flow (Fig. 2), assuming that P_{vent} does not affect P_{msf}. We have previously validated this extrapolation in piglets (8–10).

Total systemic vascular resistance (R_{sys}) was calculated as the ratio of the pressure difference between mean P_a and mean P_{cv} and COmf ($R_{sys} = (P_a - P_{cv})/COmf$). The resistance downstream of P_{msf} was taken to reflect the R_{vr} and was calculated as the ratio of the pressure difference between P_{cv} and P_{msf} and COmf ($R_{vr} = (P_{msf} - P_{cv})/COmf$). Systemic arterial resistance (R_a) was taken to be the difference between systemic and venous resistance. The ratio of R_{vr} and R_{sys} describes the location within the circulation where P_{msf} exists. A higher ratio implies a more upstream P_{msf} location.

Systemic compliance (C_{sys}) was calculated by dividing the amount of fluid (V_{load}) administrated to induce the hyper state by the P_{msf} difference between baseline and hyper ($C_{sys} = V_{load}/(P_{msfHyper} - P_{msfBaseline})$. We assume C_{sys} to be constant for the three volemic conditions studied.

Stressed vascular volume (V_s) was calculated as the product of C_{sys} and P_{msf}. We calculated V_s for all three relative volume conditions.

Data are presented as mean ± SD. Linear regressions were fitted using a least-squares method. The changes between the three conditions were tested by a paired Student's *t* test, with differences corresponding to a $p < 0.05$ considered significant. We compared baseline to both hypo and hyper.

RESULTS

Sixteen patients were recruited into the study, but four were excluded from analysis because they could not receive an additional volume challenge. Table 1

Table 1. Patient characteristics

No	Sex	Age (yrs)	Weight (kg)	Length (cm)	HR (min^{-1})	P_{cv} (mm Hg)	CO ($L \cdot min^{-1}$)	MAP (mm Hg)	Temp (°C)	Surgery	Inotropics ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	Propofol ($mg \cdot hr^{-1}$)	Sufentanil ($\mu g \cdot hr^{-1}$)
1	M	60	80	172	85	8.2	4.6	72	36.8	CABG	—	300	15
2	M	57	78	169	119	9.9	5.7	73	36.9	CABG	Dobu 2	300	15
3	M	79	78	174	86	7.5	6.3	88	36.9	AVR	Dobu 5	200	10
4	M	50	90	190	93	7.4	3.2	138	36.3	AVR	NPN 0.25	300	15
5	M	80	90	172	99	8.0	6.1	80	36.7	CABG	Nor 0.01	200	10
6	F	64	83	167	76	7.1	5.8	88	37.4	CABG	Nor 0.04, Dobu 3	200	10
7	M	50	112	183	83	4.0	5.7	85	37.0	CABG offpump	Nor 0.06	500	15
8	M	57	91	177	63	4.9	6.4	78	35.1	CABG offpump	—	300	10
9	M	71	73	179	93	8.0	8.8	91	37.1	CABG	Nor 0.09, Dobu 4	120	5
10	M	66	88	178	69	3.0	7.4	71	35.8	CABG offpump	Nor 0.02	200	10
11	M	75	95	173	77	9.0	4.4	130	36.5	CABG offpump	—	300	10
12	F	60	74	158	89	3.7	5.3	86	36.6	CABG offpump	Nor 0.04, Enox 2	150	5
Mean		64	86	174	86	6.7	5.8	90	36.6			256	11
SD		10	11	8	15	2.3	1.4	22	0.6			101	4

HR, heart rate; P_{cv}, central venous pressure; CO, cardiac output; MAP, mean arterial pressure; Temp, body temperature; CABG, coronary artery bypass grafting; AVR, aortic valve replacement; Dobu, dobutamine; NPN, nitroprusside sodium; Nor, norepinephrine; Enox, enoximone; SD, standard deviation.

Table 2. Hemodynamic data of patients during baseline, hypovolemic, and hypervolemic condition

	Baseline		Hypo			Hyper		
	Mean	SD	Mean	SD	*p*1	Mean	SD	*p*2
P_a (mm Hg)	89.9	21.6	75.7	17.3	0.001	96.5	14.9	0.170
P_{cv} (mm Hg)	6.72	2.26	4.02	2.12	0.001	9.67	2.63	0.007
COmf ($L \cdot min^{-1}$)	5.82	1.44	4.76	1.30	0.001	6.83	1.36	0.002
HR (min^{-1})	86.0	14.7	85.7	15.1	0.456	84.3	10.7	0.401
Slope ($L \cdot min^{-1} \cdot mm\ Hg^{-1}$)	−0.465	0.151	−0.429	0.160	0.388	−0.389	0.135	0.134
P_{msf} (mm Hg)	18.76	4.53	14.54	2.99	0.005	29.07	5.23	0.001
P_{vr} (mm Hg)	12.04	3.70	10.52	2.27	0.106	19.40	6.88	0.003
R_{vr} (mm Hg·min·L^{-1})	2.18	0.86	2.41	1.14	0.184	2.91	1.10	0.037
R_{sys} (mm Hg·min·L^{-1})	15.89	9.00	16.95	10.27	0.379	13.52	5.60	0.122
R_{vr}/R_{sys} (%)	14.94	5.00	14.84	2.37	0.931	22.62	8.07	0.006

P_a, arterial pressure; P_{cv}, central venous pressure; COmf, cardiac output; HR, heart rate; Slope, slope of venous return curve; P_{msf}, mean systemic filling pressure; P_{vr}, pressure difference between P_{msf} and P_{cv}; R_{vr}, resistance for venous return; R_{sys}, resistance of the systemic circulation; Statistical comparison, *p*1, paired *t* test between baseline and hypovolemic condition (hypo) and *p*2, paired *t* test between baseline and hypervolemic condition (hyper); SD, standard deviation.

Values are means ± SD; n = 12 patients.

shows the patient characteristics and Table 2 shows the pooled data of the 12 subjects who completed all three steps of the protocol.

Venous Return Curve Analysis. P_{cv} and COmf decreased during hypo and increased during hyper. Similarly, P_{msf} decreased during hypo and increased during hyper, whereas the slope of the VR (conductance) was not significantly different for the three conditions of baseline, hypo, and hyper. The pressure gradient for VR did not change with hypo but increased with hyper such that R_{vr} was unchanged by hypo but increased with hyper. Importantly, R_{sys}, did not change. Thus, the estimated location of P_{msf} was unchanged by hypo but migrated upstream with hyper.

Systemic Compliance and Stressed Volume. The change in stressed volume vs. P_{msf} is shown in Figure 3. Assuming a constant compliance, the loss of stressed volume due to hypo is approximately 200 mL. On average, C_{sys} was 80 ± 62 mL·mm Hg^{-1} (0.98 ± 0.82 mL·mm Hg^{-1}·kg^{-1} body weight) and stressed volume during baseline was 1677 ± 1643 mL (12.5 ± 12.1 mL·kg^{-1} body weight).

DISCUSSION

Our study demonstrates that by using a simple inspiratory-hold maneuver while simultaneously measuring P_{cv} and P_a, one can generate VR curves and derive their associated vascular parameters at the bedside. Our data suggest that volume-altering maneuvers (hypo and hyper) do not alter vascular conductance (slope of the VR curve). These clinical data are concordant with the long-described experimental data introduced by Guyton et al over 50 years ago (4, 14). Importantly, our novel approach to assessing VR allows these analyses to be done at the bedside in patients after coronary artery bypass surgery or aortic valve replacement. Patients with congestive heart failure (New York Heart Association class 4), aortic aneurysm, extensive peripheral arterial occlusive disease, postoperative valvular insufficiency, postoperative arrhythmia, or the necessity for artificial pacing or use of a cardiac assist device were excluded from this study. It will be interesting to see how these vascular parameters change in different disease states, such as septic shock and heart failure, and how treatments alter them further because these analyses allow for the repetitive estimation of circulatory vascular compliance and effective circulatory blood volume.

Methodologic Issues. During an inspiratory pause period a new steady state was attained, which can be concluded from the plateau phase in the COmf, P_a, and P_{cv} (Fig. 1). In this example, the time needed to reach the plateau was approximately 7 seconds. This duration is too short to be associated with changes in autonomic tone which would otherwise occur owing to the decrease in P_a-induced baroreceptor-mediated increase in sympathetic tone. Samar and Coleman (15) showed in rats that a total circulatory stop, by pulmonary occlusion, caused a simultaneous decrease of arterial pressure and a rise in central pressure to an equal plateau pressure within 4–5 seconds. This was followed by a second rise in P_{cv} after 10–12 seconds of circulatory arrest in rats (15, 16) and after 12–15 seconds in dogs (17). The second rise was seen in unanesthetized rats and during methoxyflurane anesthesia, however, seldom seen with pentobarbital and inhibited by hexamethonium or spinal cord transaction (18). Thus, any secondary increase in heart rate or P_{cv} was due to sympathetic reflex activation. We did not observe an increase in P_{cv} or heart rate during the last phase of our inspiratory pause, not even during pause pressures of 35 cm H_2O. Furthermore, all P_a values rapidly reached steady-state conditions within 7 seconds, making our analysis relatively free from the confounding effects of varying autonomic tone. However, our subjects were also receiving neurosuppressive agents (propofol and sufentanil) during the study interval, thus sympathetic responsiveness may have been blunted. Propofol depresses the baroreflex responses to hypotension and inhibits sympathetic nerve activity in healthy volunteers (19, 20), whereas sufentanil might depress baroreceptor reflexes (21). Thus, these studies will need to be repeated in nonanesthetized subjects to validate their usefulness in that population. Still, in the setting of general anesthesia, these findings appear valid.

During inflation venous capacitance is loaded due to an increase in P_{cv}, which leads to a transient reduction in VR, in right ventricular output and consequently in left ventricular output (1, 2). To avoid this effect on the relationship between VR and P_{cv}, we measured P_{cv} and COmf during short periods of steady state after these initial non–steady-state conditions (Fig. 1). Our P_{msf} estimation method by extrapolating the values of four pairs of P_{cv} and COmf obtained from four levels of inspiratory plateau pressures has several advantages. First, it allows the construction of Guyton-type VR curves with an intact circulation, an opportunity not presently available. Second, P_{msf} can be determined without creating stop-flow conditions, such as stopping the heart by electrical fibrillation or injection of acetylcholine or by blocking the circulation. And third, P_{msf} is not

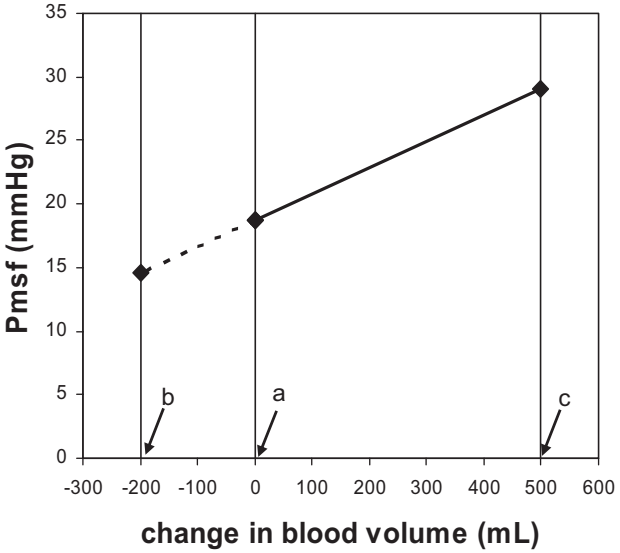

Figure 3. Relationship between change in blood volume and mean systemic filling pressure (P_{msf}) for three conditions: baseline (*a*), hypovolemia (*b*), and hypervolemia (*c*). See text for discussion.

influenced by changes in lung or thorax compliance. Lung or thorax compliance effects the transfer of the applied P_{vent} to intrathoracic pressures. Thus, during an inspiratory hold the resulting P_{cv} depends on these compliances. But, indeed, the measured P_{cv} and CO will always be on the same line in the VR plot. For instance, in a patient with stiffer lungs, during an inspiratory hold the transfer from P_{vent} to intrathoracic pressure will be less, resulting in a smaller increase in P_{cv} and a smaller decrease in CO.

We assumed a linear relation between P_{cv} and COmf to extrapolate to the condition where COmf is zero (Fig. 2). This assumption is based on the observation of linearity of the VR curves presented by Guyton and colleagues (4, 14) and is expressed by the mathematical relation $VR = CO = (P_{msf} - P_{cv})/R_{vr}$. Furthermore, this linearity has been confirmed in the intact circulation in several animal studies (7–10, 22, 23). Our VR curves were best fitted with straight lines allowing extrapolating the VR curve to flow zero. This linearity was neither affected by hypo nor hyper.

Our estimated P_{msf} values are higher than those described in highly instrumented animals, which are 7–12.5 mm Hg in dogs (4, 7, 14, 17, 24, 25), 7–9 mm Hg in rats (15, 16), 10–12 mm Hg in pigs (8–10), and as high as 20–30 mm Hg in conscious calves implanted with an artificial heart (26). We report baseline P_{msf} values of 18.8 mm Hg in our cardiovascular surgical patients. A primary difference between the prior animal studies and our patient observations is the difference in baseline P_{cv}. In the animals studies, this value is close to zero whereas P_{cv} in our patient population is on average 6.7 mm Hg. If one assumes a similar R_{vr}, this P_{cv} pressure difference would extrapolate to a P_{msf} of 12 mm Hg for our subjects if their P_{cv} was zero (see Table 2). Thus, our P_{msf} values are coupled with the increased P_{cv}.

Our present data seem to be in conflict with those of our previous study, wherein we demonstrated that inspiratory-hold maneuvers did not decrease blood flow, as estimated by thermodilution pulmonary artery flow (27) despite an increase in P_{cv}. There were no differences between the two studies in terms of P_a (75 ± 15 vs. 88 ± 18 mm Hg), P_{cv} (9 ± 4 vs. 8 ± 2 mm Hg) and CO (5.7 ± 1.52 vs. 5.6 ± 1.6 $L \cdot min^{-1}$, previous to present mean pooled data, respectively). However, two major differences in the protocols exist. First, the inspiratory-hold maneuver used by van den Berg et al (27) had a temporarily higher inflation pressure at the beginning of the maneuver, which was decreased to the steady-state plateau value, and second, the bolus thermodilution method was applied during the inspiratory pause in the first study whereas we used the modelflow pulse contour CO method to measure instantaneous flow in the present one. Reexamination of the data of van den Berg et al (27) suggests that the thermodilution injections might have been performed before the plateau in blood flow had been reached. If this were the case, then the thermodilution CO values would overestimate steady-state values, resulting in an underestimation of the slope of the VR curve. Furthermore, in their study (27), plateau pressures from 0 up to 19 cm H_2O were used whereas we used plateau pressures from 5 up to 35 cm H_2O, which are comparable with those used by Versprille and Jansen (8) in their animal experiments. The limited range of applied plateau pressures in the van den Berg study (27) might have hampered the construction of proper VR curves. Jellinek et al (28) estimated in ten patients during episodes of apnea and ventricular fibrillation, induced for defibrillator testing, a mean P_{msf} value of 10.2 mm Hg, and Schipke et al (6) estimated a mean P_{msf} value of 12 mm Hg in a similar group of 85 patients. However, both studies were done on highly anesthetized nonvolume resuscitated subjects. Our method of estimation of P_{msf} differs considerably from stopping flow by defibrillation of the heart and our method allows an estimation of P_{msf} with intact circulation, applicable in the intensive care unit. Still, until paired comparisons of P_{msf} are made using the two techniques (i.e., stop flow and our method) in the same subjects, direct comparisons and interpretation of the data cannot be made.

Using These Maneuvers to Assess Cardiovascular Status. Moving patients from supine into a head-up tilt position shifts blood from the central compartment to the legs, creating a relative hypovolemic state as manifested by a decreasing P_{msf}, P_{cv}, and CO. Potentially, other conflicting processes could also be occurring simultaneously. As the blood volume shifted to the legs increase femoral venous pressure, venous vascular diameter will increase decreasing vascular resistance from the legs. The impact of the intra-abdominal volume shift off the diaphragm is less clear but may increase hepatic resistance if chest wall movement compresses the subdiaphragmatic liver. The results of these effects lead to no change in R_{vr} and a decrease in COmf, P_a, P_{cv}, and P_{msf} (Table 2).

Volume loading creates relative hypervolemia that results in an increase of P_{msf}, P_{cv}, CO, and P_a. The higher CO can only be generated by a higher filling of the right atrium reflected in an increase of P_{cv}. Because the pressure gradient for VR is increased more than R_{vr}, CO increases (Table 2).

P_{msf} is the pressure at the midpoint of the vascular pressure drop from the aorta to the right atrium. In practice, it is usually located in the venules and is less than arteriolar pressure and more than P_{cv} but close to capillary–venule tissue pressure (8, 18). The localization of P_{msf} within the circulation is a conceptual model at best, because it reflects a lumped parameter of all the vascular beds. However, its position in the pooled vascular beds will shift depending on changes in arterial and venous resistances as was pointed out by Versprille and Jansen (8). Our data suggest that the vascular site for P_{msf} exists in the range of the capillary–venule pressures, i.e., $R_{vr}/R_{sys} = 15\%$ (Table 2). And, indeed, this site shifted upstream ($R_{vr}/R_{sys} = 23\%$) with hyper, whereas hypo had no effect on the site of P_{msf} ($R_{vr}/R_{sys} = 15\%$). These data suggest that in the immediate postoperative period increased sympathetic tone keeps P_{msf} in the venular side but with volume loading and a presumed reduction of vasomotor tone, this point shifts retrograde toward the arterial system. It will be interesting to see how this location changes with the use of vasoactive drug therapy and in patients with either sepsis or heart failure. We also saw that R_{vr} increased during hypervolemic conditions whereas conductance (conductance = $1/R_{vr}$) was constant. We are not sure why this would be the case, because anatomically and physiologically speaking, the same factors affect both resistance and conductance. Potentially, our technique systematically overestimated P_{msf}, and thus pressure gradient for VR under hypervolemic conditions due to squeezing of blood volume out of the lung, or the associated increase in P_{cv} decreased the flow through the more dependent venous conduits. Our study design does not allow us to speculate further on these R_{vr} changes.

Whole body vascular compliance is calculated as the ratio of the change of

volume to the change in estimated P_{msf} ([Delta]V/[Delta]P). Using our inspiratory-hold technique, we found a vascular compliance, C_{sys}, of 0.98 mL·mm Hg^{-1}·kg^{-1} body weight. The administration of 500 mL colloid can expand plasma volume by more than 500 mL, because fluid recruitment of the extravascular space and fluid loss (urine and blood loss) contribute to the volume expansion. Previous studies in instrumented anesthetized animals have reported a linear relation between P_{msf} and blood volume over a P_{msf} of 5–20 mm Hg (18). Thus, vascular compliance over this P_{msf} range may be considered constant. From this constant total systemic vascular compliance and the change in P_{msf} from baseline to hypo, we calculated an effective volume loss of about 200 mL. This loss is due to a shift of blood from stressed to unstressed blood volume.

The stressed volume can be estimated from the compliance and P_{msf}. In normovolemic patients in supine position, we estimated an averaged stressed volume of 1677 mL or 19.5 mL·kg^{-1}. To our surprise, this calculated stressed volume is close to the stressed volume of 20.2 mL·kg^{-1} reported by Magder and De Varennes (29) in patients undergoing hypothermic circulatory arrest for surgery on major vessels. They measured stressed volume as the volume that drained from the patient into the reservoir of the pump when the pump was turned off.

Previously reported values for C_{sys} ranged from 1.4 to 2.6 mL·mm Hg^{-1}·kg^{-1} in dogs (17, 30–33) and from 1.5 to 2.4 mL·mm Hg^{-1}·kg^{-1} in rats (15, 16, 34). The lower compliance (0.98 mL·mm Hg^{-1}·kg^{-1}) observed in our patients may reflect species differences or differences in methodology used. The main difference in methodology is related to the time between volume loading and the determination of P_{msf}. In animal studies, the P_{msf} measurement is performed 30 seconds after volume loading, whereas we finished our measurements after >20 minutes following volume loading. According to Rothe (18), it is virtually impossible to measure the vascular capacitance characteristics, and, thus, passive V/P curves and stressed volume of the total body in reflex-intact animals and humans. This limitation is because one cannot change blood volume and measure P_{msf} in <7–10 seconds, which is the maximal delay before reflex venoconstriction normally becomes evident, unless these reflexes are blocked. In our patients, the use of propofol and sufentanil might have blocked these reflexes (19–21) and might be the explanation for the corresponding stressed volume results of our study and the study of Magder and De Varennes (29).

CONCLUSIONS

P_{msf} can be determined in intensive care patients with an intact circulation with use of inspiratory pause procedures, making estimations of circulatory compliance and serial measures of circulatory stressed volume feasible.

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