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Fluid loading responsiveness

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Citation

Geerts, B. (2011, May 25). *Fluid loading responsiveness*.
Retrieved from <https://hdl.handle.net/1887/17663>

Version: Corrected Publisher's Version
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Note: To cite this publication please use the final published version (if applicable).

Chapter 8

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

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Critical Care Medicine 2009; 37(3): 912-8

The cardiovascular system is a closed circuit with varying blood flow out of the heart into the arterial system (cardiac output) and flow back to the heart from the venous system (venous return) that may not be equal at any point in time owing to ventilation-induced changes in venous return, but which over time must be equal ^[1,2]. Thus, under steady state apnoeic conditions cardiac output (CO) and venous return (VR) equal. Guyton *et al.* ^[3,4] showed that the relationship between stepwise changes in right atrial pressure (Pra) and the resulting changes in venous return describes a venous return curve, which itself is a function of the circulating blood volume, vasomotor tone and blood flow distribution. Importantly, right atrial pressure at the extrapolated zero flow pressure-intercept reflects mean systemic filling pressure (Pmsf) and the slope of this relation describes the resistance for venous return (Rvr) ^[3,5]. This relationship between right atrial pressure 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 venous return curves could be easily calculated 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 in unstressed volume (the blood volume necessary to fill the blood vessels without generating an intravascular pressure), and stressed volume (the blood volume which generates the intravascular pressure, which is mean systemic filling pressure in no flow conditions).

Previously, Pinsky ^[7] constructed instantaneous venous return curves based on the beat to beat changes in Pra and simultaneously measured right ventricular output during a single mechanical breath, neglecting possible transient effects of increasing Pra on venous return ^[1,2]. Versprille and Jansen ^[8] prevented these transient changes by measuring Pra 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 manoeuvres that increase right atrial pressure create a new steady state then venous return and cardiac output would again be equal and direct measures of left-sided cardiac output could be used to estimate steady state venous return.

Thus, we studied the effect of 12-second inspiratory hold manoeuvres on the relation between central venous pressure (Pcv), as a surrogate for right atrial pressure, and arterial pulse contour-derived cardiac output (COMf), as a surrogate for venous return, as Pcv was varied by inspiratory hold manoeuvres and intravascular volume status altered by a head-up tilt body position (relative hypovolemia) and intravascular volume loading (hypervolaemia).

Methods

Patients

Twelve post-operative patients after elective coronary artery bypass surgery or aortic valve replacement were included into 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 (NYHA class 4), aortic aneurysm, extensive peripheral arterial occlusive disease, or postoperative valvular insufficiency, were not considered for this study. Patients with postoperative arrhythmia or the necessity for artificial pacing or use of a cardiac assist device were also excluded.

Anaesthesia during surgery was maintained with sufentanil and propofol and patients were ventilated in synchronized intermittent mandatory surgery was maintained with propofol and ventilation (SIMV) mode (Evita4 servo ventilator Draeger, Lubeck, Germany) adjusted to achieve normocapnia (arterial PCO_2 between 40 and 45 mmHg) with tidal volumes of 6-8 ml · kg⁻¹ and a respiratory rate of 12-14 breaths · min⁻¹. Fraction of inspired oxygen (FiO_2) was 0.4 and a positive end-expiratory pressure (PEEP) of 5 cmH₂O was applied. A hemodynamic stability was achieved using fluids and catecholamines. During the study interval all subjects were haemodynamically stable and no changes were made in their vasoactive drug therapy. Every patient experienced full recovery from anaesthesia within 8 hours following surgery and was discharged from intensive care unit on the first post-operative day.

(135

Measurements

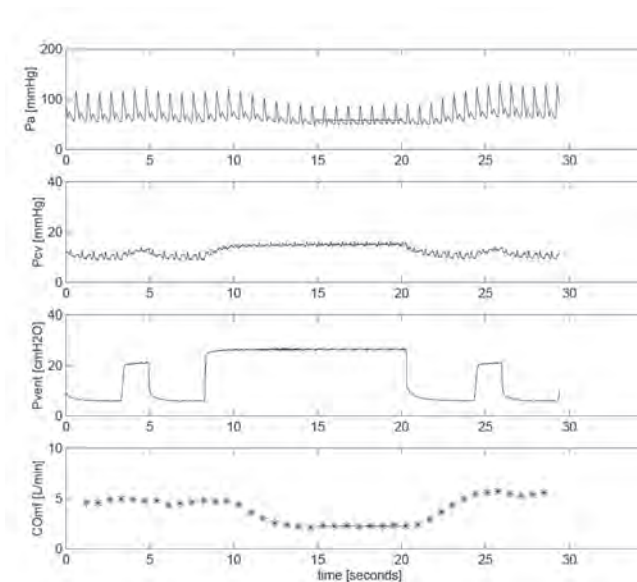
Arterial blood pressure (Pa) was monitored via a 20 Gauge, 3.8 cm long radial arterial catheter inserted by Seldinger technique and connected to a pressure transducer (PX600F, Edwards Lifesciences). Pcv was measured with a central venous catheter inserted through the right internal jugular vein (MultiCath 3 venous catheter, Vigon GmbH & Co, Aachen, Germany) and connected to a pressure transducer (PX600F, Edwards Lifesciences). Both Pa and Pcv transducers were referenced to the intersection of the anterior axillary line and the 5th intercostal space. Airway pressure (Pvent) was measured at the entrance of the endotracheal tube. Pvent was balanced at zero level against ambient air. Standard ECG leads were used to monitor heart rate (HR). Beat to beat cardiac output was obtained by modelflow (COMf) pulse contour analysis as previously described by us^[11-13]. We calibrated the pulse contour cardiac output measurements with 3 thermodilution cardiac output 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 (APRV) with the same rate, FiO_2 , and PEEP 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. Pa, Pcv and Pvent were recorded on computer disk for offline data analysis at a sample frequency of 100 Hz and 0.2 mmHg resolution. We constructed venous return curves by measuring steady state Pa, Pcv and COMf over the final 3 seconds for a set of four 12-second inspiratory hold manoeuvres at Pvent plateau pressures of 5, 15, 25, 35 cmH₂O. The inspiratory hold manoeuvres were separated by 1-minute intervals to re-establish the initial hemodynamic steady state. An example of the hemodynamic changes during an inspiratory hold is presented in Figure 1.

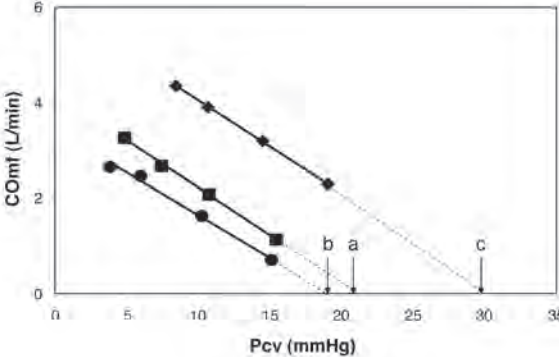
Figure 1 Effects of an inspiratory hold manoeuvre on arterial pressure (Pa), central venous pressure (Pcv), airway pressure (Pvent) and beat to beat cardiac output (COMf). Preceding the hold manoeuvre the effects of a normal ventilatory cycle are plotted.

136)



When Pvent increases, Pcv increases concomitantly, while COMf and Pa decrease with a delay of 3-4 beats, reaching a steady state between 7 and 12 seconds after start of inflation. From the steady state values of Pcv and COMf during the four inspiratory pause periods a venous return curve was constructed by fitting a linear regression line through these data points (Figure 2).

Figure 2 Relationship between venous return (COMf) and central venous pressure (Pcv) for an individual patient. Venous return curves are plotted for three conditions, baseline (a), hypovolemia (b) and hypervolaemia (c).



(137

The four inspiratory hold manoeuvres were performed under three sequential volumetric conditions: initial baseline conditions (Baseline) with the subject lying supine, relative hypovolemia by rotating the bed to a 30° head-up (anti-Trendelenburg) position (Hypo), and after administration of 500 ml HydroxyethylStarch (HES 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 4 data points of Pcv and COMf by linear regression for each volume state to define the venous return curve. We defined Pmsf as the extrapolation of this linear regression to zero flow (Figure 2), assuming that airway pressure does not affects Pmsf. We have previously validated this extrapolation in piglets [8-10].

Total systemic vascular resistance (Rsys) was calculated as the ratio of the pressure difference between mean Pa and mean Pcv and COMf ($R_{sys} = (Pa - Pcv) / COMf$). The resistance downstream of Pmsf was taken to reflect the resistance to venous return (Rvr) and was

calculated as the ratio of the pressure difference between Pcv and Pmsf and COMf ($R_{vr} = (P_{msf} - P_{cv}) / COMf$). Systemic arterial resistance (Ra) was taken to be the difference between systemic and venous resistance. The ratio of Rvr and Rsys describes the location within the circulation where Pmsf exists. A higher ratio implies a more upstream Pmsf location. Systemic compliance (Csys) was calculated by dividing the amount of fluid (Vload) administered to induce the Hyper state by the Pmsf difference between Baseline and Hyper ($C_{sys} = Vload / (P_{msf_{Hyper}} - P_{msf_{Baseline}})$). We assume systemic compliance to be constant for the three volaemic conditions studied. Stressed vascular volume (Vs) was calculated as the product of Csys and Pmsf. We calculated Vs for all three relative volume conditions. Data are presented as mean \pm SD. Linear regressions were fitted using a least-squares method. The changes between the three conditions were tested by a paired 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 4 were excluded from analysis because they could not receive an additional volume challenge. We report in Table 1 the patient characteristics and in Table 2 the pooled data of the 12 subjects who completed all three steps of the protocol.

Table 1 Patient characteristics.

No.	Gender	Age (years)	Weight (kg)	Length (cm)	HR (min ⁻¹)	Pcv (mmHg)	CO (L·min ⁻¹)	MAP (mmHg)	Temp (°C)	Surgery	Inotropics (µg·kg ⁻¹ ·min ⁻¹)	Propofol (mg·h ⁻¹)	Sufentanil (µg·h ⁻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	Nor 0.06	500	15
8	M	57	91	177	63	4.9	6.4	78	35.1	CABG	-	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	Nor 0.02	200	10
11	M	75	95	173	77	9.0	4.4	130	36.5	CABG	-	300	10
12	F	60	74	158	89	3.7	5.3	86	36.6	CABG	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; Pcv, 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

Venous return curve analysis

Pcv and COmf decreased during Hypo and increased during Hyper. Similarly, Pmsf decreased during Hypo and increased during Hyper, whereas the slope of the venous return (conductance) was not significantly different for the three conditions of Baseline, Hypo and Hyper. The pressure gradient for venous return did not change with Hypo but increased with Hyper such that Rvr was unchanged by Hypo but increased with Hyper. Importantly, Rsys, did not change. Thus, the estimated location of Pmsf was unchanged by Hypo but migrated upstream with Hyper.

Table 2 Hemodynamic data of patients during baseline, hypo- and hypervolaemic condition.

	Baseline mean	SD	Hypo mean	SD	p1	Hyper mean	SD	p2
Pa (mmHg)	89.9	21.6	75.7	17.3	0.001	96.5	14.9	0.17
Pcv (mmHg)	6.72	2.26	4.02	2.12	0.001	9.67	2.63	0.007
COmf (L·min ⁻¹)	5.82	1.44	4.76	1.3	0.001	6.83	1.36	0.002
HR (min ⁻¹)	86	14.7	85.7	15.1	0.456	84.3	10.7	0.401
Slope (L·min ⁻¹ ·mmHg ⁻¹)	-0.465	0.151	-0.429	0.16	0.388	-0.389	0.135	0.134
Pmsf (mmHg)	18.76	4.53	14.54	2.99	0.005	29.07	5.23	0.001
Pvr (mmHg)	12.04	3.70	10.52	2.27	0.106	19.40	6.88	0.003
Rvr (mmHg·min·L ⁻¹)	2.18	0.86	2.41	1.14	0.184	2.91	1.10	0.037
Rsys (mmHg·min·L ⁻¹)	15.89	9.00	16.95	10.27	0.379	13.52	5.60	0.122
Rvr/ Rsys (%)	14.94	5.00	14.84	2.37	0.931	22.62	8.07	0.006

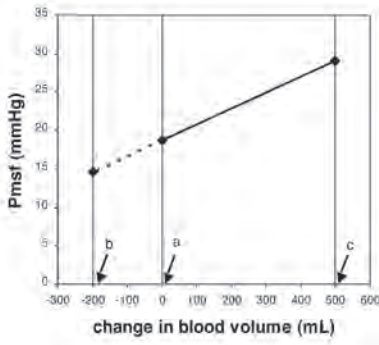
Values are means ± SD; n=12 patients. Pa, arterial pressure; Pcv, central venous pressure; COmf, cardiac output; HR, heart rate; Slope, slope of venous return curve; Pmsf, mean systemic filling pressure; Pvr, pressure difference between Pmsf and Pcv; Rvr, resistance for venous return; Rsys, resistance of the systemic circulation. Statistical comparison, p1, paired t-test between baseline and hypovolaemic condition (hypo) and p2, paired t-test between baseline and hypervolaemic condition (hyper)

(139)

Systemic compliance and stressed volume

The change in stressed volume versus Pmsf is shown in Figure 3. Assuming a constant compliance the loss of stressed volume due to Hypo is approximately 200 ml. On average systemic compliance was $80 \pm 62 \text{ ml} \cdot \text{mmHg}^{-1}$ ($0.98 \pm 0.82 \text{ ml} \cdot \text{mmHg}^{-1} \cdot \text{kg}^{-1}$ body weight) and stressed volume during Baseline was $1677 \pm 1643 \text{ ml}$ ($12.5 \pm 12.1 \text{ ml} \cdot \text{kg}^{-1}$ body weight).

Figure 3 Relationship between change in blood volume and mean systemic filling pressure (Pmsf) for three conditions, baseline (a), hypovolemia (b) and hypervolaemia (c). See text for discussion.



Discussion

140)

Our study demonstrates that by using a simple inspiratory hold manoeuvre while simultaneously measuring Pcv and Pa one can generate venous return curves and derive their associated vascular parameters at the bedside. Our data suggest that volume altering manoeuvres (Hypo and Hyper) do not alter vascular conductance (slope of the venous return curve). These clinical data are concordant with the long-described experimental data introduced by Guyton and colleagues over 50 years ago ^[4,14]. Importantly, our novel approach to assessing venous return 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 (NYHA 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.

Methodological issues

During an inspiratory pause period a new steady state was attained, which can be concluded from the plateau phase in the COMf, Pa and Pcv (Figure 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 Pa-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 to 5 seconds. This was followed by a second rise in Pcv 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 unanaesthetized rats and during methoxyflurane anaesthesia, however, seldom seen with pentobarbital and inhibited by hexamethonium or spinal-cord transaction ^[18]. Thus, any secondary increase in HR or Pcv was due to sympathetic reflex activation. We did not observe an increase in Pcv or HR during the last phase of our inspiratory pause, not even during pause pressures of 35 cmH₂O. Furthermore, all Pa values rapidly reached steady state conditions within 7 seconds, making our analysis relatively free of the confounding effects of varying autonomic tone. However, our subjects were also receiving neuro-suppressive 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 non-anesthetized subjects to validate their usefulness in that population. Still, in the setting of general anaesthesia, these findings appear valid.

During inflation venous capacitance is loaded due to an increase in central venous pressure, which leads to a transient reduction in venous return, in right ventricular output and consequently in left ventricular output ^[1,2]. To avoid this effect on the relationship between venous return and Pcv we measured Pcv and COMf during short periods of steady state following these initial non-steady state conditions (Figure 1). Our Pmsf estimation method by extrapolating the values of four pairs of Pcv and COMf obtained from four levels of inspiratory plateau pressures has several advantages. First, it allows the construction of Guyton-type venous return curves with an intact circulation, an opportunity not presently available. Second, Pmsf 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 thirdly, mean systemic filling pressure is not influenced by changes in lung or thorax compliance. Lung or thorax compliance effects the transfer of the applied airway pressures to intra-thoracic pressures. Thus, during an inspiratory hold the resulting Pcv depends on these compliances. But, indeed, the measured Pcv and CO will always be on the same line in the venous return plot. For instance, in a patient with stiffer lungs, during an inspiratory hold the transfer from airway pressure to intra-thoracic pressure will be less, resulting in a smaller increase in Pcv and a smaller decrease in CO.

(14)

We assumed a linear relation between Pcv and COMf to extrapolate to the condition of COMf is zero (Figure 2). This assumption is based on the observation of linearity of the

venous return curves presented by Guyton and co-workers [4,14] and is expressed by the mathematical relation $VR=CO=(Pmsf - Pcv)/Rvr$. Furthermore, this linearity has been confirmed in the intact circulation in several animal studies [7-10,22,23]. Our venous return curves were best fitted with straight lines allowing extrapolating the venous return curve to flow zero. This linearity was neither affected by Hypo or Hyper.

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

142) Our present data seem to be in conflict with those of our previous study, wherein we demonstrated that inspiratory hold manoeuvres did not decrease blood flow, as estimated by thermodilution pulmonary artery flow [27] despite an increase in Pcv. There were no differences between the two studies in terms of Pa (75 ± 15 versus 88 ± 18 mmHg), Pcv (9 ± 4 versus 8 ± 2 mmHg) and cardiac output (5.7 ± 1.52 versus 5.6 ± 1.6 L·min⁻¹, previous to present mean pooled data, respectively). However, two major differences in the protocols exist. First, the inspiratory hold manoeuvre used by van den Berg *et al.* [27] had a temporarily higher inflation pressure at the beginning of the manoeuvre 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 cardiac output method to measure instantaneous flow in the present one. Re-examination 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 cardiac output values would over-estimate steady state values, resulting in an underestimation of the slope of the venous return curve. Furthermore, in their study [27] plateau pressures from 0 up to 19 cmH₂O were used whereas we used plateau pressures from 5 up to 35 cmH₂O, which are comparable to 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 venous return curves. Jellinek *et al.* [28] estimated in 10 patients during episodes of apnoea and ventricular

fibrillation, induced for defibrillator testing, and found a mean Pmsf value of 10.2 mmHg and Schipke *et al.* [6] estimated a mean Pmsf value of 12 mmHg in a similar group of 85 patients. However, both studies were done on highly anesthetized non-volume resuscitated subjects. Our method of estimation of Pmsf differs considerably from stopping flow by defibrillation of the heart and our method allows an estimation of Pmsf with intact circulation, applicable in the intensive care unit. Still, until paired comparisons of Pmsf are made using the two techniques (i.e. stop flow and our method) in the same subjects direct comparisons and interpretation of the data can not be made.

Using these manoeuvres 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 hypovolaemic state as manifest by a decreasing Pmsf, Pcv and cardiac output. 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 sub-diaphragmatic liver. The results of these effects lead to no change in Rvr and a decrease in COmf, Pa, Pcv and Pmsf (Table 2).

(143

Volume loading creates relative hypervolaemia which results in an increase of Pmsf, Pcv, CO and Pa. The higher CO can only be generated by a higher filling of the right atrium reflected in an increase of Pcv. Because the pressure gradient for venous return is increased more than Rvr, CO increases (Table 2).

Pmsf is the pressure at the mid-point of the vascular pressure drop from the aorta to the right atrium. In practice, it is usually locate in the venules and is less than arteriolar pressure and more than Pcv but close to capillary-venule tissue pressure [8,18]. The localization of Pmsf within the circulation is a conceptual model at best, since 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 suggests that the vascular site for Pmsf exists in the range of the capillary-venule pressures, i.e. Rvr/Rsys= 15% (Table 2). And, indeed, this site shifted upstream (Rvr/Rsys=23%) with Hyper, whereas Hypo had no effect on the site of Pmsf (Rvr/Rsys=15%). These data suggest that in the immediate post-operative period increased sympathetic tone keeps Pmsf 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 Rvr increased during

hypervolaemic 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 Pmsf, and thus pressure gradient for venous return under hypervolaemic conditions due to squeezing of blood volume out of the lung; or the associated increase in Pcv decreased the flow through the more dependent venous conduits. Our study design does not allow us to speculate further on these Rvr changes.

144) Whole body vascular compliance is calculated as the ratio of the change of volume to the change in estimated Pmsf ($\Delta V/\Delta P$). Using our inspiratory hold technique we found a vascular compliance, Csys, of $0.98 \text{ ml} \cdot \text{mmHg}^{-1} \cdot \text{kg}^{-1}$ body weight. Because the administration of 500 ml of colloid can expand plasma volume with more than 500 ml, because of fluid recruitment of the extravascular space and because of fluid loss (urine and blood loss), the amount of 500 ml is an approximation of the actual volume expansion. Previous studies in instrumented anesthetized animals have reported a linear relation between Pmsf and blood volume over a Pmsf of 5 to 20 mmHg [18]. Thus, vascular compliance over this Pmsf range may be considered constant. From this constant total systemic vascular compliance and the change in Pmsf from Baseline to Hypo we calculated an effective volume loss to be 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 Pmsf. In normovolemic patients in supine position we estimated an averaged stressed volume of 1677 ml or $19.5 \text{ ml} \cdot \text{kg}^{-1}$. To our surprise this calculated stressed volume is close to the stressed volume of $20.2 \text{ ml} \cdot \text{kg}^{-1}$ 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 Csys ranged from 1.4 to $2.6 \text{ ml} \cdot \text{mmHg}^{-1} \cdot \text{kg}^{-1}$ in dogs [17,30-33] and from 1.5 to $2.4 \text{ ml} \cdot \text{mmHg}^{-1} \cdot \text{kg}^{-1}$ in rats [15,16,34]. The lower compliance ($0.98 \text{ ml} \cdot \text{mmHg}^{-1} \cdot \text{kg}^{-1}$) 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 Pmsf. In animal studies the Pmsf measurement is performed 30 seconds after volume loading, whereas we finished our measurements after more than 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 Pmsf in less than 7-10 seconds, which is the maximal delay before reflex vasoconstriction 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

Mean systemic filling pressure 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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