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Author: Maas, Jacinta

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Mean systemic filling pressure

from Guyton to the ICU

Jacinta Maas

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Mean systemic filling pressure

from Guyton to the ICU

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Chapter 1

General introduction and outline of this thesis

Jacinta J. Maas and Jos R.C. Jansen

Department of Intensive Care Medicine, Leiden University Medical Center, The Netherlands

General introduction and outline of this thesis

The circulation is a closed circuit, in which blood flows to the heart (venous return), to be pumped by the heart (via the lungs) to the aorta (cardiac output, CO). Starling placed the heart centrally in the circulation as demonstrated by the cardiac function curve (figure 1.1). Consequently, analysis of CO mostly focuses on preload, heart rate, contractility and afterload. However, it is important to realize that CO and *venous return* (VR) are intertwined, because the heart can only pump out that which it receives. In this respect preload can be redefined as VR. In steady-state conditions VR equals CO:

$$VR = CO$$

CO can differ from VR only for short periods of time, for example when contractility is changed with a positive or negative inotropic agent. However, as the heart cannot store blood volume or pump out more than venous return, CO and VR must reach a new equilibrium.

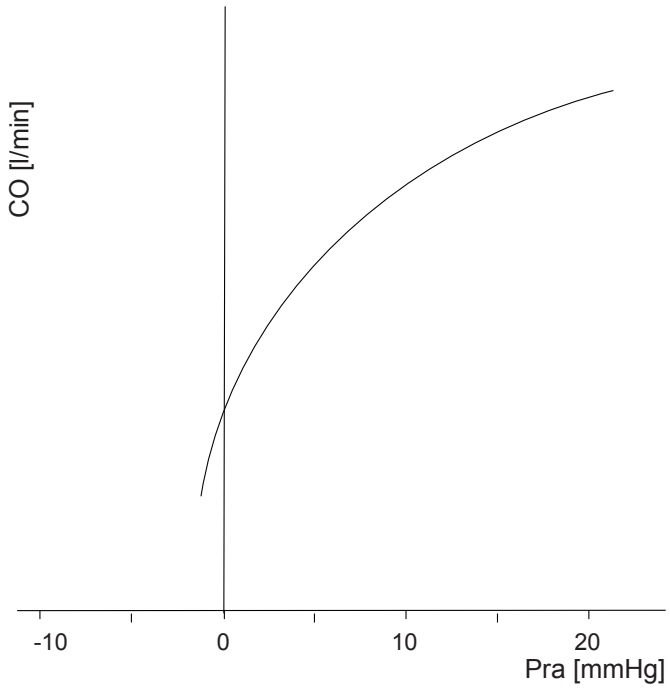

Figure 1.1 Cardiac function curve
Relationship between right atrial pressure (Pra) and cardiac output (CO).

Basic physiology of the circulation

Whether it is the heart or the VR that maintains circulation is still subject to debate.[1,2] In cardiac failure, the heart obviously is the impeding component in the circulation and will determine the upper limit of CO. However, in persons without heart failure the question above still remains. Anderson makes a strong case for the VR as the driving force of the circulation.

During diastole the heart is filled with blood. Transmural intracardiac pressures remain positive even during diastole.[3] Yet, only negative intracardiac pressures could suck blood into the heart. It follows that the heart does not actively suck blood, but instead fills passively. The heart can therefore be described as a passive filling pump, which even offers some resistance to filling, because of the heart's limited volume-pressure compliance. So which force drives blood into the heart? Logically only a peripheral venous pressure in excess of right atrial pressure (Pra) could direct blood into the heart. The pressure gradient of this peripheral venous pressure and Pra determines VR.[4,5] The function of the heart is to lower the pressure at the ventricular inlet (Pra) and to raise the pressure at its outlet into the arterial system.[6] The resulting pressure gradient between the arterial and venous system will in turn maintain flow, completing the circle.

Is it possible to primarily increase CO? Positive inotropic agents, which increase contractility, also affect vascular tone.[7,8] Thus theoretically, the most direct way to increase CO would be to increase heart rate (HR); but will this work in practice? Cowley and Guyton[9] showed that HR did not influence CO at normal levels of VR; only in cases of increased VR with use of an arteriovenous fistula, when the heart became the limiting factor, a higher HR increased CO. Thus, in patients with unimpaired cardiac function the only way to increase CO is to increase VR. Subsequently, the heart has two built-in mechanisms that enable the heart to pump out what it receives. One of these mechanisms is increasing contractility, i.e. the Frank-Starling mechanism, and the other mechanism is increasing HR, i.e. the Bainbridge reflex caused by stretching of the right atrium. Thus, selectively increasing HR or increasing contractility and thereby augmenting stroke volume (SV), will not increase CO, simply because the heart cannot pump out more than it receives from the venous system. When VR is stable, an increase in HR will be compensated for with a decrease in SV. Similarly a decrease in HR rate will result in increased SV.
Late in the 19th century, Bayliss and Starling[10] already acknowledged the role of the venous part of the circulation, as a "forgotten or disregarded chapter in the physiology of circulation". And although Guyton *et al*.[11-13] studied the physiology of venous return extensively, the statement of Bayliss and Starling still holds today, primarily because of the inability to determine venous return in the clinical situation.

Venous system

The venous system contains approximately 75% of total blood volume. Most of this venous blood volume is located in small veins and venules, which act as a reservoir of blood (*capacitance* vessels). The total intravascular blood volume can be divided into *unstressed volume* and *stressed volume*. The blood volume that fills up the blood vessels without building up an intravascular pressure is called unstressed volume (Vu), while the volume that stretches the blood vessels is called stressed volume (Vs). The

pressure that exists in the stressed volume compartment is called *mean systemic filling pressure* (Pmsf), which is the main subject of this thesis.

Bathtub model

Using a bathtub with a drain opening as model for the circulation, Magder[1] describes the total of Vu and Vs as the water in the bathtub (figure 1.2A). The fluid below the drain opening is Vu and the fluid above is Vs. Vs is the effective circulating volume, just like in the bathtub model the water above the drainage point will be drained from the bathtub, while the water below (Vu) will remain in the bathtub. The pressure of the fluid column above the drainage point is Pmsf. By adding a reservoir with lower pressure (Pra), fluid flows from the bathtub to this reservoir (right atrium). A pump (heart) then pumps the fluid into the tap (arterial system), which fills the bathtub again.

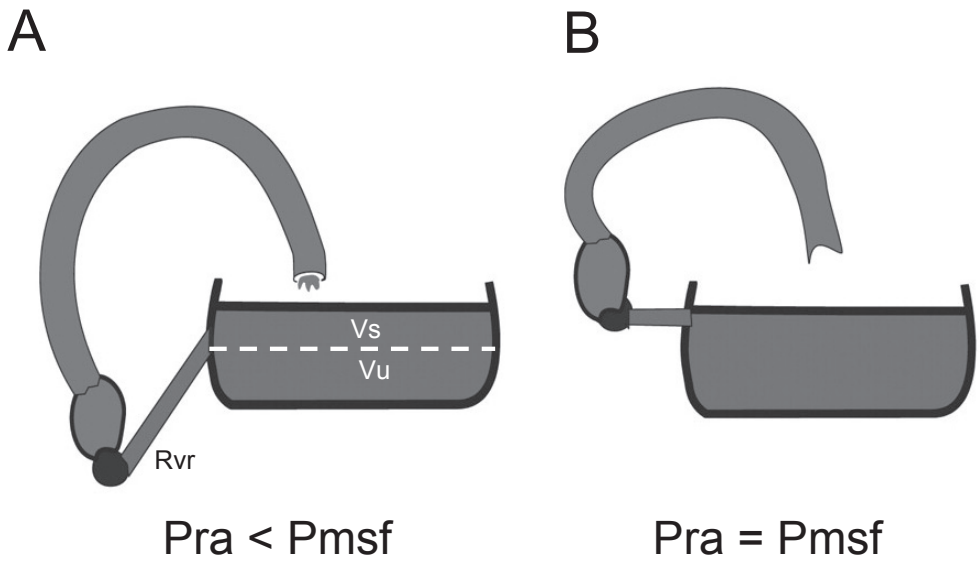

Figure 1.2 Bathtub model of the circulation
The water beneath the drainage pipe, which cannot leave the bathtub, resembles unstressed volume (Vu). The water above the drainage pipe, which can be drained from the bathtub, resembles stressed volume (Vs). The height of the water column above the drainage pipe is the hydrostatic pressure, which is mean systemic filling pressure (Pmsf). Water leaves the bathtub via a drainage pipe to a reservoir (right atrium) and will be pumped again into the bathtub by the heart. The pressure in the reservoir is right atrial pressure (Pra).
Drainage from the bathtub (which is venous return) is determined by the pressure difference between Pmsf and Pra as well as by the characteristics op the drainage pipe (resistance to venous return, Rvr).
Panel A: The pressure in the bathtub (Pmsf) exceeds the pressure in the reservoir (Pra) and water will flow to the reservoir.
Panel B: The reservoir is placed higher, Pra now equals Pmsf, and flow will cease. Note that the function of the pump (heart) is to lower Pra and to return water to the tub. Adopted from Magder.[1]

In this analogy the height of the water in the bathtub (Pmsf), the height of the reservoir (Pra) and the characteristics of the drain are the primary determinants of the rate of emptying of the bath (i.e. VR). The height of the water above the Pra (the presure

difference between Pmsf and Pra) is called the pressure gradient for VR. In this model inflow by the tap (i.e. CO) is important to fill the bathtub, but does not influence the emptying of the bath. Thus the role of the heart is to lower Pra[14], allowing a better drainage from the bathtub, and to restore volume for VR. Only in heart failure the heart becomes a limiting factor, because Pra increases and volume cannot be restored.
Ultimately when Pra is raised to a value equal to Pmsf, flow will stop (figure 1.2B). On the other hand, when flow is ceased by stopping the heart, Pra will increase until it reaches the value of Pmsf. It follows that Pmsf is not directly influenced by cardiac function. Pmsf is influenced by Vs and by *compliance*, which is the change in blood volume due to a given change in blood pressure ($C = \Delta V/\Delta P$). In a less compliant venous system a small change in volume will induce a greater increase in pressure.

In conclusion, the pressure gradient between Pmsf and Pra is the driving force for VR and consequently CO. Pmsf can be seen as a measure of Vs, because Pmsf is the pressure present in Vs. Vs can be enlarged by volume loading, but also by recruitment of fluid from the unstressed to the stressed compartment (through venoconstriction).

Venous return curve

VR is the amount of blood returning to the heart. Flow, and also VR, can only exist when there is a pressure gradient. Pra is the back pressure in the pressure gradient for VR. Guyton *et al*.[4,12] showed in his classical experiments in dogs that when Pra is elevated, CO and VR are reduced. As described above, when Pra is increased further and further, VR declines until it ultimately ceases. This relation between Pra and CO can be depicted in a venous return curve (figure 1.3). The value that Pra reaches at zero flow is equal to Pmsf. Oppositely, with decreasing Pra, VR increases. When Pra becomes close to atmospheric pressure, transmural pressure of the great veins will become negative, resulting in a collapse of the great veins. This collapse will limit VR to a maximum value.
In the bathtub analogy, the characteristics of the drain are also important for the drainage of the bathtub. A narrow drain will slow down drainage, while a wide drain will increase drainage. In the circulation the impeding factor for drainage is the resistance for venous return (Rvr). Venous return can now be defined as the ratio of the pressure gradient for venous return and the resistance to venous return (Rvr):

$$VR = (Pmsf - Pra)/Rvr$$

Rvr is also included in the VR curve, as the reciprocal of the slope of the curve (figures 1.3 and 1.4). When Rvr is increased, the slope of the VR curve becomes less steep, while Pmsf is unchanged and VR decreases. Increasing stressed volume by either by adding fluid or recruitment from the unstressed compartment will increase Pmsf, which will shift the VR curve to the right and increase VR.

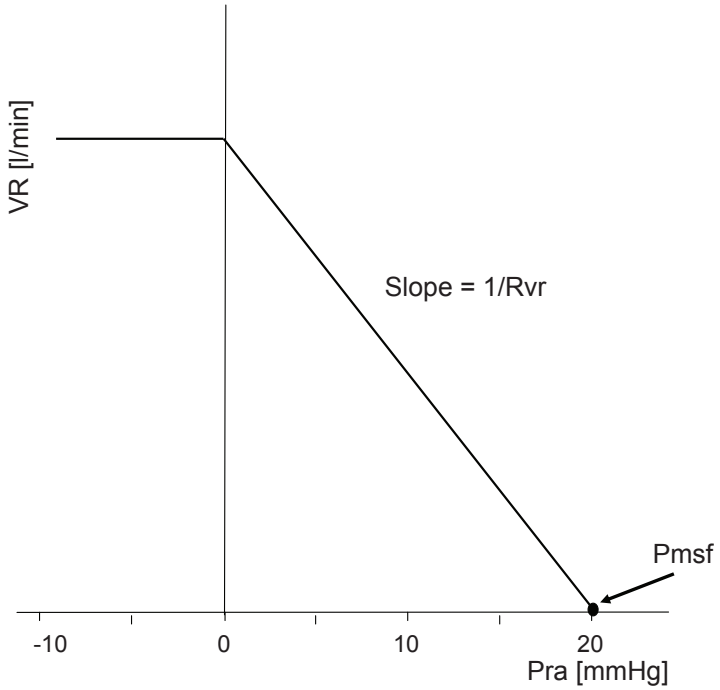

Figure 1.3 Venous return curve
The relationship between right atrial pressure (Pra) and cardiac output (CO), called the venous return (VR) curve, during spontaneous breathing. When VR is zero, Pra is equal to Pmsf. When Pra approaches atmospheric pressure (around 0), VR is maximal. At negative values of Pra, the great veins will collapse, limiting VR. The slope of the curve is determined by the resistance to venous return (Rvr).

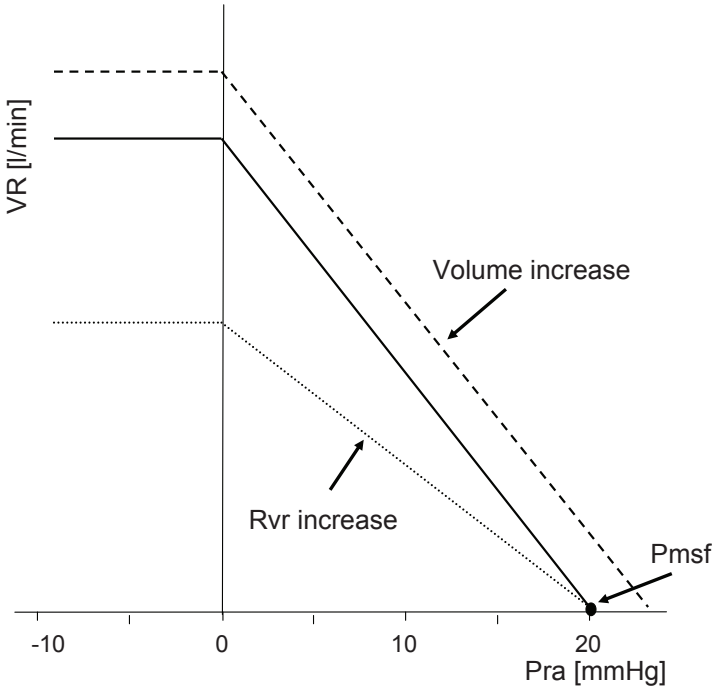

Figure 1.4 Changes in venous return curve
Influences of resistance to venous return (Rvr) and volume increase on the venous return curve. An increase in Rvr will limit venous return (VR), without changing mean systemic filling pressure (Pmsf), flattening the curve. Volume loading will increase Pmsf, without changing Rvr, leading to an increase in VR.

Combining cardiac function curve and venous return curve

One of Guyton's major contributions was that he combined the VR curve and the cardiac function curve. Because during steady state VR and CO must be equal, both curves can be combined[4], with Pra on the x-axis and with VR and CO on the y-axis (figure 1.5). The intersection of these curves resembles the operating point of the circulation. As we described before, the VR curve can be influenced by changing the volemic state (Pmsf) or by changing Rvr. Similarly, the cardiac function curve can be altered by a change in cardiac performance (i.e. myocardial infarction, positive or negative inotropic agents). However, for an increase in CO an increase in VR is essential.

In steady state, the VR curve and the cardiac function curve can be depicted as in figure 1.5. For simplicity we used Pra as parameter for the x-axis for the combining of VR and cardiac function curve. For the latter the actual parameter on the x-axis should be right atrial *transmural* pressure. After all the heart is located in the thoracic cavity, which has a pressure different from atmospheric pressure. It follows that the degree of stress on the cardiac fibers before contraction is related to transmural pressure (Pra minus pleural pressure). For the VR curve the absolute value of Pra can be used, because the pressure surrounding veins and venules is atmospheric pressure and Pra is calibrated against atmospheric pressure. Still, for the combined graph with cardiac function and VR curve, we will use the absolute value of Pra instead of right atrial transmural pressure, although respiration will influence the curves in a different way.

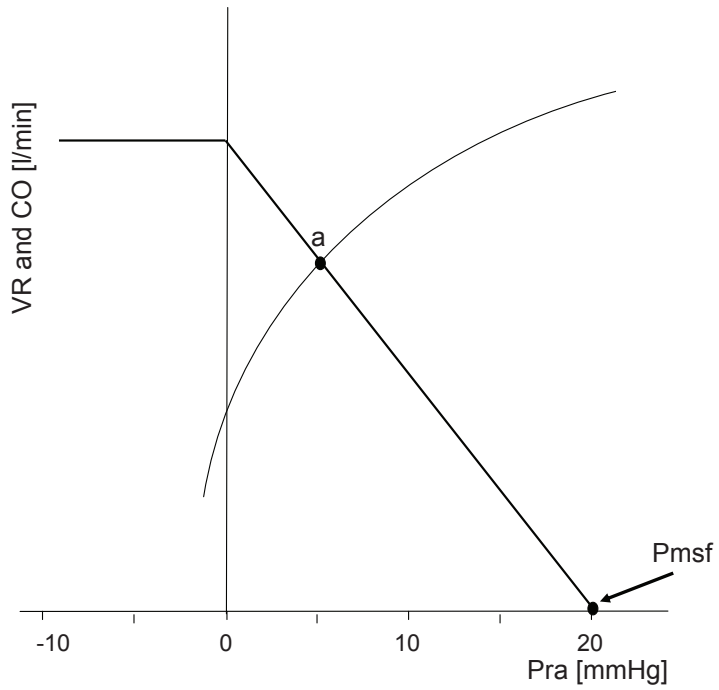

Figure 1.5 Combination of cardiac function curve and venous return curve
The venous return curve and the cardiac output curve are depicted in one graph. The point where venous return (VR) and cardiac output (CO) are equal, is the operating point of the circulation (point a).

Respiratory influences on cardiac function curve and venous return curve

Spontaneous breathing. Pleural pressure continuously changes during the respiratory cycle. In a spontaneously breathing patient inspiration causes a negative pleural pressure and a smaller decrease in Pra, increasing transmural pressure. The increase in transmural pressure leads to a rise in CO. During expiration the opposite occurs: pleural pressure increases, Pra increases to a lesser degree and transmural pressure decreases. The decrease in transmural pressure will decrease CO. Accordingly these respiratory induced changes in Pra cause a shift of the cardiac function curve during the respiratory cycle[15], while the VR curve remains unchanged (figure 1.6).

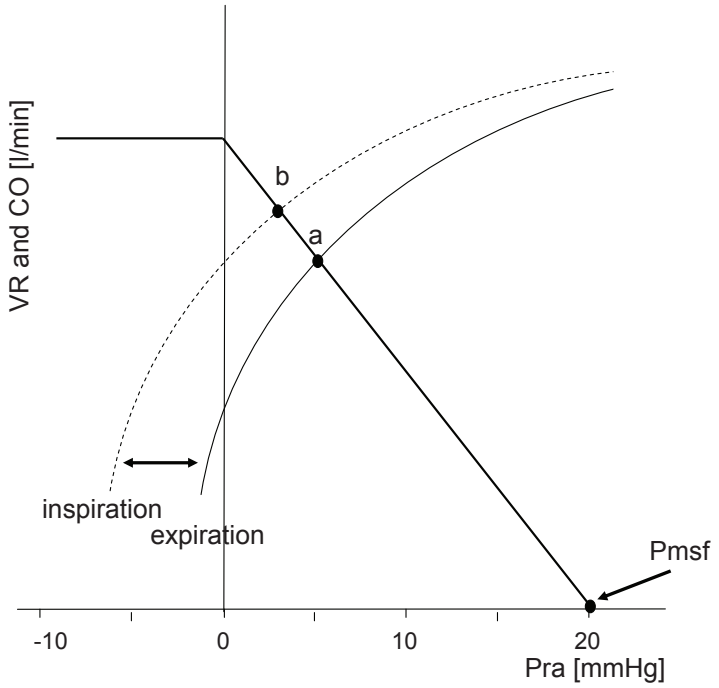

Figure 1.6 Influence of respiration
During spontaneous inspiration intrathoracic pressure and right atrial pressure (Pra) decrease, while venous return (VR) increases. The operating point of the circulation shifts from a to b. Cardiac output (CO) increases, because right atrial transmural pressure increases. To account for this increase in CO, the cardiac function curve shifts to the left as the parameter on the x-axis should actually be right atrial transmural pressure.

Positive end-expiratory pressure. Pleural pressure and Pra will be increased when positive end-expiratory pressure (PEEP) is applied. Transmural pressure decreases because Pra increases less than pleural pressure increases.[16,17] As a result the cardiac function curve will shift to the right as pleural pressure and Pra increase (figure 1.7). In left ventricular dysfunction PEEP can have a different effect and even augment CO. In this case the increase in CO is caused by a reduction in left ventricular afterload, because left ventricular *transmural* pressure is decreased due to the increased intrathoracic pressure.[18]

PEEP also influences the VR curve. Via downward displacement of the diaphragm, increasing intra-abdominal pressure and compression of the liver, and by squeezing of the lungs, stressed volume is increased. This leads to an increase in Pmsf[19], and the VR curve will therefore shift to the right. Will VR change? If both Pra and Pmsf are increased by applying PEEP, the pressure gradient for VR will remain constant.[20] At positive intrathoracic pressures, transmural pressure of the great veins will become negative at higher values of Pra. This will result in a collapse of the great veins at higher Pra values and thus the point reflecting the maximal value of VR (Pcrit) will shift to the right (figure 1.7). In conclusion, PEEP interferes with CO and VR in a more complicated manner than just by increasing Pra.

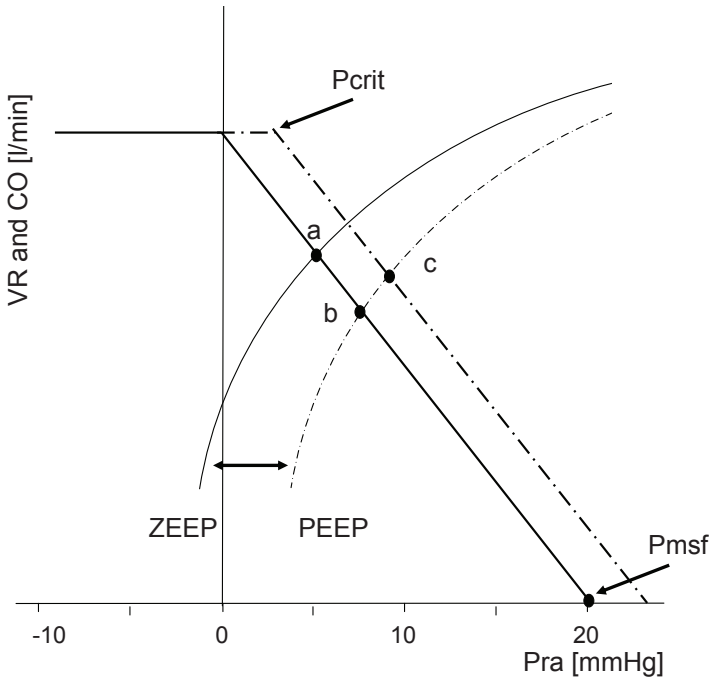

Figure 1.7 Influence of positive end-expiratory pressure
The baseline curve is with zero end-expiratory pressure (ZEEP); point a is the operating point of the circulation. When positive end-expiratory pressure (PEEP) is applied, right atrial pressure (Pra) increases and venous return (VR) decreases; the operating point shifts to b. Transmural right atrial pressure decreases, and cardiac output (CO) decreases with a shift of the cardiac function curve to the right. PEEP has three additional effects: 1. recruitment of volume by squeezing liver and lungs, resulting in a rise in mean systemic filling pressure (Pmsf; shift of VR curve to the right) and 2. collapse of the great veins at higher values of Pra (thus the point reflecting the maximal value of VR (Pcrit) will shift to the right). The combined effect is the shift of the operating point of the circulation to c.

Clinical conditions interpreted with cardiac function curve and venous return curve

Hemorrhagic shock. In a patient with hemorrhage Vs and Pmsf are decreased. The VR curve is shifted to the left, decreasing VR and CO. This can be compensated for by intrinsic catecholamine release via the baroreceptor reflex causing venoconstriction.

Venoconstriction will recruit volume from Vu to Vs, successively restoring Vs, Pmsf and VR. When this compensatory mechanism fails and hypovolemic shock occurs, administration of positive inotropic agents clearly will not increase CO. HR increases as a side effect of intrinsic catecholamine release, but will not increase CO either, because VR is insufficient. It follows that VR and CO will be restored by volume loading, or (less effectively) by venoconstrictive medication facilitating the volume recruitment from the unstressed compartment.

Distributive shock. Distributive shock, e.g. septic shock, is characterized by arterial and venous vasodilation. Vs and Pmsf, but also Rvr will be decreased; the VR curve is shifted to the left and has become steeper. Volume resuscitation will restore Vs, Pmsf and shift the VR curve to the right. The reduced Rvr will maintain a steeper VR curve, and VR and CO can even exceed the premorbid values, provided there is no cardiac limitation, e.g. due to myocardial depression. Venoconstrictive agents will also shift the VR curve to the right by recruitment of volume from Vu to Vs, thereby increasing Pmsf. Additionally by increasing Rvr, the VR curve will become less steep. Thus therapeutic measures, besides antibiotics and sepsis source control, are volume resuscitation, vasoconstrictive medication or in case of myocardial depression, positive inotropic agents.

Cardiac failure. In heart failure, Pcv increases and CO can only be maintained by increasing Pmsf. Thus compensatory mechanisms are fluid retention and venoconstriction to increase Pmsf. The drawback of this compensatory mechanism is the development of edema due to the increased hydrostatic pressures, when these exceed osmotic pressures. Volume infusion or administration of venoconstrictive agents will also increase Pmsf, but have the same hazard of causing edema, without improving VR and CO much. Rvr will be increased as well, impeding an increase in VR. What we need is medication that moves the cardiac function curve upward and decreases the Rvr. Dobutamine and phosphodiesterase inhibitors possess those qualities.

In conclusion, in daily practice the VR curve could be altered by changes in volume status or by redistribution of volume from Vu to Vs (venoconstriction or venodilation), and by changes in Rvr (e.g. by vasoactive medication). The cardiac function curve can be influenced by several interventions such as medication (positive or negative inotropic agents) and level of PEEP. If the VR curve and cardiac function curve of a patient are known, more insight in the pathology and natural compensation mechanisms could be achieved. Moreover the effects of interventions as volume loading or medication could be predicted and evaluated using both curves.

Measurement of mean systemic filling pressure

In order to determine the gradient for VR, we need to know both Pra and Pmsf. Measurement of Pra or central venous pressure (Pcv) is part of clinical routine in the ICU. But how can we determine Pmsf? One possible method could be to reduce VR to zero, then Pcv would become equal to Pmsf. Thus, Pmsf could be measured during cardiac arrest, when CO and VR are equal to zero. Furthermore, Pmsf could theoretically be measured anywhere in the circulation during the circulatory stop-flow, because during a cardiac arrest the pressure equilibrates throughout the entire vascular system.

In 1894 Bayliss and Starling[10] were the first to conclude that intravascular pressures equilibrated during cardiac arrest induced by vagal stimulation in a dog model (figure 1.8). Also in a dog model, Guyton[12] increased Pra by varying the height of a tube in the right atrium, which was connected to a pump, thereby replacing the right ventricle (figure 1.9). When Pra was increased to a level that CO stopped, Pmsf could be measured. Guyton constructed venous return curves with this method. In humans, Starr[21] was the first to measure Pmsf by inserting a needle into the heart or a great vein in patients who had died shortly before. He observed that patients who died after prolonged cardiac congestion had significantly higher values of Pmsf than the patients who died without congestion or cardiac disease (figure 1.10). The higher Pmsf values in heart failure patients can be explained as a compensation mechanism for the increased Pcv in order to maintain a pressure gradient for venous return as described earlier.

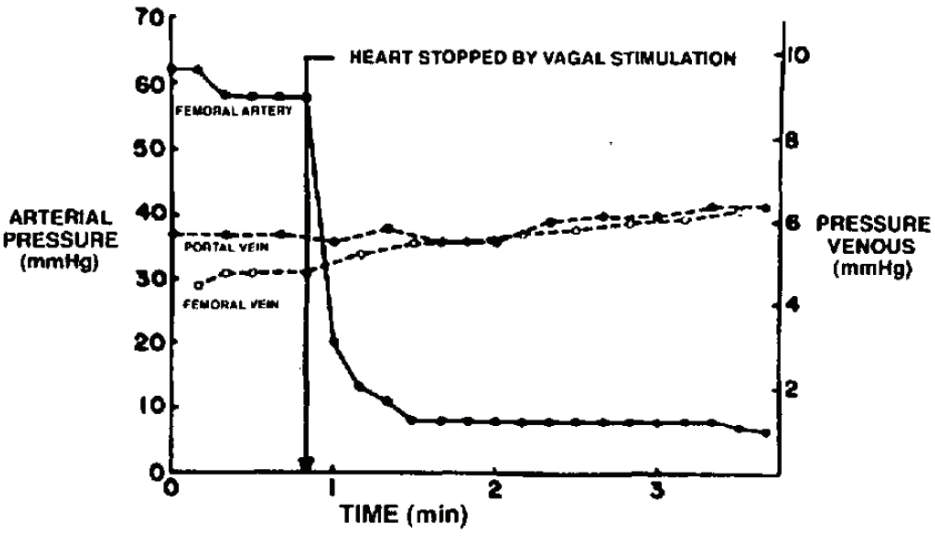

Figure 1.8 Pressure course during cardiac arrest
Bayliss and Starling's[10] experiment to measure mean systemic filling pressure (Pmsf) in a dog. When the circulation is arrested by vagal stimulation, the arterial and venous pressures equilibrate to Pmsf. Figure adopted from Bayliss.[10]

Pmsf in animals using stop-flow

In animal studies Pmsf was measured by inducing a circulatory arrest or a stop-flow using different measurement techniques. Stopping the heart was achieved by either inducing ventricular fibrillation[22-24] or administration of acetylcholine.[22,25,26] During the circulatory arrest Pcv increased and arterial pressure decreased. Because the development of equilibrium takes time, and a venoconstrictive reflex can occur within 5-12 seconds[23,27], a pump was used for rapid arterial-to-venous blood transfer. Pmsf was then estimated by measuring Pcv is equal to Pa after approximately 7-10 seconds. Another method to stop circulation is by applying a circulatory obstruction. With an inflatable balloon around the pulmonary artery[27,28] or by inflating a balloon inside the right atrium[29] circulatory obstruction was achieved in rats. However, with the circulatory obstruction technique venous pressure (Pv) remained lower than arterial pressure (Pa), when no arteriovenous pump was used. Pmsf was then calculated with the formula: $Pmsf = Pv + 1/30 \bullet (Pa-Pv)$.[28] The correction factor 1/30 was based on compliance measurements, where venous compliance was 30-fold higher in comparison to arterial compliance.[30] Yamamoto *et al*.[29] compared the circulatory obstruction technique with and without rapid arteriovenous blood transfer and found a different correction factor of 1/60.

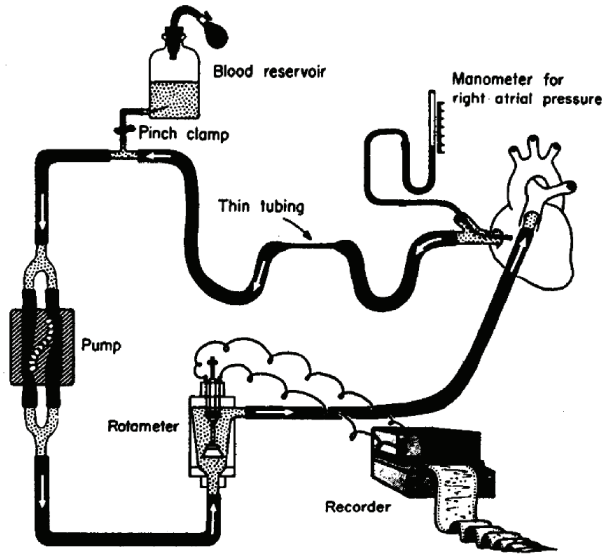

Figure 1.9 Experimental model for controlling right atrial pressure and venous return
The external perfusion system, bypassing the right ventricle, for controlling right atrial pressure and venous return to construct venous return curves. Figure adopted from Guyton.[12]

Pmsf in animals using inspiratory holds

Without the necessity to create a circulatory stop-flow, Pmsf can be measured with a method based on the hemodynamic effects of mechanical ventilation. Pcv can be increased by changing intrathoracic pressures with inspiratory holds created by a mechanical ventilator. Positive airway pressure increases Pcv and thereby compromises

VR and CO. In a study in pigs, Versprille[31] randomly applied tidal volumes between 25 and 300 ml, i.e. 2.5-30 ml·kg^{-1}, during inspiratory holds of 7.2 seconds. During these inspiratory pauses hemodynamic steady-state conditions were met to assure that VR and CO were equal. Pcv and pulmonary artery flow were measured at the end of each inspiratory hold. A venous return curve was then plotted, showing an inverse linear relationship between VR and Pcv. Pmsf was calculated by extrapolation of the curve to a venous return value of zero, where Pcv becomes equal to Pmsf (figure 1.11). Pmsf measurement with use of flow measurement in the aorta, instead of in the pulmonary artery, lead to comparable values.[32] Finally, Pinsky[33] showed that Pmsf and instantaneous venous return curves could be achieved by applying smaller tidal volume ventilation (< 10 ml·kg^{-1}) in canines.

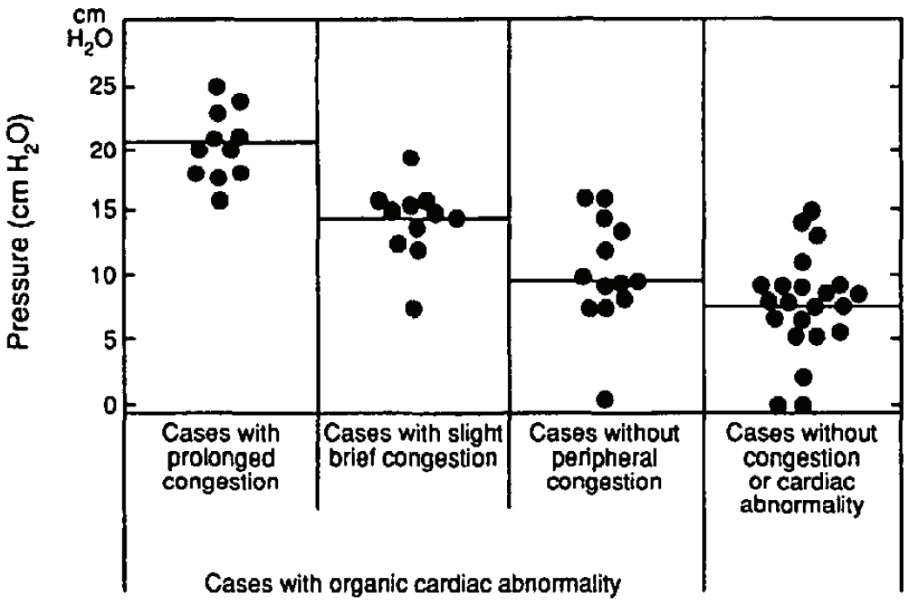

Figure 1.10 Measurement of mean systemic filling pressure (Pmsf)
Starr's measurement of mean systemic filling pressure (Pmsf) in humans soon after death. The crossbars indicate average values. Pmsf in patients with organic heart disease and prolonged congestion is higher than in patients without congestion or cardiac abnormalities. Figure adopted from Starr.[21]

Pmsf in humans during cardiac arrest

In 2000 and 2003 the first measurements of Pmsf in humans during induced cardiac arrest were reported.[20,34] By inducing ventricular fibrillation in patients undergoing surgical implantation of an implantable cardioverter-defibrillator a circulatory arrest was created. In both studies equilibrium of arterial and venous pressure was not met. Jellinek[20] considered Pra to be Pmsf after 7.5 seconds of stop-flow. After 13 seconds the average arteriovenous pressure difference was 13.2 ± 6.2 mmHg and even after 20 seconds of cardiac arrest there was no equilibration of pressures.[34] The lack of equilibrium was attributed to a waterfall mechanism, but could also be explained by short duration of the cardiac arrest. However, longer periods of cardiac arrest are considered

to be unethical[34] and potentially influenced by vasomotor reflexes.[20] Disadvantages of this method of assessing Pmsf are: 1. equilibrium between arterial and venous pressure is not reached, thus the value Pmsf can only be estimated and 2. more importantly the method is not applicable during routine patient care. Thus far, only the method with inspiratory holds lends itself for measuring Pmsf in patients at the bedside.

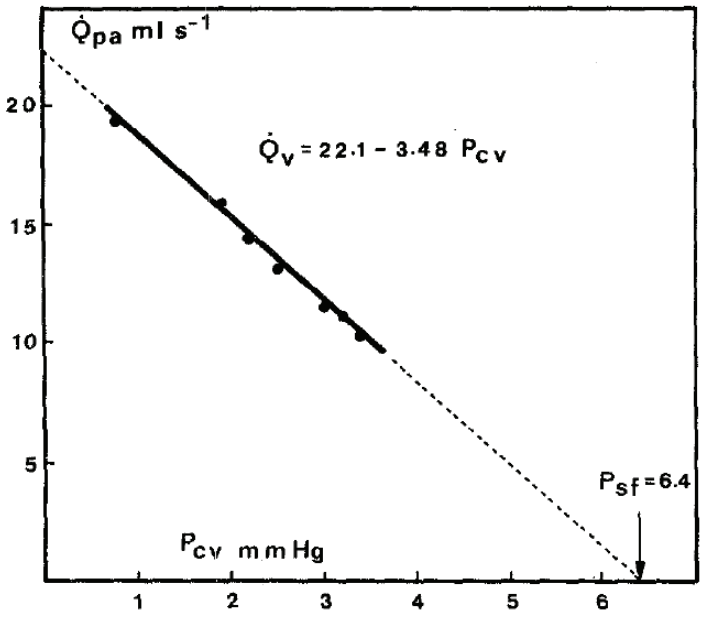

Figure 1.11 Measurement of mean systemic filling pressure with inspiratory holds
Relationship between flow (Qpa, measured in the pulmonary artery, on the y-axis) and central venous pressure (Pcv) during inspiratory hold procedures at 7 different airway pressures. The arrow indicates the value that Pcv reaches at zero flow, which is mean systemic filling pressure (Psf). Figure adopted from Versprille.[31]

In this thesis measurement of Pmsf and Guytonian analysis of venous return curve are taken from the animal laboratory to the intensive care unit.

The measurement of Pmsf with inspiratory holds in pigs and in ICU patients is described in part 1 (Chapter 2, 3 and 4). Chapter 2 contains a historic overview of Pmsf measurement and an overview of other parameters in control of venous return. In Chapter 3 the assessment of venous return curve and Pmsf in postoperative cardiac surgery patients is described. Chapter 4 explores in pigs if pulse contour analysis can be used in measurement of Pmsf and if the number of inspiratory holds can be reduced.

In part 2 the implications of measurement of Pmsf are explored: the possibility of measuring Pmsf in the arm during regional stop-flow and the comparison of Pmsf with a model analog value of mean systemic pressure (Chapter 5), prediction of fluid responsiveness (Chapter 6), bedside assessment of vascular compliance, stressed

volume and cardiac function curves (Chapter 7) and determination of critical closing pressure with inspiratory holds and its implications regarding the existence of a vascular waterfall (Chapter 8).

In part 3 the effects of vasoactive medication on the hemodynamic status are explored: dobutamine effects on venous return curve and vascular resistances (Chapter 9) and norepinephrine effects on cardiac function and venous return curves (Chapter 10).

In part 4 the clinical relevance of determination of Pmsf and venous return curves, and suggestions for further research are discussed (Chapter 11). Finally a summary is given in Chapter 12.

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References

1 Magder S. Point: the classical Guyton view that mean systemic pressure, right atrial pressure, and venous resistance govern venous return is/is not correct. *J Appl Physiol* 2006; 101**:**1523-1525.

2 Brengelmann GL. Counterpoint: the classical Guyton view that mean systemic pressure, right atrial pressure, and venous resistance govern venous return is not correct. *J Appl Physiol* 2006; 101**:**1525-1526.

3 Guyton AC, Jones C, Coleman T: Heart muscle, the heart as a pump. In *Circulatory Physiology*, edn 2. Philadelphia: W.B. Saunders Company; 1973:96-106.

4 Guyton AC, Hall JE: Cardiac output, venous return, and their regulation. In *Textbook of medical physiology*, edn 10. Edited by Schmitt W, Gruliow R. Philadelphia: W.B. Saunders Company; 2000:210-222.

5 Jacobsohn E, Chorn R, O'Connor M. The role of the vasculature in regulating venous return and cardiac output: historical and graphical approach. *Can J Anaesth* 1997; 44**:**849-867.

6 Anderson RM: *The gross physiology of the cardiovascular system*. Tucson, Arizona: Racquet Press; 1993.

7 Ruffolo RR, Jr. The pharmacology of dobutamine. *Am J Med Sci* 1987; 294**:**244-248.

8 Banfor PN, Preusser LC, Campbell TJ, Marsh KC, Polakowski JS, Reinhart GA, Cox BF, Fryer RM. Comparative effects of levosimendan, OR-1896, OR-1855, dobutamine, and milrinone on vascular resistance, indexes of cardiac function, and O2 consumption in dogs. *Am J Physiol Heart Circ Physiol* 2008; 294**:**H238-H248.

9 Cowley AW, Jr., Guyton AC. Heart rate as a determinant of cardiac output in dogs with arteriovenous fistula. *Am J Cardiol* 1971; 28**:**321-325.

10 Bayliss WM, Starling EH. Observations on Venous Pressures and their Relationship to Capillary Pressures. *J Physiol 1894 Apr 17* 16**:**159-318.

11 Guyton AC. Determination of cardiac output by equating venous return curves with cardiac response curves. *Physiol Rev* 1955; 35**:**123-129.

12 Guyton AC, Lindsey AW, Abernathy B, Richardson T. Venous return at various right atrial pressures and the normal venous return curve. *Am J Physiol* 1957; 189**:**609-615.

13 Guyton AC, Lindsey AW, Abernathy B, Langston JB. Mechanism of the increased venous return and cardiac output caused by epinephrine. *Am J Physiol* 1958; 192**:**126-130.

14 Levy MN. The cardiac and vascular factors that determine systemic blood flow. *Circ Res* 1979; 44**:**739-747.

15 Magder S. Central venous pressure monitoring. *Curr Opin Crit Care* 2006; 12(3)**:**219-227.

16 Scharf SM, Caldini P, Ingram RH, Jr. Cardiovascular effects of increasing airway pressure in the dog. *Am J Physiol* 1977; 232**:**H35-H43.

17 Magder S, Lagonidis D, Erice F. The use of respiratory variations in right atrial pressure to predict the cardiac output response to PEEP. *J Crit Care* 2001; 16**:**108-114.

18 Grace MP, Greenbaum DM. Cardiac performance in response to PEEP in patients with cardiac dysfunction. *Crit Care Med* 1982; 10**:**358-360.

19 van den Berg PC, Jansen JR, Pinsky MR. Effect of positive pressure on venous return in volume-loaded cardiac surgical patients. *J Appl Physiol* 2002; 92**:**1223-1231.

20 Jellinek H, Krenn H, Oczenski W, Veit F, Schwarz S, Fitzgerald RD. Influence of positive airway pressure on the pressure gradient for venous return in humans. *J Appl Physiol* 2000; 88**:**926-932.

21 Starr I. Role of the static blood pressure in abnormal increments of venous presure, especially in heart failure.II. Clinical and experimental studies. *Am J Med Sci* 1940; 199**:**40-55.

22 Gaddis ML, Rothe CF, Tunin RS, Moran M, MacAnespie CL. Mean circulatory filling pressure: potential problems with measurement. *Am J Physiol* 1986; 251**:**H857-H862.

23 Drees JA, Rothe CF. Reflex venoconstriction and capacity vessel pressure-volume relationships in dogs. *Circ Res* 1974; 34**:**360-373.

24 Fessler HE, Brower RG, Wise RA, Permutt S. Effects of positive end-expiratory pressure on the gradient for venous return. *Am Rev Respir Dis* 1991; 143**:**19-24.

25 Nekooeian AA, Ogilvie RI, Zborowska-Sluis D. Acute hemodynamic effects of drugs acting on the renin-angiotensin system in acute heart failure. *Can J Cardiol* 1995; 11**:**59-64.

26 Lee RW, Lancaster LD, Gay RG, Paquin M, Goldman S. Use of acetylcholine to measure total vascular pressure-volume relationship in dogs. *Am J Physiol* 1988; 254**:**H115-H119.

27 Samar RE, Coleman TG. Mean circulatory pressure and vascular compliances in the spontaneously hypertensive rat. *Am J Physiol* 1979; 237**:**H584-H589.

28 Samar RE, Coleman TG. Measurement of mean circulatory filling pressure and vascular capacitance in the rat. *Am J Physiol* 1978; 234**:**H94-100.

29 Yamamoto J, Trippodo NC, Ishise S, Frohlich ED. Total vascular pressure-volume relationship in the conscious rat. *Am J Physiol* 1980; 238**:**H823-H828.

30 Shoukas AA, Sagawa K. Control of total systemic vascular capacity by the carotid sinus baroreceptor reflex. *Circ Res* 1973; 33**:**22-33.

31 Versprille A, Jansen JR. Mean systemic filling pressure as a characteristic pressure for venous return. *Pflugers Arch* 1985; 405**:**226-233.

32 Den Hartog EA, Versprille A, Jansen JR. Systemic filling pressure in intact circulation determined on basis of aortic vs. central venous pressure relationships. *Am J Physiol* 1994; 267**:**H2255-H2258.

33 Pinsky MR. Instantaneous venous return curves in an intact canine preparation. *J Appl Physiol* 1984; 56**:**765-771.

34 Schipke JD, Heusch G, Sanii AP, Gams E, Winter J. Static filling pressure in patients during induced ventricular fibrillation. *Am J Physiol Heart Circ Physiol* 2003; 285**:**H2510-H2515.

Chapter 2

Bedside assessment of mean systemic filling pressure

Jos R.C. Jansen[1], Jacinta J. Maas[1] and Michael R. Pinsky[2]

[1]Department of Intensive Care Medicine, Leiden University Medical Center, The Netherlands,
[2]Department of Critical Care Medicine, University of Pittsburgh, PA, USA

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Abstract

The physiology of the venous part of the human circulation seems to be a forgotten component of the circulation in critical care medicine. One of the main reasons, probably, is that measures of right atrial pressure (Pra) do not seem to be directly linked to blood flow. This perception is primarily due to an inability to measure the pressure gradient for venous return. The upstream pressure for venous return is mean systemic filling pressure (Pmsf) and it does not lend itself easily to be measured. Recent clinical studies now demonstrate the basic principles underpinning the measure of Pmsf at the bedside. Using routinely available minimally invasive monitoring of continuous cardiac output and Pra one can accurately construct venous return curves by performing a series of end-inspiratory hold maneuvers, in ventilator-dependent patients. From these venous return curves, the clinician can now finally obtain at the bedside not only Pmsf, but also the derived parameters: resistance to venous return, systemic compliance and stressed volume. In conclusion, measurement of Pmsf is essential to describe the control of vascular capacitance. It is the key to distinguish between passive and active mechanisms of blood volume redistribution and partitioning total blood volume in stressed and unstressed volume.

Introduction

Starling and Bayliss[1] late in the 19th century described the control and function of the venous circulation. This work and the subsequent rediscovery of the venous circulation by Guyton *et al.* represent the forgotten side of the physiology of the circulation. The lack of appreciation of the venous side of the circulation persists today. To a large extent this void in our training of critical care physicians and lack of use of these principles at the bedside reflect the inability of the practicing physician to appropriately assess the venous side of the circulation. Clearly, measures of central venous pressure (Pcv) as estimates of right atrial pressure (Pra) bear little relation to cardiac preload. Furthermore, most physicians adhere to the philosophy that the energy necessary to cause cardiac output is due to the mechanical force of ventricular contraction. Accordingly, most analysis of the determinants of cardiac output centralizes in the influence of preload, contractility, afterload, and heart rate on the heart. However, it is axiomatic that the heart can only pump into the arteries that which it receives. The heart has minimal reservoir capacity and even in heart failure states venous return matches the cardiac output very closely over a few heart beats. It follows, therefore, that the only way cardiac output can increase is if venous return increases. Thus, apart for relative short periods of changing blood flow, the heart can only put out as much blood as it receives from the venous system. The venous system contains as much as 75% of the total blood volume with approximately 3 fourths of it in the small veins and venules. It is the pressure difference between these venous capacitance vessels and the right atrium that defines the pressure gradient for venous return. However, this venous driving pressure reflects only stressed volume and not the total venous blood volume. Importantly, changes in venous vasomotor tone and blood flow distribution can markedly alter this upstream venous pressure without any change in total blood volume. For more details, the reader is invited to read several excellent review articles.[2-5]

Short history and basic concepts

When Starling and Bayliss[1] performed a sympathectomy and induced a cardiac arrest by vagal stimulation in a dog model with cannulae in the femoral vein, femoral artery, portal vein, inferior caval vein and aorta, they observed that all vascular pressures rapidly equilibrated. They called this common stop-flow pressure "mean systemic pressure" (Pms).

Half a century later, Starr[6] postulated that Pms was the driving pressure for venous return. He was the first to measure Pms in humans by inserting a needle into a great vein or into the heart in patients who had died, within 30 minutes after occurrence of death. Mean systemic pressure was higher in patients dying from prolonged heart failure (average 20 cmH_2O) than in patients dying from other causes (average 10.6 cmH_2O). He concluded that the increase of Pms in heart failure patients was due to

compensatory mechanisms such as fluid retention and vasoconstriction.

Guyton *et al.*[7,8] 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), that is venous return = (Pmsf – Pra)/Rvr.[7,8] We use the term Pmsf to connote the pressure in the systemic vascular compartment. In practice the mean pressure of the entire circulation is slightly higher than Pmsf because of the addition of pulmonary venous blood to the systemic circulation due to the higher left atrial than right atrial pressure normally seen. The relationship between Pra and venous return was described in animal models with an artificial circulation[8,9] and in animals with an intact circulation using invasive hemodynamic monitoring.[10-13] However, until recently, it had never been properly evaluated in humans with an intact circulation.

Bedside determination of Pmsf

Venous return as a controller of cardiac output is a very useful concept in explaining the pathophysiology of shock[3,11], congestive heart failure[14], circulatory effect of mechanical ventilation[15] and the physiological effects of vasoactive drugs.[16-19] However, it has not been used in common medical practice. One of the main reasons, probably, is that its main variable Pmsf does not lend itself to be easily measured in patients. Indeed, until recently Pmsf could only be estimated during stop-flow conditions[20,21], conditions that occur rarely in clinical critical care settings.

We[22] recently reported on a novel method to determine Pmsf, Rvr, stressed volume (Vs) and systemic circulatory compliance (Cs) using clinical available minimally invasive monitoring at the patient's bedside. To our knowledge, no other clinical studies have been undertaken to measure Pmsf in patients at the bedside. We reasoned that since Pra is the back pressure to venous return, then just like Guyton *et al.*[7,8] demonstrated in intact dogs 50 years ago that if Pra was transiently elevated, then cardiac output would rapidly decrease to a new equilibrium point along a line describing the patient's venous return curve. Basically, we could construct venous return curves by measuring steady-state mean Pcv – as surrogate for Pra - and pulse contour cardiac output (COmf) during 12-second inspiratory hold maneuvers at different ventilatory plateau pressures (Pvent). For practical purposes, we chose Pvent of 5, 15, 25, 35 cm H_2O, because they were easily attained with acceptable change in lung volume and within safe limits of airway pressure rises during ventilation. An example of the hemodynamic changes during such an inspiratory hold is presented in figure 2.1. When Pvent increases, Pcv increases concomitantly, whereas COmf and arterial pressure (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 obtained during a series of four inspiratory pause periods a venous return curve can be constructed by fitting a linear regression line through these data points (figure 2.2). Extrapolation to the point of zero flow gives a direct estimate of Pmsf. To validate that this derived Pmsf behaved in a fashion predicted by classic Guytonian physiology, we studied the effect of volume loading on both Pmsf and the slope of the venous return curve. We would have predicted that if volume loading increased stressed volume, Pmsf would increase as a function of the venous vascular compliance and that cardiac output would increase only if the pressure gradient for venous return (Pcv – Pmsf) increased without an increase in the resistance to venous return. Indeed, in response to fluid loading we observed an increase in Pmsf and no change in the slope of the venous return curve, similar to the results shown by Guyton *et al.*[8] From the change in Pmsf (point a to point b) in response to the 500 ml fluid loading, we calculated circulatory compliance and stressed volume (figure 2.3). Stressed volume is the volume that extends the blood vessels (see below). Thus measuring Pmsf and its change with volume loading or removal allows more insight in parameters and mechanisms that control the peripheral circulation in critically ill patients.

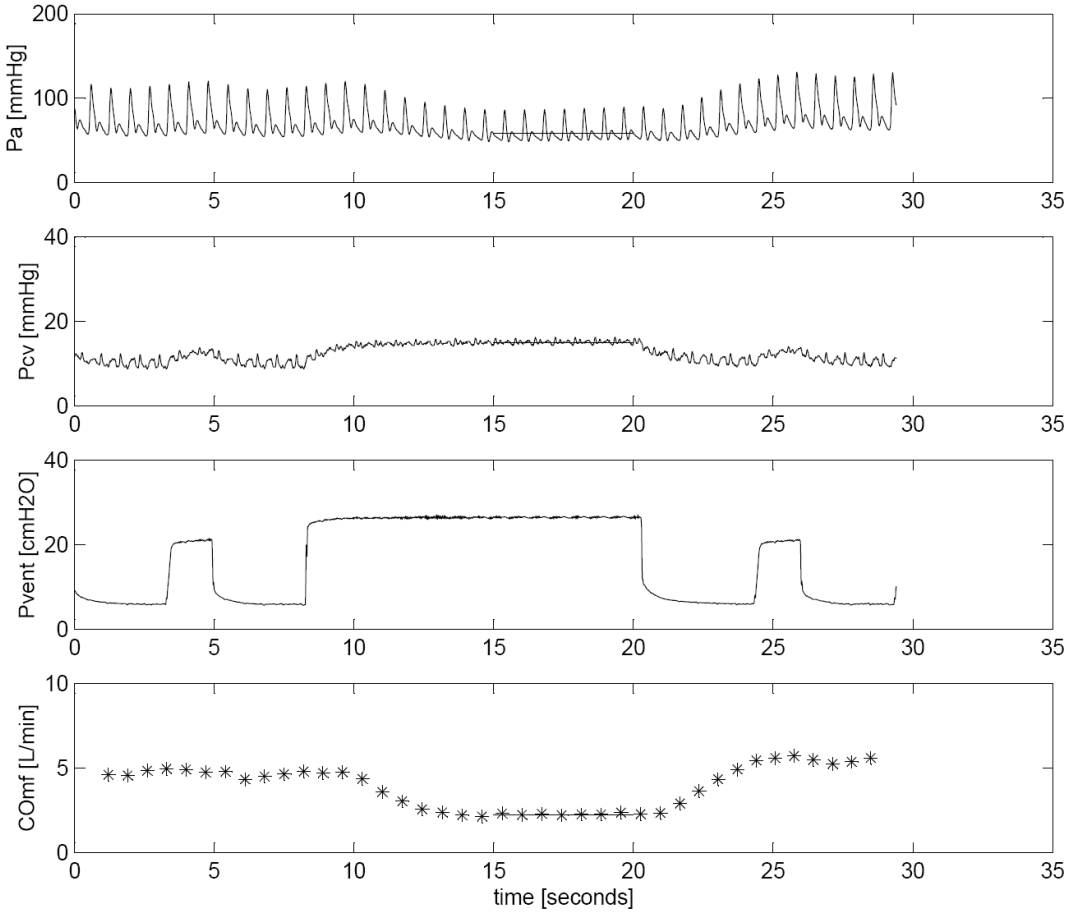

Figure 2.1 Example of an inspiratory hold maneuver
Effects of an inspiratory hold maneuver on arterial pressure (Pa), central venous pressure (Pcv), airway pressure (Pvent) and beat-to-beat cardiac output (COmf). Preceding the hold maneuver the effects of a normal ventilatory cycle are plotted. From [22] with permission.

Parameters for venous return

Parameters that determine venous return and thus cardiac output are: mean systemic filling pressure, right atrial pressure, resistance to venous return, systemic compliance, stressed and unstressed volume. These parameters are indicated in the figures 2.2 and 2.3. Different aspects of their control will be reviewed below.

Mean systemic filling pressure

Pmsf is a measure of effective volume status, otherwise known as the effective circulating blood volume, and (theoretically) independent on cardiac function. Importantly, volume status and fluid responsiveness (i.e. a significant increase in cardiac output on fluid loading) are not synonymous. Even hypovolemic patients can be non-responders to fluid loading. Fluid responsiveness depends on the intersection of the venous return curve and the cardiac function curve. Fluid expansion will lead to a greater improvement in cardiac output in a patient with a normal cardiac function than in a patient with impaired cardiac function.[3,23]

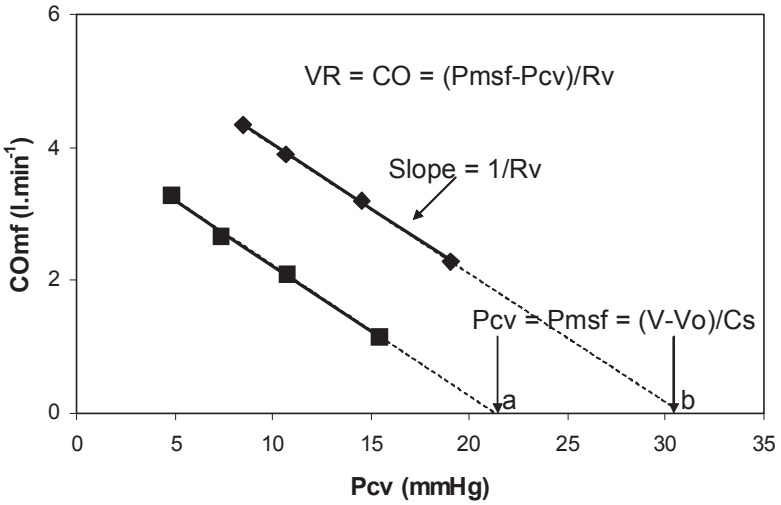

Figure 2.2 Venous return curves

Relationship between venous return (COmf) and central venous pressure (Pcv) for an individual patient. Venous return curves are plotted for normovolemia (a) and after volume loading with 500 ml, that is hypervolemia (b). Venous return is the blood flow that returns to the heart, Pmsf is mean systemic filling pressure, Pcv is central venous pressure and Rv the resistance for blood flow from Pmsf to Pcv measured near the entrance of the right atrium. The inverse of the slope of the lines is Rv. V is the total blood volume and V0 is unstressed volume, the difference is stressed volume (Vs). Cs is systemic compliance (see also figure.2.3). The points a and b indicate Pmsf for normovolemia and hypervolemia respectively.

Our[22] reported Pmsf values in postoperative cardiac surgery patients were higher than those postulated to be present under normal resting conditions. This might be explained by the fact that we were studying a selected group of patients following cardiac surgery and in whom aggressive volume resuscitation and vasoactive drug therapy are routinely used. Indeed, all of our patients in this study were receiving vasoactive drug therapy.

Furthermore, in a previous hemodynamic study on similar postoperative patients by our group, we have documented that these patients are hypervolemic.[24] Presumably, Pmsf would be lower in subjects not experiencing these marked circulatory stressors. However, in our intensive care unit, we were limited to study Pmsf in patients following cardiac surgery in whom inspiratory hold maneuvers could be readily performed.

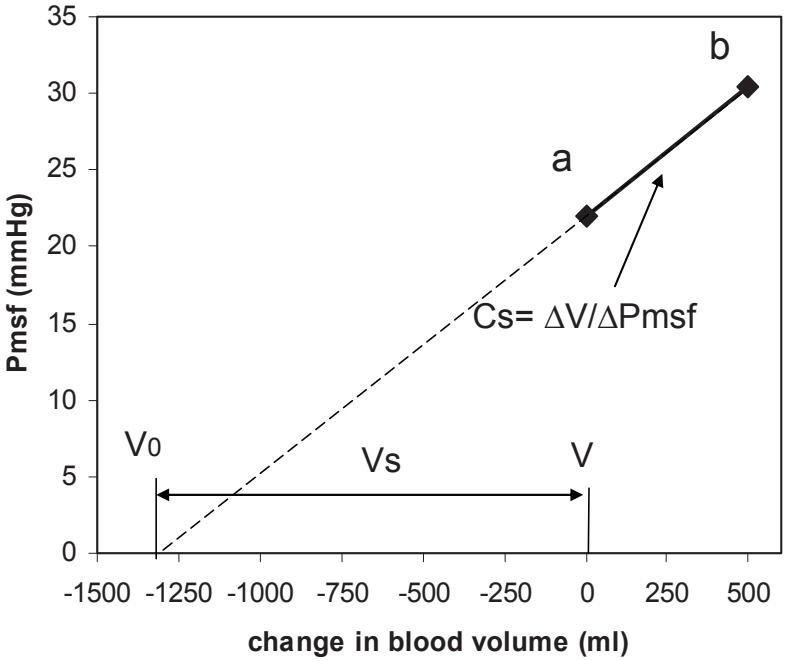

Figure 2.3 Determination of systemic compliance and stressed volume
Relationship between change in blood volume and mean systemic filling pressure (Pmsf) for normovolemia (a) and after volume loading with 500 ml, that is hypervolemia (b). In the figure systemic compliance (Cs), stressed (Vs) and unstressed volume (V0) are indicated. The value of Cs can be found by dividing the administered volume of 500 ml by the change in Pmsf (from a to b) of figure 2.2. Removal of 1270 ml blood in this patient will lead to a Pmsf of 0 mmHg, what rests in the circulation is unstressed volume with no blood flow.

Venous resistance

The slope of the venous return curve is proportional to the reciprocal of the resistance to venous return. Thus, changes in the resistance of venous return (Rvr) must alter the slope of the venous return curve. An increase in slope means a decrease in Rvr such that for the same Pra and Pmsf cardiac output will be greater and a decrease in slope means an increased Rvr. Venous resistance can be altered in many ways. An increase of Rvr can occur due to constriction of the conducting veins, however, unlike the arterial side which has thick muscular vessel walls venoconstriction causes only a minimal increase in Rvr. Rvr can also be increased by increased blood viscosity. However, the major mechanism by which Rvr is altered is by redistribution of blood between different vascular beds.

Venoconstriction of an organ decreases its unstressed blood volume, causing its local upstream pressure to transiently rise, expelling blood into the systemic circulation because some of the unstressed volume is shifted to stressed volume (see below). Most of the venoconstriction with change in unstressed volume occurs in the splanchnic circulation, which has a more prominent innervation.[2,3] However, as splanchnic blood flow must subsequently pass across a second parenchymal bed, the liver, splanchnic Rvr is much higher than for other organs including the brain, kidney, muscle and skin any change in splanchnic Rvr has minimal effect on total Rvr.[3,25] Accordingly, venoconstriction of the splanchnic circulation has a minimal incremental effect on Rvr but a significant ability to increase Pmsf. The balance between venoconstriction of venous vessels outside and inside the splanchnic area is controlled by α- and β2-adrenenergic activation of the different parts of the systemic circulation and is the primary means of controlling cardiac output and matching metabolic needs to blood flow distribution. Those interested in reading more about this important aspect of the control of the circulation are referred to the papers by Gelman[2], Rothe[5] and Pang.[17]

Compliance, stressed and unstressed volume

As described above, the intravascular volume can be divided in unstressed volume and stressed volume. The intravascular volume that fills these vessels up to the point where intravascular pressure starts to rise is called unstressed volume, whereas the volume that stretches the blood vessels and causes intravascular pressure to rise is called the stressed volume. By definition, the stressed volume results in a positive transmural vascular pressure, which is defined as the pressure inside the vessel relative to the pressure outside the vessel wall. Since the pressure gradient for venous return is from the extrathoracic venous vessels to the right atrium, the back pressure to venous return is Pra and not its transmural pressure. This is a very important concept and explains the dynamic changes in venous return that occur during breathing and whenever intrathoracic pressure is artificially varied. In the setting of circulatory shock due to inadequate venous return, as may occur with hypovolemia, sepsis and heart failure, the two main therapeutic interventions that can increase stressed blood volume and thus Pmsf so as to restore venous return to an adequate level of blood flow are the administration of intravenous fluids and pharmacological manipulation with vasopressor agents to increase vascular tone.

If one observes any blood flow in a patient then there must be a measurable Pmsf and then the unstressed volume has been filled up. Subsequent fluid administration must increase the stressed volume. If one can measure Pmsf sequentially, then one can note the change in Pmsf for a change in volume, thus allowing the physician at the bedside to directly estimate vascular compliance and stressed volume (figure 2.3). Until recently, stressed volume has only been measured in humans on cardiac bypass for major vascular surgery.[26] Patients were put on a cardiac bypass pump and when the

patients were in hypothermic cardiac arrest, the pump was turned off and blood was drained passively in a reservoir. The amount of blood drained was the stressed volume. In these hypothermic anesthetized patients Magder and De Varennes[26] found stressed volume was on average 20.2 ml/kg, which value is close to our calculated result of 19.5 ml/kg in intact patients.[22]

Administration of vasopressors and inotropes can be used to enlarge or reduce stressed volume. Vasopressors increase stressed volume by recruiting volume from the unstressed compartment. For instance, infusion of norepinephrine (an α- and β1-adrenergic agonist) into anesthesized dogs increased arterial pressure, cardiac output, total peripheral resistance, hepatic vein resistance and Pmsf and reduced heart rate and liver volume.[27] Note that the increase in venous resistance and total peripheral resistance on itself would diminish cardiac output. Evidently the increase in cardiac output by the increase in Pmsf dominated the negative impact on cardiac output by the increase of arterial and venous resistance. These results were later confirmed in rabbits by the same authors.[19] Although it is clear that norepinephrine is capable of increasing Pmsf, there are differences in Pmsf response among different species of animals.[17] The effects of catecholamines on increasing venous return and cardiac output may be significant. However, knowledge of the volume status is of great importance before administrating these drugs into a critically ill patient whose endogenous adrenergic stimulation is already maximal. Norepinephrine may reduce splanchnic blood pooling, increase Pmsf, Rvr and Rsys of the splanchnic circulation, but the resulting decrease in flow of the splanchnic circulation may increase ischemia in the gut and liver.[4,28] However, inotropic agents, like dobutamine, can cause vasodilation, owing to their peripheral β-adrenergic effect. Thus, the use of dobutamine as single-agent therapy for a hypotensive heart failure patient in whom fluid resuscitation has not been completed usually causes worsening hypotension, owing to the decrease in stressed volume despite an associated increased cardiac contractility. If measured, one would see dobutamine increasing vascular compliance.
The technique of estimating vascular compliance presented in our study[22] might enable one to perform studies on the effects of vasoactive drug infusion (e.g. norepinephrine infusion) on Pmsf, Vs, Rvr and Cs in humans with an intact circulation. In this way we may validate the theories on the control of venous return obtained from animal studies. More extended description of different vasoactive drugs on venous return can be found in the review of Pang.[17]

Localization of Pmsf

Pmsf reflects a physiological concept: the circulation behaves as if the upstream pressure for venous return is Pmsf because if Pra is rapidly varied, blood flow co-varies in a fashion consistent with that specific Pmsf. One may ask, where is this Pmsf located and is Pmsf common to all organs? 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.[11,13] The ratio of the resistance of venous return and systemic vascular resistance describes the location within the circulation where Pmsf exists. A higher ratio implies a more upstream Pmsf location. Still, Pmsf usually resides in the small venous lacunae downstream from the capillary beds. It will be interesting to see how this location of Pmsf within the circulation may change with the use of vasoactive drug therapy and in patients with either sepsis or heart failure. Finally, if one were to perfuse individual organs in isolation, their respective Pmsf values would also be different because of their differing degrees of stressed and unstressed volumes as well as their extravascular tissue pressures. However, during steady-state conditions, flow through all organs is stable and not changing. As all organs drain into a common vena caval drainage circuit, to the extent that venous resistance upstream from those sites is not high, then the Pmsf of all vascular beds should be nearly the same. Otherwise, flow would vary among organs until the Pmsf became common. Thus, theoretically, one should be able to measure Pmsf from an arm vessel during stop-flow conditions as long as tissue pressure and venous blood volume are not transiently altered by the measuring technique. This intriguing construct opens the possibility to simplify the direct measurement of Pmsf without the need of continuous measures of cardiac output and Pcv. Studies exploring this concept are on-going.

Conclusion

The determination and regulation of venous return defines cardiac output and allows the clinician to understand the most important mechanisms regulating cardiovascular homeostasis. Recently, we developed a novel method to measure Pmsf, Rvr, systemic compliance and stressed volume at the bedside in ventilated patients. This exciting technique opens the door of future studies of the determinants of venous return and the control of cardiac output in different patient populations, different pathophysiologic conditions and under different pharmacologic conditions. In the future, cardiovascular therapy will be based on assumptions derived by venous return physiology and can be directed by measuring Pmsf, Rvr, stressed volume and systemic compliance in a fashion like the way we now measure cardiac output and arterial pressure.

References

1 Bayliss M, Starling EH: Observations on Venous Pressures and their Relationship to Capillary Pressures. *J Physiol 1894 Apr 17* 16:159-318.

2 Gelman S: Venous function and central venous pressure: a physiologic story. *Anesthesiology* 2008; 108:735-748.

3 Jacobsohn E, Chorn R, O'Connor M: The role of the vasculature in regulating venous return and cardiac output: historical and graphical approach. *Can J Anaesth* 1997; 44:849-867.

4 Peters J, Mack GW, Lister G: The importance of the peripheral circulation in critical illnesses. *Intensive Care Med* 2001; 27:1446-1458.

5 Rothe CF: Mean circulatory filling pressure: its meaning and measurement. *J Appl Physiol* 1993; 74:499-509.

6 Starr I: Role of the static blood pressure in abnormal increments of venous presure, especially in heart failure.II. Clinical and experimental studies. *Am J Med Sci* 1940; 199:40-55.

7 Guyton AC, Jones C, Coleman T: Cardiac output and its regulation. In *Circulatory Physiology*, edn 2. Philadelphia: W.B. Saunders Company; 1973.

8 Guyton AC, Lindsey AW, Abernathy B, Richardson T: Venous return at various right atrial pressures and the normal venous return curve. *Am J Physiol* 1957; 189:609-615.

9 Green JF: Pressure-flow and volume-flow relationships of the systemic circulation of the dog. *Am J Physiol* 1975; 229:761-769.

10 Den Hartog EA, Versprille A, Jansen JR: Systemic filling pressure in intact circulation determined on basis of aortic vs. central venous pressure relationships. *Am J Physiol* 1994; 267:H2255-H2258.

11 Hiesmayr M, Jansen JR, Versprille A: Effects of endotoxin infusion on mean systemic filling pressure and flow resistance to venous return. *Pflugers Arch* 1996; 431:741-747.

12 Pinsky MR: Instantaneous venous return curves in an intact canine preparation. *J Appl Physiol* 1984; 56:765-771.

13 Versprille A, Jansen JR: Mean systemic filling pressure as a characteristic pressure for venous return. *Pflugers Arch* 1985; 405:226-233.

14 Burkhoff D, Tyberg JV: Why does pulmonary venous pressure rise after onset of LV dysfunction: a theoretical analysis. *Am J Physiol* 1993; 265:H1819-H1828.

15 Nanas S, Magder S: Adaptations of the peripheral circulation to PEEP. *Am Rev Respir Dis* 1992; 146:688-693.

16 Caldini P, Permutt S, Waddell JA, Riley RL: Effect of epinephrine on pressure, flow, and volume relationships in the systemic circulation of dogs. *Circ Res* 1974; 34:606-623.

17 Pang CC: Autonomic control of the venous system in health and disease: effects of drugs. *Pharmacol Ther* 2001; 90:179-230.

18 Pouleur H, Covell JW, Ross J, Jr.: Effects of nitroprusside on venous return and central blood volume in

the absence and presence of acute heart failure. *Circulation* 1980; 61:328-337.

19 Rothe CF, Maass-Moreno R: Active and passive liver microvascular responses from angiotensin, endothelin, norepinephrine, and vasopressin. *Am J Physiol Heart Circ Physiol* 2000; 279:H1147-H1156.

20 Jellinek H, Krenn H, Oczenski W, Veit F, Schwarz S, Fitzgerald RD: Influence of positive airway pressure on the pressure gradient for venous return in humans. *J Appl Physiol* 2000; 88:926-932.

21 Schipke JD, Heusch G, Sanii AP, Gams E, Winter J: Static filling pressure in patients during induced ventricular fibrillation. *Am J Physiol Heart Circ Physiol* 2003; 285:H2510-H2515.

22 Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, Jansen JR: Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. *Crit Care Med* 2009; 37:912-918.

23 Guyton AC: Determination of cardiac output by equating venous return curves with cardiac response curves. *Physiol Rev* 1955; 35:123-129.

24 van den Berg PC, Jansen JR, Pinsky MR: Effect of positive pressure on venous return in volume-loaded cardiac surgical patients. *J Appl Physiol* 2002; 92:1223-1231.

25 Deschamps A, Fournier A, Magder S: Influence of neuropeptide Y on regional vascular capacitance in dogs. *Am J Physiol* 1994; 266:H165-H170.

26 Magder S, De Varennes B: Clinical death and the measurement of stressed vascular volume. *Crit Care Med* 1998; 26:1061-1064.

27 Rothe CF, Flanagan AD, Maass-Moreno R: Role of beta-adrenergic agonists in the control of vascular capacitance. *Can J Physiol Pharmacol* 1990; 68:575-585.

28 Dahn MS, Lange P, Lobdell K, Hans B, Jacobs LA, Mitchell RA: Splanchnic and total body oxygen consumption differences in septic and injured patients. *Surgery* 1987; 101:69-80.

Chapter 3

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

Jacinta J. Maas[1], Bart F. Geerts[2], Paul C.M. van den Berg[1],
Michael R. Pinsky[3] and Jos R.C. Jansen[1]

[1]Department of Intensive Care Medicine, Leiden University Medical Center, The Netherlands,
[2]Department of Anesthesiology, Leiden University Medical Center, The Netherlands,
[3]Department of Critical Care Medicine, University of Pittsburgh, PA, USA

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Abstract

With the determination of the relationship between blood flow and central venous pressure (Pcv) mean systemic filling pressure (Pmsf), circulatory compliance and stressed volume can be estimated in patients in the intensive care unit (ICU). We measured the relationship between blood flow and Pcv using 12-second inspiratory hold maneuvers transiently increasing Pcv to three different steady-state levels and monitored the resultant blood flow via the pulse contour method during the last 3 seconds in twelve mechanically ventilated postoperative cardiac surgery patients in the intensive care unit. Inspiratory holds were performed during normovolemia in supine position (baseline), relative hypovolemia by placing the patients in 30° head-up position (hypo), and relative hypervolemia by volume loading with 0.5 l colloid (hyper). The Pcv to blood flow relation was linear for all measurements with a slope unaltered by relative volume status. Pmsf decreased with hypo and increased with hyper (18.8 ± 4.5 mmHg, to 14.5 ± 3.0 mmHg, to 29.1 ± 5.2 mmHg [baseline, hypo, hyper, respectively, $p < 0.05$)]. Baseline total circulatory compliance was 0.98 $ml \cdot mmHg^{-1} \cdot kg^{-1}$ and stressed volume was 1677 ml. In conclusion, Pmsf 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.

Introduction

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 venous return, 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 (Pra) 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, Pra 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 Pra 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 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 Pmsf in no-flow conditions).

Previously, Pinsky[7] constructed instantaneous VR 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 VR.[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 maneuvers that increase Pra 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 (Pcv), as a surrogate for Pra, and arterial pulse contour-derived cardiac output (COmf), as a surrogate for VR, as Pcv 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).

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 or the necessity for artificial pacing, or use of a cardiac assist device were also excluded.

Anesthesia during surgery was maintained with sufentanil and propofol and patients were ventilated in synchronized intermittent mandatory ventilation mode (Evita 4 servo ventilator Dräger, Lübeck, Germany) adjusted to achieve normocapnia (arterial pCO_2 between 40 and 45 mmHg) 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 (FiO_2) was 0.4 and a positive end-expiratory pressure of 5 cmH_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 following surgery and was discharged from intensive care unit on the first postoperative day.

Measurements. Arterial blood pressure (Pa) 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). 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 fifth intercostal space. Airway pressure (Pvent) was measured at the entrance of the endotracheal tube. Pvent 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 3 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 with the same rate, FiO_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. 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 VR curves by measuring steady-state Pa, Pcv and COmf over the final 3 seconds for a set of four 12-second inspiratory hold maneuvers at Pvent 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 presented in figure 3.1. When Pvent increases, Pcv increases concomitantly, whereas COmf and Pa 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 Pcv and COmf during the four inspiratory pause periods, a VR curve was constructed by fitting a linear regression line through these data points (figure 3.2).

The four inspiratory hold maneuvers 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 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.

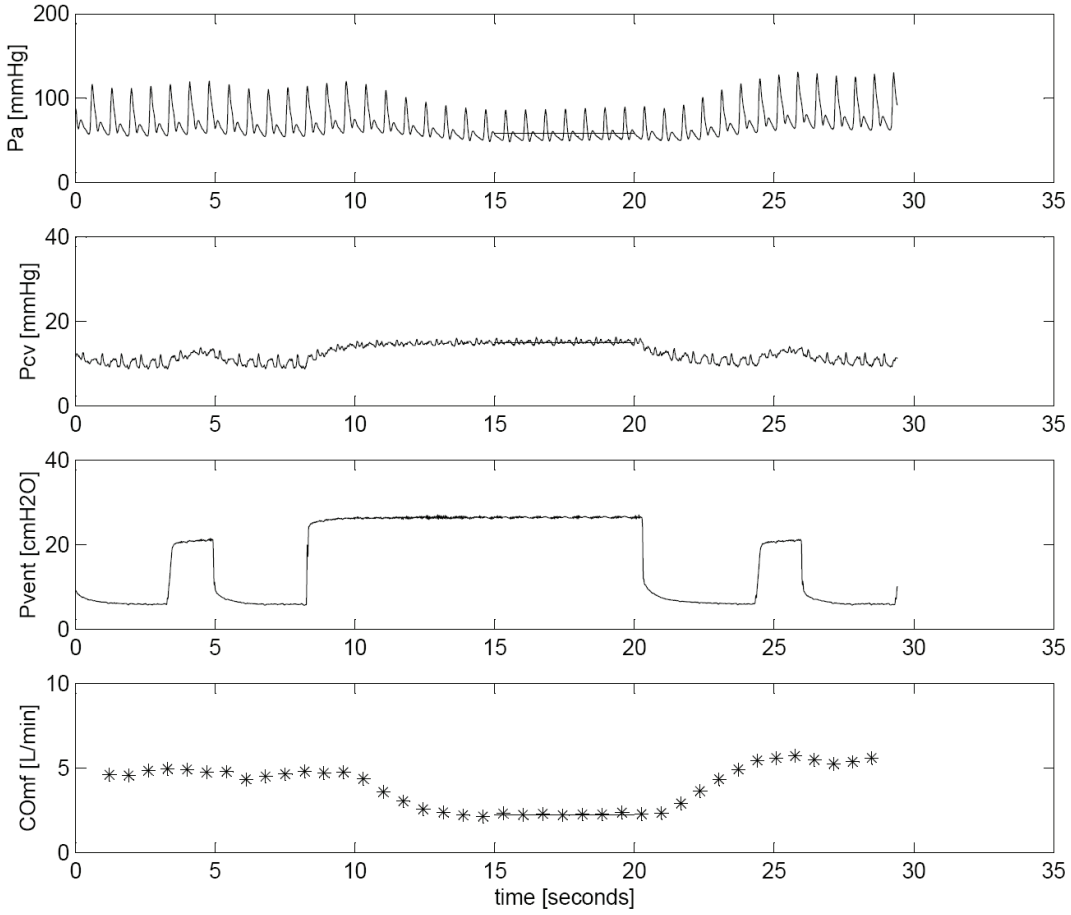

Figure 3.1 Example of an inspiratory hold maneuver

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

Data analysis and statistics. We fitted the set of four data points of Pcv and COmf by linear regression for each volume state to define the VR curve. We defined Pmsf as the extrapolation of this linear regression to zero flow (figure 3.2), assuming that Pvent does not affect 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 (Rsys = (Pa - Pcv)/COmf). The resistance downstream of Pmsf was taken to reflect the Rvr and was calculated as the ratio of the pressure difference between Pcv and Pmsf and COmf (Rvr = (Pmsf-Pcv)/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) administrated to induce the hyper state by the Pmsf difference between baseline and hyper (Csys = Vload /($Pmsf_{Hyper}$ –$Pmsf_{Baseline}$). We assume Csys to be constant for the three volemic 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 ± 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.

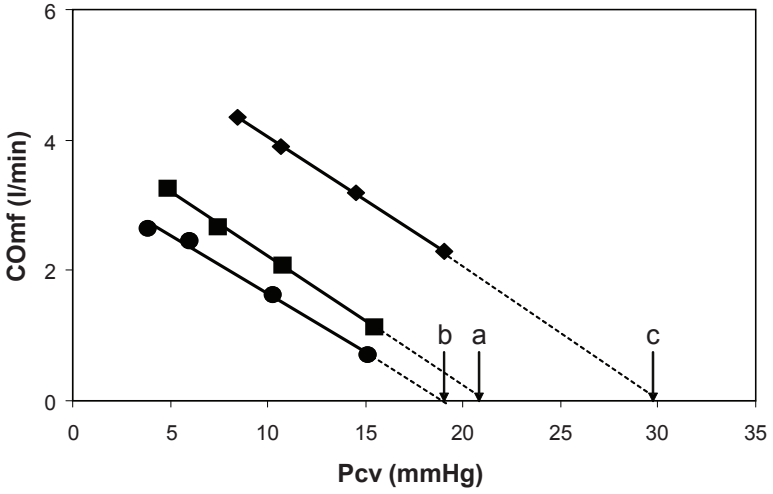

Figure 3.2 Venous return curves
Relationship between venous return (COmf) and central venous pressure (Pcv) for an individual patient. Venous return curves are plotted for three conditions, baseline (a), hypovolemia (b) and hypervolemia (c).

Results

Sixteen patients were recruited into the study, but four were excluded from analysis because they could not receive an additional volume challenge. Table 3.1 shows the patient characteristics and table 3.2 shows the pooled data of the 12 subjects who completed all three steps of the protocol.

Table 3.1 Patient Characteristics

No	Gender	Age (years)	Weight (kg)	Length (cm)	HR (min^{-1})	Pcv (mmHg)	CO ($l \cdot min^{-1}$)	mean Pa (mmHg)	Temp (˚C)	Surgery	Inotropics ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	Propofol ($mg \cdot h^{-1}$)	Sufenta ($\mu g \cdot h^{-1}$)
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	D 2	300	15
3	M	79	78	174	86	7.5	6.3	88	36.9	AVR	D 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	N 0.01	200	10
6	F	64	83	167	76	7.1	5.8	88	37.4	CABG	N 0.04, D 3	200	10
7	M	50	112	183	83	4.0	5.7	85	37.0	CABG	N 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	N 0.09, D 4	120	5
10	M	66	88	178	69	3.0	7.4	71	35.8	CABG	N 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	N 0.04, E 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; mean Pa, mean arterial pressure; Temp, body temperature; CABG, coronary artery bypass grafting; AVR, aortic valve replacement; D, dobutamine; NPN, nitroprusside sodium; N, norepinephrine; E, 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 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 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 3.2 Hemodynamic data of patients during baseline, hypo- and hypervolemic 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	0.170
Pcv (mmHg)	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 ($l \cdot min^{-1} \cdot mmHg^{-1}$)	-0.465	0.151	-0.429	0.160	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 ($mmHg \cdot min \cdot l^{-1}$)	2.18	0.86	2.41	1.14	0.184	2.91	1.10	0.037
Rsys ($mmHg \cdot min \cdot l^{-1}$)	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 hypovolemic condition (hypo) and p2, paired t-test between baseline and hypervolemic condition (hyper).

Systemic compliance and stressed volume. The change in stressed volume vs. Pmsf is shown in figure 3.3. Assuming a constant compliance, the loss of stressed volume due to hypo is approximately 200 ml. On average, Csys was 80 ± 62 ml·mmHg^{-1} (0.98 ± 0.82 ml·mmHg^{-1}·kg^{-1} body weight) and stressed volume during baseline was 1677 ± 1643 ml (19.5 ± 12.1 ml·kg^{-1} body weight).

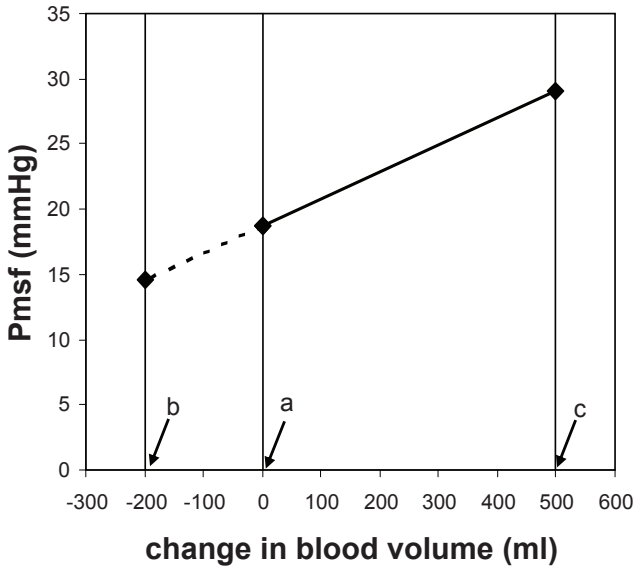

Figure 3.3 Pressure - volume curve
Relationship between change in blood volume and mean systemic filling pressure (Pmsf) for three conditions, baseline (a), hypovolemia (b) and hypervolemia (c). See text for discussion.

Discussion

Our study demonstrates that by using a simple inspiratory hold maneuver while simultaneously measuring Pcv and Pa, 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.

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 3.1). 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 4-5 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 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 Pcv was due to sympathetic reflex activation. We did not observe an increase in Pcv or heart rate during the last phase of our inspiratory pause, not even during pause pressures of 35 cm H_2O. 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 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 Pcv, 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 Pcv we measured Pcv and COmf during short periods of steady state following these initial non-steady-state conditions (figure 3.1). 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 VR 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 third, Pmsf is not influenced by changes in lung or thorax compliance. Lung or thorax compliance affects the transfer of the applied Pvent 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 VR plot. For instance, in a patient with stiffer lungs, during an inspiratory hold the transfer from Pvent to intra-thoracic pressure will be less, resulting in a smaller increase in Pcv and a smaller decrease in CO.

We assumed a linear relation between Pcv and COmf to extrapolate to the condition of

COmf is zero (figure 3.2). This assumption is based on the observation of linearity of the VR curves presented by Guyton and colleagues[4,14] and 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 VR curves were best fitted with straight lines allowing extrapolating the venous return curve to flow zero. This linearity was neither affected by hypo nor 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 mm Hg 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 animal studies, this value is close to zero whereas Pcv in our patient population is on average 6.7 mm Hg. If one assumes a similar Rvr, this Pcv pressure difference would extrapolate to a Pmsf of 12 mm Hg for our subjects if their Pcv was zero (see table 3.2). Thus, our Pmsf values are coupled with the increased Pcv.

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 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 CO (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 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 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 VR curves. Jellinek *et al.*[28] estimated in ten patients during episodes of apnea and ventricular fibrillation, induced for defibrillator testing, a mean Pmsf value of 10.2 mmHg and Schipke *et al.*[6] estimated a mean Pmsf 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 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 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 manifest by a decreasing Pmsf, Pcv 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 Rvr and a decrease in COmf, Pa, Pcv and Pmsf (table 3.2).

Volume loading creates relative hypervolemia 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 VR is increased more than Rvr, CO increases (table 3.2).
Pmsf 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 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 3.2). 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 postoperative 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 hypervolemic conditions whereas conductance (conductance = 1/Rvr) 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 VR under hypervolemic 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.
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 $ml \cdot mmHg^{-1} \cdot kg^{-1}$ body weight. 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 fluid loss (urine and blood loss), contribute to the volume expansion. Previous studies in instrumented anesthetized animals have reported a linear relation between Pmsf and blood volume over a Pmsf of 5-20 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 $ml \cdot kg^{-1}$. To our surprise, this calculated stressed volume is close to the stressed volume of 20.2 $ml \cdot kg^{-1}$ 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 $ml \cdot mmHg^{-1} \cdot kg^{-1}$ in dogs[17,30-33] and from 1.5 to 2.4 $ml \cdot mmHg^{-1} \cdot kg^{-1}$ in rats.[15,16,34] The lower compliance (0.98 $ml \cdot mmHg^{-1} \cdot kg^{-1}$) 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 > 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 < 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

Pmsf 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.

References

1 Versprille A, Jansen JR. Tidal variation of pulmonary blood flow and blood volume in piglets during mechanical ventilation during hyper-, normo- and hypovolaemia. *Pflugers Arch* 1993; 424**:**255-265.

2 Brengelmann GL. A critical analysis of the view that right atrial pressure determines venous return. *J Appl Physiol* 2003; 94**:**849-859.

3 Guyton AC, Jones C, Coleman T: Cardiac output and its regulation. In *Circulatory Physiology*, edn 2. Philadelphia: W.B. Saunders Company; 1973.

4 Guyton AC, Lindsey AW, Abernathy B, Richardson T. Venous return at various right atrial pressures and the normal venous return curve. *Am J Physiol* 1957; 189**:**609-615.

5 Green JF. Pressure-flow and volume-flow relationships of the systemic circulation of the dog. *Am J Physiol* 1975; 229**:**761-769.

6 Schipke JD, Heusch G, Sanii AP, Gams E, Winter J. Static filling pressure in patients during induced ventricular fibrillation. *Am J Physiol Heart Circ Physiol* 2003; 285**:**H2510-H2515.

7 Pinsky MR. Instantaneous venous return curves in an intact canine preparation. *J Appl Physiol* 1984; 56**:**765-771.

8 Versprille A, Jansen JR. Mean systemic filling pressure as a characteristic pressure for venous return. *Pflugers Arch* 1985; 405**:**226-233.

9 Den Hartog EA, Versprille A, Jansen JR. Systemic filling pressure in intact circulation determined on basis of aortic vs. central venous pressure relationships. *Am J Physiol* 1994; 267**:**H2255-H2258.

10 Hiesmayr M, Jansen JR, Versprille A. Effects of endotoxin infusion on mean systemic filling pressure and flow resistance to venous return. *Pflugers Arch* 1996; 431**:**741-747.

11 Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. *J Appl Physiol* 1993; 74**:**2566-2573.

12 Jansen JR, Schreuder JJ, Mulier JP, Smith NT, Settels JJ, Wesseling KH. A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. *Br J Anaesth* 2001; 87**:**212-222.

13 de Wilde RB, Schreuder JJ, van den Berg PC, Jansen JR. An evaluation of cardiac output by five arterial pulse contour techniques during cardiac surgery. *Anaesthesia* 2007; 62**:**760-768.

14 Guyton AC. Determination of cardiac output by equating venous return curves with cardiac response curves. *Physiol Rev* 1955; 35**:**123-129.

15 Samar RE, Coleman TG. Mean circulatory pressure and vascular compliances in the spontaneously hypertensive rat. *Am J Physiol* 1979; 237**:**H584-H589.

16 Yamamoto J, Trippodo NC, Ishise S, Frohlich ED. Total vascular pressure-volume relationship in the conscious rat. *Am J Physiol* 1980; 238**:**H823-H828.

17 Greene AS, Shoukas AA. Changes in canine cardiac function and venous return curves by the carotid baroreflex. *Am J Physiol* 1986; 251**:**H288-H296.

18 Rothe CF. Mean circulatory filling pressure: its meaning and measurement. *J Appl Physiol* 1993; 74**:**499-509.

19 Sato M, Tanaka M, Umehara S, Nishikawa T. Baroreflex control of heart rate during and after propofol infusion in humans. *Br J Anaesth* 2005; 94**:**577-581.

20 Ebert TJ. Sympathetic and hemodynamic effects of moderate and deep sedation with propofol in humans. *Anesthesiology* 2005; 103**:**20-24.

21 Lennander O, Henriksson BA, Martner J, Biber B. Effects of fentanyl, nitrous oxide, or both, on baroreceptor reflex regulation in the cat. *Br J Anaesth* 1996; 77**:**399-403.

22 Fessler HE, Brower RG, Wise RA, Permutt S. Effects of positive end-expiratory pressure on the gradient for venous return. *Am Rev Respir Dis* 1991; 143**:**19-24.

23 Uemura K, Sugimachi M, Kawada T, Kamiya A, Jin Y, Kashihara K, Sunagawa K. A novel framework of circulatory equilibrium. *Am J Physiol Heart Circ Physiol* 2004; 286**:**H2376-H2385.

24 Lee RW, Lancaster LD, Gay RG, Paquin M, Goldman S. Use of acetylcholine to measure total vascular pressure-volume relationship in dogs. *Am J Physiol* 1988; 254**:**H115-H119.

25 Fessler HE, Brower RG, Wise RA, Permutt S. Effects of positive end-expiratory pressure on the canine venous return curve. *Am Rev Respir Dis* 1992; 146**:**4-10.

26 Honda T, Fuqua JM, Edmonds CH, Hibbs CW, Akutsu T. Applications of total artificial heart for studies of circulatory physiology; measurement of resistance to venous return in postoperative awake calves. Preliminary report. *Ann Biomed Eng* 1976; 4**:**271-279.

27 van den Berg PC, Jansen JR, Pinsky MR. Effect of positive pressure on venous return in volume-loaded cardiac surgical patients. *J Appl Physiol* 2002; 92**:**1223-1231.

28 Jellinek H, Krenn H, Oczenski W, Veit F, Schwarz S, Fitzgerald RD. Influence of positive airway pressure on the pressure gradient for venous return in humans. *J Appl Physiol* 2000; 88**:**926-932.

29 Magder S, De Varennes B. Clinical death and the measurement of stressed vascular volume. *Crit Care Med* 1998; 26**:**1061-1064.

30 Shoukas AA, Sagawa K. Control of total systemic vascular capacity by the carotid sinus baroreceptor reflex. *Circ Res* 1973; 33**:**22-33.

31 Caldini P, Permutt S, Waddell JA, Riley RL. Effect of epinephrine on pressure, flow, and volume relationships in the systemic circulation of dogs. *Circ Res* 1974; 34**:**606-623.

32 Ogilvie RI, Zborowska-Sluis D. Effect of chronic rapid ventricular pacing on total vascular capacitance. *Circulation* 1992; 85**:**1524-1530.

33 Shigemi K, Brunner MJ, Shoukas AA. Alpha- and beta-adrenergic mechanisms in the control of vascular capacitance by the carotid sinus baroreflex system. *Am J Physiol* 1994; 267**:**H201-H210.

34 Chien Y, Frohlich ED, MacPhee AA, Pegram BL. Quinaprilat increases total body vascular compliance in rats with myocardial infarction. *Chin Med J (Engl)* 1992; 105**:**382-389.

Chapter 4

Evaluation of mean systemic filling pressure from pulse contour cardiac output and central venous pressure

Jacinta J. Maas[1], Bart F. Geerts[2] and Jos R.C. Jansen[1]

[1]Department of Intensive Care Medicine, Leiden University Medical Center, The Netherlands,
[2]Department of Anesthesiology, Leiden University Medical Center, The Netherlands

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Abstract

The volemic status of a patient can be determined by measuring mean systemic filling pressure (Pmsf). Pmsf is obtained from the venous return curve, i.e. the relationship between central venous pressure (Pcv) and blood flow. We evaluated the feasibility and precision of Pmsf measurement. In ten piglets we constructed venous return curves using seven 12-second inspiratory holds transiently increasing Pcv to seven different steady-state levels and monitored the resultant blood flow, by pulse contour (COpc) and by flow probes around the pulmonary artery (COr) and aorta (COl). Pmsf was obtained by extrapolation of the venous return curve to zero flow. Measurements were repeated to evaluate the precision of Pmsf.

During the inspiratory holds, 133 paired data points were obtained for COr, COl, COpc and Pcv. Bland-Altman analysis showed no difference between COr and COl, but a small significant difference was present between COl and COpc. All Pcv versus flow (COl or COpc) relationships were linear. Mean Pmsf was 10.78 with COl and 10.37 mmHg with COpc. Bland-Altman analysis for Pmsf with COl and with COpc, showed a bias of 0.40 ± 0.48 mmHg. The averaged coefficient of variation for repeated measurement of Pmsf with COl was 6.2% and with COpc 6.1%. In conclusion, during an inspiratory hold pulmonary flow and aortic flow equilibrate. Cardiac output estimates by arterial pulse contour and by a flow probe around the aorta are interchangeable. Therefore, the venous return curve and Pmsf can be estimated accurately by pulse contour methods.

Introduction

Usually, a pulmonary artery catheter (PAC) is placed for the assessment of cardiac output (CO) and of intravascular volume status, by measuring central venous pressure (Pcv) and pulmonary capillary wedge pressure (Pcwp). However, the values of Pcv and Pcwp are often considered to be misleading in estimating volume status and the effect of volume loading.[1,2] In patients on mechanical ventilation, inflation increases pleural pressure and central venous pressure, which in turn may respectively decrease systemic venous return, right ventricular (RV) filling, and transiently impair RV ejection.[3] Therefore, RV stroke volume decreases during the inflation and recovers during expiration (figure 4.1). The larger the cyclic changes in RV output induced by mechanical ventilation and hence in left ventricular (LV) preload are, the larger the cyclic changes in LV stroke volume (SVV) and arterial pulse pressure (PPV). These cyclic changes in LV output induced by mechanical ventilation are thought to be larger when the heart operates on the steep rather than on the flat portion of the Frank-Starling curve.[4,5] Therefore, SVV and PPV have been proposed as an indicator of fluid responsiveness, i.e. predictors of an increase in cardiac output with fluid loading.[5-8] However, SVV and PPV have never shown to be an effective measure of filling status (also called stressed volume) of a patient. As a consequence, SVV and PPV do not give basis for protection against a too high filling status, which can result in pulmonary edema, myocardial ischemia and difficulties in weaning of mechanical ventilation; increasing hospital stay and even mortality.[9] Therefore, the search for a measure of volume status and a predictor of fluid loading on cardiac output continues.

Given the clinical relevance of a measure of effective filling status, we investigated how this fits *with* Guyton's theory on venous return.[10,11] A theory that follows the fundamental physical law, of Newton, that a force is needed to accelerate a mass, or that flow can only be the result of a pressure gradient. According to Guyton's concept the difference between mean systemic filling pressure (Pmsf) and right atrial pressure (Pra) or Pcv is the driving force for venous return. Where Pmsf is the equilibrium pressure in the systemic circulation under condition of no flow and Pcv is the back pressure to venous return. Recently, we validated a bedside technique to estimate mean systemic filling pressure.[12] In this and previous animal research papers[3,13-15] we made several assumptions for the determination of mean systemic filling pressure. Firstly, we assumed that venous return to the heart equals left ventricular output during the end of an inspiratory hold (figure 4.1). Secondly, we expected arterial pulse contour cardiac output to be equal to left ventricular output measured by a flow probe. And thirdly in our clinical study we reasoned that three or four inspiratory holds were enough to describe reliable a venous return curve.

The aim of this study was to test the validity of these assumptions and to determine the precision of the estimated value of mean systemic filling pressure.

Materials and methods

All experiments were performed in accordance with the "Guide for Care and Use of Laboratory Animals" published by the US National Institute of Health and the protocol was approved by the local Animal Care Committee.

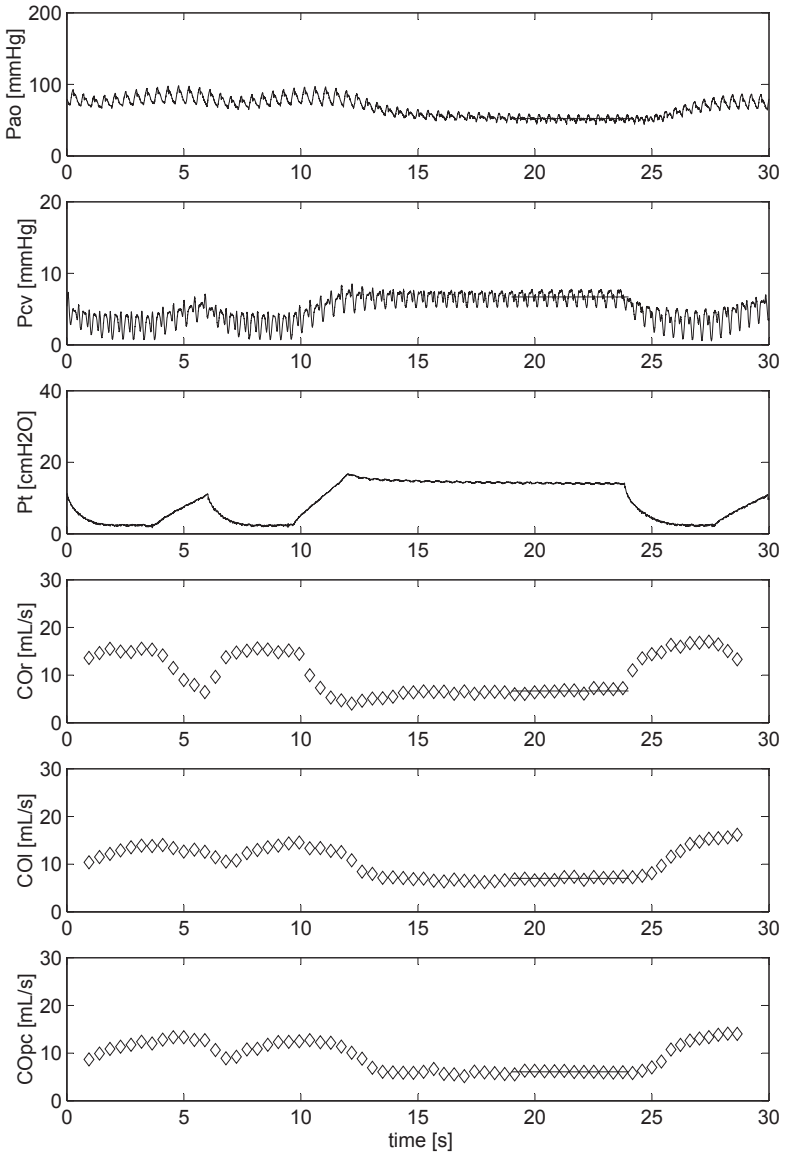

Figure 4.1 Example of an inspiratory hold procedure

Effects of an inspiratory hold on aortic pressure (Pao), central venous pressure (Pcv), airway pressure (Pt) and beat-to-beat cardiac output (CO) with a probe around the pulmonary artery (COr), around the aorta (COl) and by pulse contour analysis (COpc). Preceding the hold the effects of a normal ventilation cycle are plotted. Note the difference in beat-to-beat changes of COr and COl or COpc.

Surgery

Ten piglets (8-10 wk, mean weight 11.0 ± 0.9 kg) were studied. Anesthesia was induced with 30 $mg \cdot kg^{-1}$ sodium pentobarbital intra-peritoneally, followed by a continuous infusion of 9.0 $mg \cdot kg^{-1} \cdot h^{-1}$. After tracheostomy, the animals were ventilated at a rate of 10 breaths per min and with a tidal volume adjusted to maintain arterial pCO_2 of approximately 5.33 kPa (40 mmHg), while a positive end-expiratory pressure of 2

cmH_2O was applied. pCO_2, airway pressure (Pt) and airflow were measured in the tracheal cannula. The animals were placed in supine position on a thermo-controlled operating table (38°C). A catheter was inserted through the right common carotid artery into the aortic arch to measure arterial pressure (Pao) and to sample arterial blood. Two other catheters were inserted through the right external jugular vein. A pulmonary artery catheter was inserted to measure pulmonary artery pressure, to measure thermodilution cardiac output (COtd) and to sample mixed venous blood. A quadruple-lumen catheter was inserted into the superior vena cava to measure Pcv and to infuse sodium pentobarbital and pancuronium bromide (Organon N.V., Boxtel, the Netherlands). The catheters for vascular pressure measurements were kept patent by an infusion of saline with 2.5 IE Heparin ml^{-1} at 3 $ml \cdot h^{-1}$. The bladder was cannulated trans-abdominally to check urine loss in order to maintain fluid balance. After an intercostal thoracotomy in the second left intercostal space, two electromagnetic flow probes (type transflow 601, model 400, Skalar, Delft, the Netherlands) were placed within the pericardium with one probe around the pulmonary artery and another around the ascendant part of the aortic arch to measure pulmonary artery flow (COr) and aortic flow (COl). Two suction catheters, one dorsal and one ventral, were inserted into the left pleural space. The thorax was closed airtight and both air and fluids were evacuated for 1-2 minutes with -10 cmH_2O suction while applying a PEEP of 10 cmH_2O. After surgery and while on continuous pentobarbital infusion, the animals were paralyzed with an intravenous infusion of pancuronium bromide (0.3 $mg \cdot kg^{-1} \cdot h^{-1}$), after a loading dose of 0.1 $mg \cdot kg^{-1}$ in 3 min.

Measurements

The electrocardiogram (ECG), Pao, pulmonary artery pressure (Ppa), Pcv, flow probe signals and tracheal airway pressure (Pt) were simultaneously recorded. Zero level of blood pressures was chosen at the level of the tricuspid valves, indicated by the pulmonary artery catheter during lateral-lateral radiography. The airway pressure transducer was balanced at zero level against ambient air. During the observation periods, ECG, blood flow and pressure signals were sampled in real time for 30-second periods at 250 Hz. The mean of four thermodilution cardiac output measurements equally distributed of the ventilatory cycle was used to obtain the value of COtd (apparatus and method described in).[16-18] Areas under the pulmonary artery blood flow curve and the aortic flow curves were analyzed online and calibrated by COtd to estimate beat-to-beat cardiac output (COr and COl). Pulse contour cardiac output (COpc) from aortic pressure (for piglets adapted Modelflow method, FMS, Amsterdam, the Netherlands) was calibrated by the same COtd value. After the surgical procedure the animals were ventilated at a rate of 10 min^{-1} with an inflation time of 2.4 seconds and an expiration time of 3.6 seconds. Tidal volume was readjusted to an end-expiratory pCO_2 of approximately 5.33 kPa (40 mmHg), usually corresponding with a slightly higher arterial pCO_2. The ventilatory settings were kept constant during the observation periods.

We determined Pmsf using inspiratory holds as previously described.[3,14,15,19] Briefly: During inflation of the lungs venous capacitance is loaded due to an increase in Pcv, which leads to a transient reduction in venous return, in right ventricular output and consequently in left ventricular output (figure 4.1). To avoid transient effects on the relationship between venous return and Pcv, we measured Pcv and right and left ventricular output (COr, COl and COpc) during short periods of end-inspiratory steady state following these initial non-steady-state conditions. CO and Pcv are determined over the final 5 seconds for a set of seven 12-seconds inspiratory hold procedures at seven randomly applied tidal volumes between 0 and 300 ml. The inspiratory hold maneuvers are separated by 5-minute intervals to re-establish the initial hemodynamic steady state. From the steady-state values of Pcv and cardiac output (COl and COpc) during the seven inspiratory pause periods two venous return curves were constructed by fitting linear regression lines according to the method of least square means through these data points (figure 4.2). Pmsf,l and Pmsf,pc are defined as the extrapolation of these linear regressions to zero flow with COl and COpc respectively.[3,14,15,19]

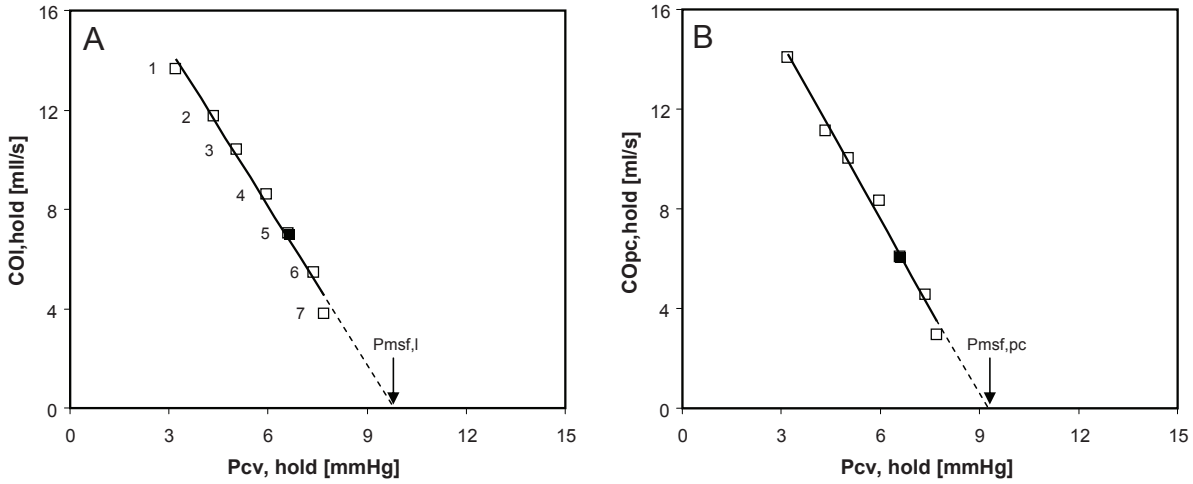

Figure 4.2 Venous return curves

Panel A, the relationship between cardiac output (CO) obtained during the end of the inspiratory hold from the flow probe around the aorta (COl,hold) and central venous pressure (Pcv,hold). Panel B, similar relationship obtained by arterial pulse pressure analysis (COpc,hold). Mean systemic filling pressure (Pmsf) is obtained by extrapolation of the linear fit to CO is 0. The bold data points are taken from figure 4.1.

Protocol

To eliminate the effects of surgery, opening of the pericardium, and applying mechanical ventilation on the hemodynamic measurements, the piglets were allowed to stabilize for 60 to 120 minutes after surgery. Data collection started once heart rate (HR), mean Pao and Pcv were stable for at least 15 minutes. After stabilization, series-1 measurements were performed by applying the seven inspiratory holds. After 50 minutes these measurements were repeated, series-2.

Data analysis and statistics

The results of the data pairs of COr, COl and COpc obtained during each inspiratory hold were compared by linear regression and the difference between them by Bland-Altman analysis. To describe the venous return curve we fitted the set of seven data points of Pcv and COl and of Pcv and COpc by linear regression for series-1 and series-2. We defined Pmsf as the extrapolation of this linear regression to zero flow (figure 4.2), assuming that airway pressure does not affect Pmsf. Repeatability was calculated from the two baseline conditions using Bland-Altman analysis. Hereto, for each animal the mean and difference of the values of series-1 and series-2 were determined. The upper and lower limits of agreement were calculated as bias ± 2SD. The coefficient of variation (COV) was calculated as 100% x (SD/mean). Differences in variables during series-1 and series-2 were analyzed using paired t-tests. The effect of reduction of the number of inspiratory holds on Pmsf values was studied as follows: 4-holds by selection of holds 1, 3, 5, 7 (see figure 4.2); 3-holds by holds 1, 4, 7 and 2-holds by 1 and 7. All values are given as mean ± SD. A p-value < 0.05 was considered statistically significant.

Results

Ten 8–10 week old piglets (all females) bodyweight of 11.0 ± 0.9 kg were studied. The first series of measurements in animal 1 were excluded for analysis because of a technical problem in recording a proper left ventricular outflow signal. Mean hemodynamic characteristics of the animals during series 1 and 2 were: Pao 75.8 ± 6.7 mmHg, Ppa 15.5 ± 3.5 mmHg, Pcv 3.7 ± 0.5 mmHg, heart rate 146 ± 42 min^{-1}, COtd 17.72 ± 3.12 $ml \cdot s^{-1}$.

The hemodynamic changes during a normal ventilatory cycle and during a ventilatory hold are illustrated in an individual example by plotting Pao, Pcv, Pt and beat-to-beat changes of COr, COl and COpc against time, see figure 4.1. The figure shows that during inflation a rise in Pcv and a concomitant decrease in CO occurs. Also, a shift between the changes in right ventricular cardiac output and left ventricular is observable. However, 8 seconds after start of the inspiratory hold a plateau in COr, COl and COpc occurs. During the normal ventilatory cycle the modulation in right ventricular output is larger than that of left ventricular output. Pooled data during normal ventilation are shown in table 4.1. A Kolmogorov-Smirnov test indicated normal distribution of all data.

CO during inspiratory hold procedures

During the inspiratory holds, illustrated in figure 4.1, Pcv increased to a constant level for 12 seconds. This increase in Pcv led to a decrease in Pao, COr, COl, and COpc. Over the last 5 seconds of the hold their CO beat-to-beat values were constant. Over this period in total 133 paired averaged data points were obtained for COr, COl, and

COpc. Regression analysis showed that COr, COl and COpc were highly related to each other (COl = 1.002·COr, R^2 = 0.955; COpc = 0.965·COr, R^2 = 0.940; and COpc = 0.961·COl, R^2 = 0.965, figure 4.3A). The result of Bland-Altman analysis for the difference between methods is given in table 4.1 and figure 4.3B. No difference was found between COr and COl, but a small significant difference was present between COr and COpc as well as between COl and COpc. The COV for repeated measurements (series-1 and series-2) of COr, COl and COpc were 12%, 10% and 12% respectively.

Table 4.1 Bland-Altman analysis of cardiac output results

	Mean	Difference			Limits of agreement		
		Bias	SD	COV	Lower	Upper	
	ml•s^{-1}	ml•s^{-1}	ml•s^{-1}	%	ml•s^{-1}	ml•s^{-1}	p
COr - COl	11.23	-0.03	0.66	5.9	1.29	-1.35	0.621
COr - COpc	11.06	0.32	0.78	7.1	1.88	-1.24	< 0.001
COl - COpc	11.08	0.34	0.62	5.6	1.58	-0.90	< 0.001

Bland-Altman analysis of cardiac output results by measurements with a flow probe around the pulmonary artery (COr), around the aorta (COl) and arterial pulse contour analysis (COpc). p-value for the difference between bias value and zero is given (n = 133).

Venous return curves and Pmsf

An individual example of the Pcv versus blood flow (COl and COpc) relationships, i.e. the venous return curves, is given in figure 4.2. Observable is the linear relationship through the data points obtained from the seven inspiratory holds. For all 10 animals this venous return curve was linear, as can be observed in figure 4.4 for Pcv versus COpc. For all observations the averaged slope of the venous return curve Pcv versus COl is -2.228 ± 0.368 and for Pcv versus COpc is -2.355 ± 0.337 (difference p = 0.03), the averaged squared correlation coefficients (R^2) are 0.912 (range 0.887-0.966) and 0.970 (range 0.929-0.993) respectively. The population averaged values of Pmsf with COl and Pmsf with COpc are 10.77 ± 1.00 mmHg and 10.38 ± 1.09 mmHg (difference p = 0.003) respectively. Bland-Altman analysis for the difference between methods (table 4.2) showed that the small difference between Pmsf,l and Pmsf,pc of 0.40 ± 0.48 mmHg (COV = 4.5%) is, however, statistically significant (p = 0.009).

Repeatability

Bland-Altman analysis for repeated measurements for Pmsf,l showed a bias of -0.18 mmHg and a precision of 0.67 mmHg (COV = 6.2%) and for Pmsf,pc these values were -0.27 mmHg and 0.63 mmHg (COV = 6.1%). There was no difference between the first and second series of Pmsf,l and Pmsf,pc (p = 0.58 and 0.22 respectively).

Data reduction

The results of reduction of the number of data points per venous return curve from 7 to 4, 3 and 2 inspiratory holds is shown in table 4.2. A remarkable good agreement

between Pmsf with COl and Pmsf with COpc was found for Pmsf with 7, 4, 3 and 2 inspiratory holds per venous return curves. The difference between the techniques was statistically significant but was maximally 4.5%. No difference between the first and second series per animal was found and the COV for repeated measurements of Pmsf ranged from 2.2 to maximally 6.5% (table 4.2).

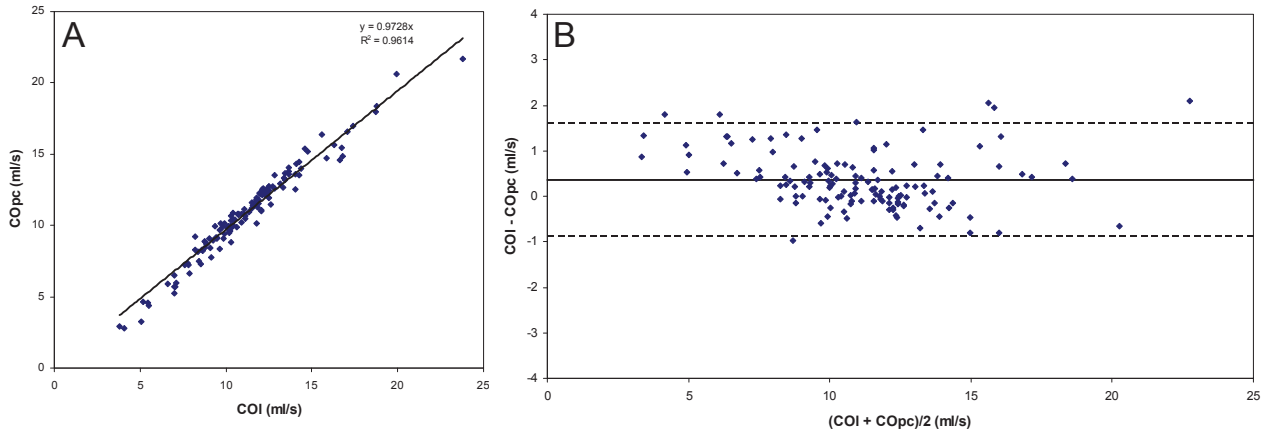

Figure 4.3 Cardiac output by aortic probe and pulse contour cardiac output
Cardiac output measured during the end of the inspiratory hold by the aortic probe (COl) and pulse contour cardiac output (COpc). In panel A, regression between COl and COpc is given. Noticeable is the small underestimation of COpc in the low output range. In panel B, Bland-Altman analysis of COl and COpc is shown.

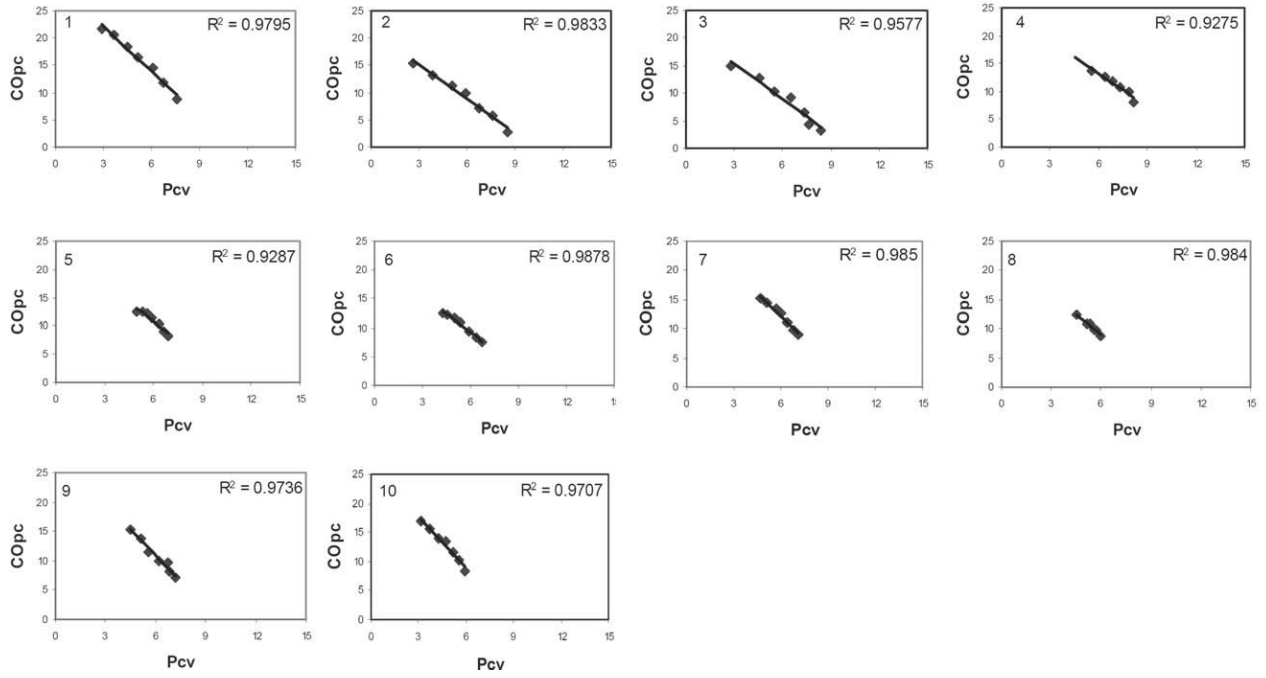

Figure 4.4 Venous return curves of the 10 individual animals.
COpc is cardiac output (ml·s^{-1}) measured by pulse contour and Pcv is central venous pressure (mmHg).

Table 4.2 Bland-Altman analysis for the difference between mean systemic filling pressures

	n,h	Mean	Difference			Limits of agreement		
			Bias	SD	COV	Lower	Upper	
		mmHg	mmHg	mmHg	%	mmHg	mmHg	p
Difference								
Pmsf,COl and	7	10.57	0.40	0.48	4.5	-0.56	1.35	0.009
Pmsf,COpc	4	10.50	0.47	0.27	2.6	-0.07	1.01	0.006
	3	10.97	0.37	0.47	4.3	-0.58	1.32	0.003
	2	10.39	0.49	0.23	2.2	-0.02	0.95	0.001
Repeatability								
Pmsf,COl	7	10.77	-0.18	0.67	6.2	-1.47	1.11	0.339
	4	10.74	-0.37	0.57	5.3	-1.50	0.77	0.073
	3	10.66	-0.39	0.64	6.0	-1.62	0.85	0.079
	2	10.63	-0.35	0.61	5.7	-1.56	0.86	0.098
Pmsf,COpc	7	10.37	-0.27	0.63	6.1	-1.54	1.01	0.218
	4	10.27	-0.39	0.62	6.0	-1.58	0.84	0.084
	3	10.42	-0.27	0.68	6.5	-1.63	1.09	0.239
	2	10.14	-0.23	0.48	4.7	-1.19	0.72	0.159

Bland-Altman analysis for the difference between mean systemic filling pressures (Pmsf) measured with a flow probe around the aorta (Pmsf,COl) and with arterial pulse pressure analyses (Pmsf,COpc) as well as Bland-Altman analysis for repeated measurements. Both analyses were done for 7, 4, 3 and 2 inspiratory hold maneuvers (n,h). p-value for the difference between bias value and zero is given.

Discussion

Our analysis shows clearly: 1. COr equals COl equals COpc at the end of the inspiratory holds; 2. the feasibility of pulse contour analysis to estimate the venous return curve and the unambiguous determination of mean systemic filling pressure; and 3. Pmsf can be estimated with 2-7 inspiratory holds.

The measurement of Pmsf under clinical conditions was limited to the availability of planned, unavoidable circulatory arrest for instance during testing of ICD.[20,21] But, recently we[12] showed the feasibility of bedside determination of effective volume-status, Pmsf, by the application of 4 inspiratory holds and measurement of Pcv and pulse contour cardiac output during these holds. In this and former animal studies[3,12,14,15] we made several assumptions for the determination of mean systemic filling pressure: 1, we assumed venous return to the heart to be equal to the left ventricular output during the end of the inspiratory holds; 2, we expected pulse contour cardiac output to be equal to left ventricular output; and 3, we reasoned that three or four inspiratory holds were enough to reliably describe the venous return curve.

Venous return equals left ventricular output

In comparing CO techniques, the limits of agreement of COr with COl (2SD/mean) were 9%. Together, with a bias for the difference between techniques which was not significantly different from zero and a COV for repeated measurements of 12% and 10% for COr and COl, the two methods are interchangeable. Thus, measurement of left ventricular output during inspiratory holds allows the estimation of right ventricular

output and most presumably also from right atrial input, as the right heart has a limited storing capacity for blood.

Left ventricular output equals arterial pulse contour cardiac output

The technical set-up with a flow probe around the pulmonary artery or aorta is not generally applicable in humans. Therefore we have chosen to evaluate a beat-to-beat determination of cardiac output by arterial pulse contour analysis. Most commercial pulse contour methods (PiCCO, LiDCO, FloTrac-Vigileo and Modelflow) use a pressure to volume conversion based on *in vitro* measurements of the human aorta. From a comparative study it became clear that there are differences in aortic compliance between humans and pigs.[22] In humans the compliance of the aorta decreases non-linearly with increasing pressures between approximately 30 and 200 mmHg.[23] This relation is age dependent. For pigs the compliance first increases in the lower pressure range and next decreases in the higher pressure range. This increase and decrease in pigs is less pronounced than the decrease in compliance in humans. No information is available about age dependency in pigs. In our present study we approximated the pressure-dependent compliance in the pig with a constant compliance. This might lead to a slightly underestimated pulse contour cardiac output in the lower arterial pressure range. Indeed in this range the actual compliance is slightly larger than the used constant compliance leading to an underestimated stroke volume and CO (figure 4.3A). Still, Bland-Altman analysis showed a good agreement between COl and COpc with limits of agreement of -0.90 to1.58 $ml \cdot s^{-1}$ and a COV of 5.6%. This was accompanied by a small, although significant, mean difference (bias = 0.34 $ml \cdot s^{-1}$) and a low coefficient of variation for repeated measurements. We conclude that our pulse contour CO measurement can replace the measurement of LV output with a probe around the aorta.

Mean systemic filling pressure by LV output and arterial pulse contour CO

The venous return curve constructed with the results of measurement of Pcv and COl or COpc during the inspiratory holds was linear in all 10 animals. The correlation coefficients with COl or COpc in the fit were high (mean R^2 = 0.971 and 0.984 respectively). The extrapolation of the linear fit to zero flow resulted in a mean Pmsf,l of 10.77 ± 1.00 mmHg and of Pmsf,pc of 10.38 ± 1.09 mmHg. Also the repeatability or precision of the results of the two series of measurements per animal is good, mean difference between the first and second series of measurements is -0.18 ± 0.67 mmHg for Pmsf,l and -0.27 ± 0.63 for Pmsf,pc. The small COV (6.2% and 6.1% for Pmsf,l and Pmsf,pc respectively) clearly indicates the unambiguous validity of our method with inspiratory holds to determine Pmsf.

Bland-Altman analysis for the difference between Pmsf,l and Pmsf,pc showed a small but significant mean difference of 0.40 ± 0.48 mmHg. Detection of this small mean difference can be explained largely by the high correlation coefficient of the linear fit. With small limits of agreement and with a small mean difference we concluded

that the two methods are interchangeable. Thus, pulse contour analysis can be used to determine the venous return curve and Pmsf.

Number of inspiratory holds to describe the venous return curve

Application of 7 inspiratory holds and recovery to baseline value takes approximately 35 – 40 minutes. Reduction of 7 to 4, 3 or even 2 inspiratory holds will shorten the time needed to determine the venous return curve and Pmsf, which makes the method more clinically feasible. The results given in table 4.2 indicate that already 2 inspiratory holds (i.e. the hold with inflation of 0 and 300 ml) allow an accurate estimate of Pmsf. The use of four inspiratory holds in our previous clinical study[12] seems thus more than sufficient.

Comparison with Pmsf values found in literature

We found difference in Pmsf values of approximately 8 mmHg between the experimental settings with our animals (10.4 mmHg) and the clinical setting with postoperative cardiac patients (18.8 mmHg)[12] using the same measurement technique. This can be explained partly by: the difference in filling status; all postoperative cardiac patients had a positive fluid balance whereas in our animal study only fluid was given to compensate for blood loss during surgery; and a difference in positive end-expiratory pressure (patients 5 cmH_2O and in our piglets zero cmH_2O). These differences during baseline condition are reflected in different Pcv values (patients 6.7 mmHg and our piglets 3.7 mmHg). Furthermore, the Pmsf may be patient population and species dependent. For animals Pmsf values between 7[24] and 30 mmHg[25] are reported.

We based our analysis on the assumption that the venous return curve is linearly dependent on applied central venous pressure. Except for a minor inflection at low or negative values of Pcv such linearity was demonstrated by Guyton *et al.*[10] in open chest experiments. Pinsky[26] in dogs and Versprille and Jansen[3] in pigs confirmed this linearity in closed chest circumstances after thoracotomy. Furthermore, Pinsky[26] demonstrated that Pmsf obtained by linear extrapolation of the venous return curves did not differ from the value measured during circulatory arrest. The Pmsf-values calculated from Pcv and COl or COpc are in agreement with the Pmsf-values determined by the inspiratory hold procedure[3,13-15] and stop-flow measurements.[27]

Conclusions

During an inspiratory hold pulmonary flow and aortic flow equilibrate. Cardiac output estimates by the pulse contour method and by a flow probe around the aorta are interchangeable. Therefore, venous return can be estimated by pulse contour methods. Mean systemic filling pressure can be estimated with equal precision with both blood flow measurement methods. Four, three or even two inspiratory holds satisfy to construct a venous return curve and to estimate Pmsf.

References

1 Gelman S: Venous function and central venous pressure: a physiologic story. *Anesthesiology* 2008; 108**:**735-748.

2 Marik PE, Baram M, Vahid B: Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest* 2008; 134**:**172-178.

3 Versprille A, Jansen JR: Mean systemic filling pressure as a characteristic pressure for venous return. *Pflugers Arch* 1985; 405**:**226-233.

4 Magder S: Clinical usefulness of respiratory variations in arterial pressure. *Am J Respir Crit Care Med* 2004; 169**:**151-155.

5 Michard F, Teboul JL: Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest* 2002; 121**:**2000-2008.

6 Berkenstadt H, Margalit N, Hadani M, Friedman Z, Segal E, Villa Y, Perel A: Stroke volume variation as a predictor of fluid responsiveness in patients undergoing brain surgery. *Anesth Analg* 2001; 92**:**984-989.

7 Magder S, Lagonidis D, Erice F: The use of respiratory variations in right atrial pressure to predict the cardiac output response to PEEP. *J Crit Care* 2001; 16**:**108-114.

8 Reuter DA, Felbinger TW, Kilger E, Schmidt C, Lamm P, Goetz AE: Optimizing fluid therapy in mechanically ventilated patients after cardiac surgery by on-line monitoring of left ventricular stroke volume variations. Comparison with aortic systolic pressure variations. *Br J Anaesth* 2002; 88**:**124-126.

9 Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M: A rational approach to perioperative fluid management. *Anesthesiology* 2008; 109**:**723-740.

10 Guyton AC, Lindsey AW, Abernathy B, Richardson T: Venous return at various right atrial pressures and the normal venous return curve. *Am J Physiol* 1957; 189**:**609-615.

11 Guyton AC: Determination of cardiac output by equating venous return curves with cardiac response curves. *Physiol Rev* 1955; 35**:**123-129.

12 Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, Jansen JR: Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. *Crit Care Med* 2009; 37**:**912-918.

13 Den Hartog EA, Versprille A, Jansen JR: Systemic filling pressure in intact circulation determined on basis of aortic vs. central venous pressure relationships. *Am J Physiol* 1994; 267**:**H2255-H2258.

14 Geerts BF, Maas JJ, Aarts LP, Pinsky MR, Jansen JR: Partitioning the resistances along the vascular tree: effects of dobutamine and hypovolemia in piglets with an intact circulation. *J Clin Monit Comput* 2010; 24**:**377-384.

15 Hiesmayr M, Jansen JR, Versprille A: Effects of endotoxin infusion on mean systemic filling pressure and flow resistance to venous return. *Pflugers Arch* 1996; 431**:**741-747.

16 Jansen JR, Schreuder JJ, Bogaard JM, van Rooyen W, Versprille A: Thermodilution technique for measurement of cardiac output during artificial ventilation. *J Appl Physiol* 1981; 51**:**584-591.

17 Jansen JR, Schreuder JJ, Settels JJ, Kloek JJ, Versprille A: An adequate strategy for the thermodilution

technique in patients during mechanical ventilation. *Intensive Care Med* 1990; 16**:**422-425.

18 Jansen JR, Schreuder JJ, Punt KD, van den Berg PC, Alfieri O: Mean cardiac output by thermodilution with a single controlled injection. *Crit Care Med* 2001; 29**:**1868-1873.

19 Jansen JR, Maas JJ, Pinsky MR: Bedside assessment of mean systemic filling pressure. *Curr Opin Crit Care* 2010; 16**:**231-236.

20 Jellinek H, Krenn H, Oczenski W, Veit F, Schwarz S, Fitzgerald RD: Influence of positive airway pressure on the pressure gradient for venous return in humans. *J Appl Physiol* 2000; 88**:**926-932.

21 Schipke JD, Heusch G, Sanii AP, Gams E, Winter J: Static filling pressure in patients during induced ventricular fibrillation. *Am J Physiol Heart Circ Physiol* 2003; 285**:**H2510-H2515.

22 Jansen JR: Standard pulse contour methods are not applicable in animals. *Intensive Care Med* 2006; 32**:**2084-2085.

23 Langewouters GJ, Wesseling KH, Goedhard WJ: The static elastic properties of 45 human thoracic and 20 abdominal aortas in vitro and the parameters of a new model. *J Biomech* 1984; 17**:**425-435.

24 Samar RE, Coleman TG: Mean circulatory pressure and vascular compliances in the spontaneously hypertensive rat. *Am J Physiol* 1979; 237**:**H584-H589.

25 Honda T, Fuqua JM, Edmonds CH, Hibbs CW, Akutsu T: Applications of total artificial heart for studies of circulatory physiology; measurement of resistance to venous return in postoperative awake calves. Preliminary report. *Ann Biomed Eng* 1976; 4**:**271-279.

26 Pinsky MR: Instantaneous venous return curves in an intact canine preparation. *J Appl Physiol* 1984; 56**:**765-771.

27 Guyton AC, Polizo D, Armstrong GG: Mean circulatory filling pressure measured immediately after cessation of heart pumping. *Am J Physiol* 1954; 179**:**261-267.

Chapter 5

Estimation of mean systemic filling pressure in postoperative cardiac surgery patients with three methods

Jacinta J. Maas[1], Michael R. Pinsky[2], Bart F. Geerts[3], Rob B.P. de Wilde[1] and Jos R.C. Jansen[1]

[1]Department of Intensive Care Medicine, Leiden University Medical Center, The Netherlands,
[2]Department of Critical Care Medicine, University of Pittsburgh, PA, USA,
[3]Department of Anesthesiology, Leiden University Medical Center, The Netherlands

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Abstract

Effective circulating blood volume can be estimated by measuring mean systemic filling pressure. We assessed the level of agreement between different bedside estimates of mean systemic filling pressure (Pmsf), arm equilibrium pressure (Parm) and model analogue (Pmsa) in eleven mechanically ventilated postoperative cardiac surgery patients. Sequential measures were made in supine position, rotating the bed to 30° head-up tilt and after fluid loading (500 ml colloid). During each condition four inspiratory hold maneuvers were done to determine Pmsf, arm stop-flow was created by inflating a cuff around the upper arm for 30 seconds to measure Parm, and Pmsa was estimated from a Guytonian model of the systemic circulation. Mean Pmsf, Parm and Pmsa across all three states were 20.9 ± 5.6, 19.8 ± 5.7 and 15.9 ± 4.9 mmHg, respectively.

Bland-Altman analysis for the difference between Parm and Pmsf showed a non-significant bias of -1.0 ± 3.08 mmHg ($p = 0.062$), a coefficient of variation (COV) of 15% and limits of agreement (LOA) of -7.3 and 5.2 mmHg. For the difference between Pmsf and Pmsa we found a bias of -6.0 ± 3.1 mmHg ($p < 0.001$), COV 17% and LOA -12.4 and 0.3 mmHg. Changes in Pmsf and Parm and in Pmsf and Pmsa were directionally concordant in response to head-up tilt and volume loading. In conclusion, Parm and Pmsf are interchangeable. Changes in effective circulatory volume are tracked well by changes in Parm and Pmsa.

Introduction

Accurate assessment of cardiovascular state in the critically ill is difficult because easily measured parameters, such as blood pressure and cardiac output (CO), can co-exist with different levels of ventricular pump function and effective circulating blood volume. Thus, identifying the appropriate therapy and targeting specific measurable endpoints of therapy are problematic. Although assessing dynamic changes in arterial pulse pressure or left ventricular stroke volume during ventilation and passive leg-raising maneuvers improves identification of fluid responsiveness, they do not quantify effective circulating blood volume or the cause or lack thereof. Although fluid resuscitation therapy is important in the management of unstable patients, excessive fluid resuscitation can be harmful in acute lung injury[1], head injury[2] and postoperative patients.[3] Thus, a measure of effective volume status is useful to avoid volume overload since even volume-overloaded patients may remain volume responsive.

Mean systemic filling pressure (Pmsf) is a functional measure of effective intravascular volume status. It is the pressure anywhere in the circulation during circulatory arrest.[4] Importantly, central venous pressure (Pcv) to Pmsf pressure difference defines the driving pressure for venous return, and together with the resistance to venous return defines CO. We have shown that Pmsf can be measured in ventilator-dependent patients using inspiratory hold maneuvers defining Pcv-CO data pairs that when extrapolated to zero CO reports Pmsf.[5,6] This calculated Pmsf parameter accurately follows changes in intravascular volume.[5,7]

Unfortunately, this inspiratory hold technique requires a sedated and ventilated patient, not universally seen in critically ill patients. We thus studied two simpler bedside methods for determining Pmsf as previously suggested by Anderson[8] and Parkin.[9] Anderson hypothesized that the circulation of the arm behaves similar to total systemic circulation during steady-state conditions. Accordingly, we measured transient stop-flow forearm arterial and venous equilibrium pressure, referred to as arm equilibrium pressure (Parm). Parkin[9] proposed estimating the effective circulatory volume based on an electrical analog simplification of Guytonian circulatory physiology estimating mean circulatory pressure (Pmsa) from directly measured Pcv, mean arterial pressure and CO. The aim of our study was to compare the level of agreement between simultaneously measured Pmsf, Parm and Pmsa in three intravascular volume states in critically ill patients.

Materials and methods

The study was approved by the hospital ethics committee of Leiden University Medical Center (P01.111, 29 January 2002) and carried out in Leiden. Written informed consent was obtained from all patients prior to surgery. The institutional review board of University of Pittsburgh approved review and analysis of data. Eleven patients were enrolled and studied after cardiac surgery.

Patients

We limited our study to cardiac surgery patients requiring pulmonary artery and radial artery catheters for perioperative monitoring. Our study partially used hemodynamic data from the same patients reported in another study but examined different protocol-based measures.[7] All patients had coronary artery or valvular disease with preserved ventricular function (EFlv > 0.4). Patients with aortic aneurysm, severe peripheral vascular disease, postoperative arrhythmia, postoperative valvular insufficiency or needing artificial pacing or the use of a cardiac assist device were excluded. All subjects were studied during their initial postoperative period in the ICU, while sedated (propofol 3.0 $mg \cdot kg^{-1} \cdot h^{-1}$ and sufentanil 0.06-0.19 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and mechanically ventilated with airway pressure release ventilation adjusted to achieve normocapnia, with 7-11 $ml \cdot kg^{-1}$ tidal volumes, 5 cmH_2O positive end-expiratory pressure, FiO_2 0.4 and f = 11-13 min^{-1} (Evita 4, Dräger AG, Lübeck, Germany). During the study interval all subjects were hemodynamically stable and no changes were made in their vasoactive drug therapy.

Measurements

All subjects also had a central venous catheter. Arterial pressure (Pa) and Pcv were recorded onto a computer for offline analysis. Pa and Pcv pressure transducers were referenced to the intersection of the anterior axillar line and the 5th intercostal space and re-referenced after a 30° head-up rotation. Airway pressure (Paw) was measured at the proximal end of the endotracheal tube. Beat-to-beat cardiac output (CO) was obtained by Modelflow pulse contour analysis as previously described by us.[10-12] We calibrated the pulse contour CO measurements with 3 therm odilution CO measurements equally spread over the ventilatory cycle.[11]

We have previously described the inspiratory hold method for estimating Pmsf.[5] Briefly, four 12-second inspiratory holds were applied at Paw of 5, 15, 25 and 35 cmH_2O respectively. The resulting Pcv and CO were measured during the plateau phase (between 7-12 seconds of each inspiratory hold maneuver), and the zero CO intercept of the Pcv and CO pairs estimated Pmsf.

Parm estimates of Pmsf[8] assumes Pa and Pv equilibrium following rapid vascular occlusion. We performed a pilot study in nine patients after either cardiac surgery or cardiopulmonary resuscitation to determine the stop-flow time. We measured arterial and venous pressures in the same hand and created upper extremity blood stop-flow using a rapid cuff inflator (Hokanson E20, Bellevue, Washington) to pressures 50 mmHg above systolic pressure and held occlusion for 35-60 seconds (figure 5.1). Measurements were performed three times to assess repeatability (table 5.1). Arterial and venous pressures equilibrated after 25-30 seconds of stop-flow, with a mean difference of -0.73 ± 1.07 mmHg at 30 seconds. Thus, we chose the 30-second value of the arterial pressure for Parm for the present study.

The Pmsa estimate[9] uses a mathematical model of the systemic circulation comprising compliant arterial and venous compartments and resistances to blood flow. The model

parameters are adjusted to match those of the patient's current measured variables, such that Pmsa = a•Pcv + b•Pa + c•CO, where a and b are dimensionless constants (a + b = 1, typically a = 0.96, b = 0.04) and c has the dimensions of resistance and is a function of patient's height, weight and age.

$$c=0.038\bullet(94.17+0.193\bullet age)/(4.5\bullet[0.99^{(age-15)}]\bullet 0.007184\bullet [height^{0.725}]\bullet[weight^{0.425}])$$

Protocol

Measurements were carried out within 2 hours of arrival in the ICU following initial hemodynamic stabilization. To induce changes in volume status, measurements were performed in supine position (baseline), in a 30° head-up tilt (HUT) and again in supine position after 500 ml hydroxyethylstarch (HES 130/0.4) rapid fluid administration (VOL). Measurements of Pa, Pv, Pcv, CO were done during baseline in supine position, 2 minutes after change to HUT and 2-5 minutes after fluid loading with Pmsf, Parm and Pmsa calculated for each step. Repeatability of Parm was determined by two measurements during baseline and after VOL. The study protocol lasted about 60 minutes. All patients completed all steps of the protocol and there were no adverse events.

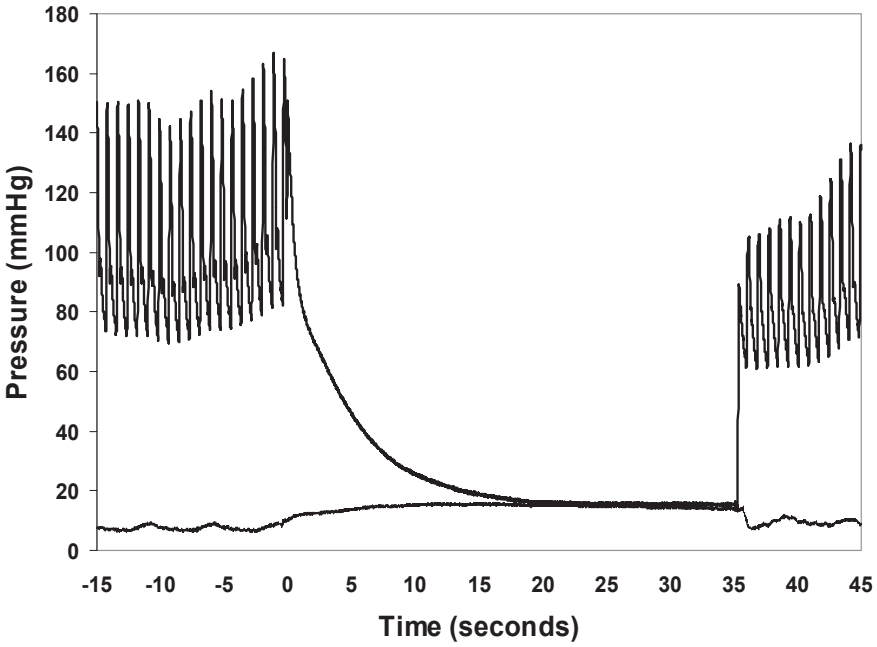

Figure 5.1 Example of an inspiratory hold maneuver

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. Arm vascular occlusion equilibrium pressure (Parm) is taken as the arterial pressure 30 seconds after stop-flow. Note the influence of mechanical ventilation on arterial and venous pressure before and after occlusion.

Statistical analysis

After confirming normal distribution of data with the Kolmogorov–Smirnov test, differences among Pmsf, Parm and Pmsa during baseline, HUT and VOL were analyzed

using paired t-tests. Calculations of bias, precision and limits of agreement (LOA) between Pmsf and both Parm and Pmsa were performed using Bland-Altman analysis with bias reflecting the mean difference between Pmsf and either Parm or Pmsa and precision as the standard deviation (SD) of these differences. After adjustment for the number of observations (n = 33) LOA are defined as bias ± 2.04 • SD. For repeatability of Parm (n = 40) LOA are bias ± 2.02 • SD. The coefficient of variation (COV) is calculated as 100% • SD/mean. Repeatability of Parm was calculated by Bland-Altman analysis using duplicate measurements at baseline and after VOL, which were pooled together. A p-value < 0.05 was considered statistically significant. Unless otherwise stated, data are presented as mean ± SD.

Table 5.1 Pilot study arm equilibrium pressure

Time	Pa			Pv			Pa-Pv		
	Mean	SD	Repeat	Mean	SD	Repeat	Mean	SD	Repeat
sec	mmHg	mmHg	%	mmHg	mmHg	%	mmHg	mmHg	%
15	23.32	2.41	5.45	21.96	2.05	9.20	1.35	2.69	4.89
20	22.11	1.88	6.11	22.12	2.02	9.58	-0.01	1.62	5.52
25	21.42	1.56	6.91	22.06	1.91	9.79	-0.63	1.02	5.18
30	21.08	1.38	6.55	21.81	2.05	9.58	-0.73	1.07	4.55

Effect of time on arterial pressure (Pa), venous pressure (Pv) and the difference between Pa and Pv during upper arm stop-flow. The results of a pilot study in 9 patients are indicated. Repeat, the averaged repeatability of three sequential measurements and SD, standard deviation.

Results

Patient characteristics are presented in table 5.2 and mean hemodynamic data for the protocol in table 5.3. Mean Pa decreased during HUT and was unchanged with VOL. Pcv, CO, Pmsf, Parm and Pmsa decreased during HUT and increased with VOL.
Pmsf, Parm and Pmsa decreased in all patients during HUT (3.4 ± 2.6, 3.0 ± 2.0 and 3.7 ± 2.3 mmHg, p < 0.001, p = 0.001 respectively). VOL was associated with an increase in Pmsf, Parm and Pmsa (8.7 ± 5.3, 8.7 ± 3.8 and 4.5 ± 2.1 mmHg, p < 0.001 all, respectively). Parm was not different from the Pmsf during baseline, HUT or VOL (p = 0.236, p = 0.423 and p = 0.173 respectively). However, Pmsf and Pmsa differed significantly for the three conditions (p < 0.001 all). Pmsf regressed significantly with Parm (figure 5.2A) (slope = 0.944, correlation coefficient (R) = 0.847) and Pmsa (figure 5.2B) (slope = 0.704, R = 0.822).

Baseline Pmsf and Parm did not correlate with Pcv, Pa and pulse pressure. Baseline Pmsa correlated with Pcv (Pearson correlation coefficient R = 0.846, p = 0.001) and with pulse pressure (R = 0.697, p = 0.017). Pmsa did not correlate with mean, systolic and diastolic arterial pressure (p > 0.28 for all).
For the changes in Pmsf, Parm and Pmsa induced by HUT only Pmsa correlated significantly with changes in Pcv (R = 0.931, p < 0.001). For the changes induced by

VOL both Pmsf and Pmsa correlated with changes in Pcv (R = 0.781, p = 0.005 and R = 0.911, p < 0.001). No significant correlation was found with changes in Pa or pulse pressure for changes in Pmsf, Parm and Pmsa.

Table 5.2 Patient Characteristics

		Mean	Range
Age (years)		64	50-80
Gender		9 male, 2 female	
Weight (kg)		86	73-112
Length (cm)		174	158-190
Surgery			
	CABG	9	
	AVR	2	
Respiratory rate (min^{-1})		12	11-13
Tidal volume/predicted ($ml \bullet kg^{-1}$)		9	7-11
PEEP (cm H_2O)		5	

		Number of patients	Range dose ($\mu g \bullet kg^{-1} \bullet min^{-1}$)
Vasoactive medication			
	Dobutamine	4	2-4
	Enoximone	1	2
	Norepinephrine	5	0.01-0.09
	Sodium nitroprusside	1	0.25

CABG, coronary artery bypass grafting; AVR, aortic valve replacement

Table 5.3 Hemodynamic data of patients during baseline, head-up tilt and fluid loading

	Baseline		HUT			+ 500 ml		
	Mean	SD	Mean	SD	p1	Mean	SD	p2
Pa (mmHg)	88.8	17.9	77.3	17.0	< 0.001	97.9	15.3	0.003
Psys (mmHg)	128.5	21.9	107.2	16.9	0.001	143.3	17.7	0.004
Pdias (mmHg)	69.0	17.7	62.4	17.9	0.001	75.2	15.6	0.040
PP (mmHg)	59.5	14.7	44.8	9.9	0.016	68.1	12.1	0.076
Pcv (mmHg)	7.1	2.0	4.4	1.8	0.001	10.4	1.3	0.001
CO ($l \bullet min^{-1}$)	5.8	1.6	4.8	1.2	0.006	7.0	1.7	0.004
HR (min^{-1})	88	14	87	15	0.574	86	10	0.475
Pmsf (mmHg)	19.7	3.9	16.2	3.0	0.001	28.3	3.6	< 0.001
Parm (mmHg)	18.4	3.7	15.4	3.1	0.001	27.1	4.0	< 0.001
Pmsa (mmHg)	14.7	2.7	10.9	2.0	< 0.001	19.2	1.1	< 0.001

Values are means ± SD; n = 11 patients. Pa, mean arterial pressure; Psys, systolic arterial pressure; Pdias, diastolic arterial pressure; PP, pulse pressure; Pcv, central venous pressure; CO, cardiac output; HR, heart rate; Pmsf, mean systemic filling, pressure; Parm arm equilibrium pressure; Pmsa, model analogue mean circulatory pressure. Statistical comparison, p1, paired t-test between baseline and head-up tilt condition (HUT) and p2, paired t-test between baseline and after fluid loading condition (+ 500 ml).

Agreement of methods

For all measurements Pmsf and Parm displayed a non-significant bias of -1.0 ± 3.08 mmHg (p = 0.062), COV of 15% and with LOA of -7.3 and 5.2 mmHg (figure 5.2B). The biases for Pmsf and Parm were: baseline -1.3 ± 3.4, HUT -0.8 ± 3.2, VOL -1.2 ±

2.8 mmHg. For all measurements Pmsf and Pmsa displayed a bias of -6.0 ± 3.1 mmHg ($p < 0.001$), COV of 17% and LOA of -12.4 and 0.3 mmHg (figure 5.3B). The biases for Pmsf and Pmsa were: baseline -5.0 ± 2.8, HUT -5.3 ± 3.2, VOL -8.1 ± 2.7 mmHg. Mean Pmsf, Parm and Pmsa across all three states were 20.9 ± 5.6, 19.8 ± 5.7 and 14.9 ± 4.0 mmHg, respectively.

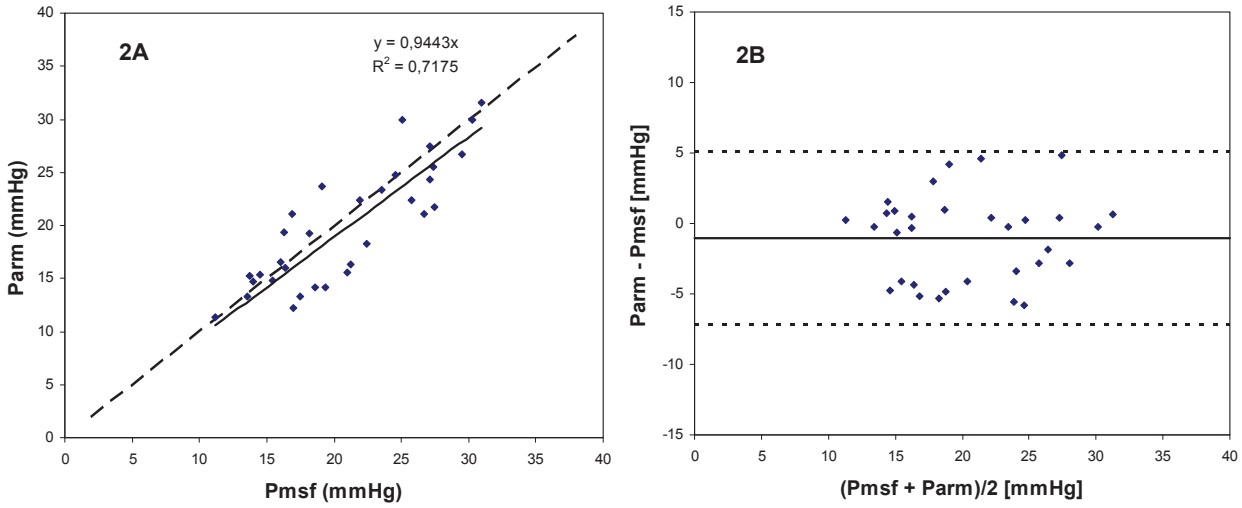

Figure 5.2 Regression (A) and Bland-Altman analysis (B) of arm equilibrium pressure (Parm) and mean systemic filling pressure (Pmsf).
In panel A, the solid line is the regression line and the dashed line is the line of identity. In Panel B, the solid line indicates the bias and the dashed lines are the limits of agreement.

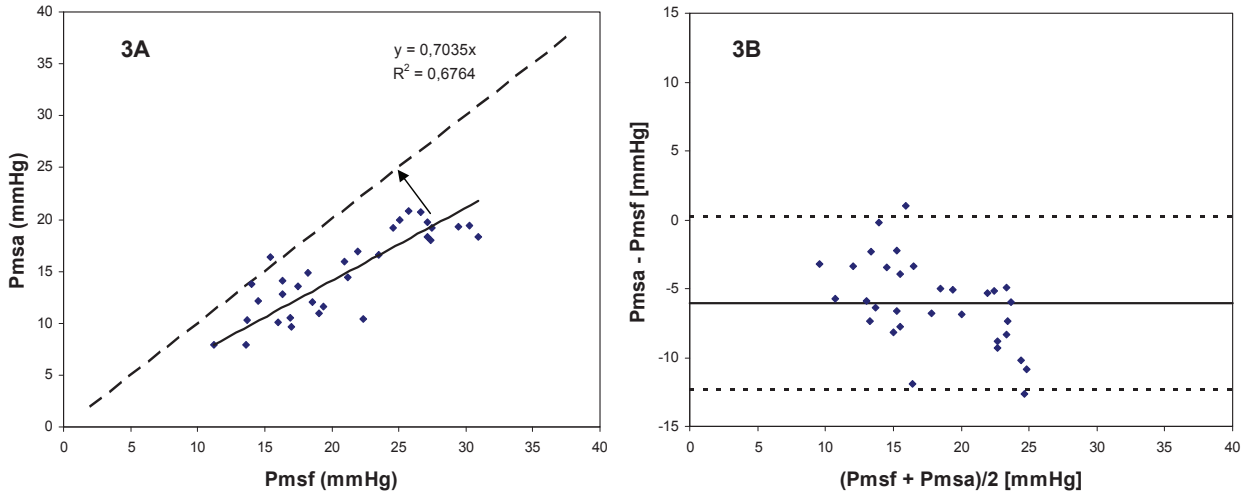

Figure 5.3 Regression (A) and Bland-Altman analysis (B) of model analogue pressure (Pmsa) and mean systemic filling pressure (Pmsf).
In panel A, the solid line is the regression line and the dashed line is the line of identity. In Panel B, the solid line indicates the bias and the dashed lines are the limits of agreement.

Changes of Parm (∆Parm) and Pmsa (∆Pmsa) versus changes in Pmsf (∆Pmsf) are shown in figure 5.4. Both ∆Parm and ∆Pmsa regressed significantly ($p < 0.001$) with ∆Pmsf (slope = 0.85, R = 0.896 and slope = 0.53, R = 0.871, respectively). The cross

tabulation agreement of positive and negative changes in each of the methods for HUT and VOL displayed directionally balanced concordance for all data pairs for both ΔParm and ΔPmsa versus ΔPmsf.

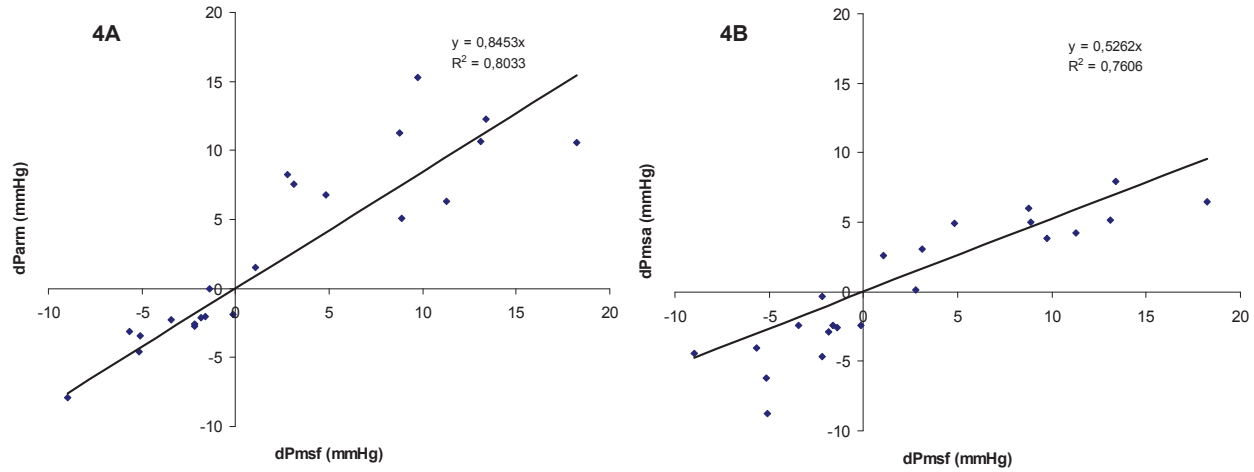

Figure 5.4 Changes in mean systemic filling pressures.
Changes in mean systemic filling pressure by arm equilibrium pressure (Parm) (A) and by model analogue (Pmsa) (B) plotted against changes in mean systemic filling pressure by inspiratory hold procedures (Pmsf). The regression line is indicated by a solid line.

Repeatability of Parm

Bland-Altman analysis for Parm duplicate measurements during both baseline and VOL revealed a bias of 0.03 ± 1.02 mmHg, LOA from -2.04 to 2.09 mmHg and COV of 5%. No difference was found between the first and second of the duplicate Parm measurements (p = 0.915).

Discussion

Our study demonstrates that estimates of Pmsf measured 30 seconds after arm stop-flow (Parm) are interchangeable with Pmsf calculated using inspiratory hold maneuvers in mechanically ventilated postoperative cardiac surgery patients. Furthermore, changes in volume status by HUT and VOL are similarly tracked by Pmsf, Parm and Pmsa. These data support the hypothesis formulated, but not previously validated, by Anderson[8], that during steady-state flow conditions the arm is representative of the entire circulation, such that a rapid vascular occlusion will result in its stop-flow Pa approximating Pmsf. Thus, both Pmsf and Parm can be used at the bedside to measure effective circulating blood volume. Furthermore, Pmsa can reliably tract changes in effective circulating blood volume status.

The use of both Parm and Pmsa has practical advantages over our previously validated inspiratory hold maneuver Pmsf approach. Neither requires positive-pressure breathing or multiple simultaneous measures of Pcv and CO during inspiratory hold maneuvers, and both can be rapidly and repeatedly measured sequentially as treatment or time

progresses. Parm requires only the peripheral arterial catheter. Pmsa requires both central venous and peripheral arterial catheters. Thus, these two novel approaches markedly increase the applicability of assessment of effective circulating blood volume to a broader patient population.

Methodological consideration

Radial artery pressure. Shortly after cardiopulmonary bypass, radial artery pressure can be significantly less than aortic pressure[13-15], but this difference disappears after about 60 minutes, coinciding with hemodynamic stabilization.[13] Our study started after approximately 2 hours after cardiopulmonary bypass in stable patients. Therefore, we believe that mean radial artery pressure reliably reflected central aortic pressure. We recently documented in a porcine model of acute endotoxemia[16] that similar central to regional arterial pulse pressure changes occur. However, the value of Pmsf is not dependent on the calibration of the pulse contour method as long as a linear change in CO is followed by a linear change in CO derived from pulse contour. Indeed, Pcv at CO equal to zero is not even influenced by a calibration factor.

Arm stop-flow procedure. In the pilot stop-flow study described above, we observed that a plateau pressure developed in both arterial and venous pressures after 20-30 seconds as predicted by Anderson.[8] However, a further decrement in both Pa and Pv developed after 35-40 seconds, indicating probable hypoxia-induced vasodilation. We also observed the best repeatability and lowest standard deviations between the arterial and venous pressure at 25-30 seconds of stop-flow, which was the time we used in this study. Furthermore, stop-flow durations longer than 5 minutes are needed to produce reactive hyperemia in the human forearm.[17,18] Thus, if stop-flow maneuvers are limited to < 1 minute, regional blood flow will also normalize after an additional 1 minute.[19] The rapid cuff inflator inflates in less than 0.3 seconds.[20] In this time there is only a brief cessation of venous return prior to arterial stop-flow equal to approximately one heart beat. We expect this overestimation to be negligible because the amount of inflow is small compared to the total distal arm blood volume. Finally, since longer vascular occlusion maneuvers are routinely used to assess dynamic changes in tissue O_2 saturation without complications[21], we feel that this much shorter vascular occlusion maneuver is safe.

Model analogue Pmsa. No clinical evaluation of Pmsa against other methods to measure Pmsf has been done so far. The validity of the Pmsa algorithm was successfully tested using a closed loop control of fluid replacement during continuous hemodiafiltration.[22] Our data support these findings because ∆Pmsf and ∆Pmsa faithfully track each other.

Pmsf. We showed that Modelflow pulse contour CO was interchangeable with pulmonary artery and aortic flow probe derived CO in swine[23], and that Modelflow-

derived Pmsf was interchangeable with flow probe-derived Pmsf with a COV for duplicate measurements of 6.1%. Still, we report mean baseline Pmsf values of 19.7 mmHg in our cardiac surgical patients, which are higher than Pmsf values reported between 7-12 mmHg in animal studies.[24-27] Using the same inspiratory hold technique and pulse contour analysis we found Pmsf values of 10.38 ± 1.09 mmHg in pigs.[23] 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 7.1 mmHg. The pressure gradient for venous return (Pmsf minus Pcv) in our study (12-13 mmHg) is therefore similar to the pressure gradient for venous return in the animal studies. Thus, our Pmsf values are coupled with the increased Pcv. However, high values of Pmsf still predispose to peripheral edema formation.

Jellinek *et al*.[28] and Schipke *et al*.[29] estimated Pmsf in patients during episodes of apnea and ventricular fibrillation, and found a mean Pmsf value of 10.2 mmHg and 12 mmHg, respectively. However, both studies were done on highly anesthetized non-volume resuscitated subjects. Our method of estimation of Pmsf differs considerably from stopping flow by ventricular fibrillation, and our method allows an estimation of Pmsf with intact circulation, applicable in the intensive care unit.[5,30]

Agreement between Parm, Pmsa and Pmsf. We found agreement between Pmsf and Parm (figure 5.2) and ∆Pmsf and ∆Parm were concordant in all interventions (figure 5.4). Therefore, both methods should equally measure and follow changes in effective circulating blood volume. There was poor agreement between Pmsa and Pmsf. The large bias makes the methods non-interchangeable. However, the full concordance between ΔPmsf and ΔPmsa indicates that the Pmsa method is very applicable to track changes in effective circulating blood volume, as indeed was documented by Parkin *et al*. in dialysis patients.[22]

Finally, effective circulating blood volume is a functional measure, not an absolute one. In our study the vasoactive medication was not changed. Changing vasomotor tone will alter unstressed volume, stressed volume and compliance. Any treatment that alters unstressed volume will also alter effective circulating blood volume independent of changes in blood volume, as was demonstrated by Guyton *et al*.[4]

Can either Parm or Pmsa replace the Pmsf method in the bedside assessment of effective circulating blood volume? Based on the established argument of Critchley and Critchley[31], a new method may replace an older established method if the new method itself has errors not greater than the older method. The Parm method showed a non-significant bias when compared to Pmsf. A single measurement of Pmsf has a COV of about 6%.[23] We found a 5% repeatability for Parm. Thus, our data support the argument that Parm may replace inspiratory hold-maneuver generated Pmsf.

A significant bias ($p < 0.001$) was observed between Pmsf and Pmsa, precluding the substitution of raw Pmsa values for Pmsf. However, based on the linearity of Pmsf and

Pmsa (figure 5.3A) one can adjust the Pmsa values using a calibration factor of 1.42 (i.e. the reciprocal of the slope of the regression 0.704). After this calibration is applied to Pmsa values, indicated in figure 5.3A by an arrow from the regression line to the line of identity, the bias reduces to zero. The expected precision of the calculation of Pmsa is approximately 10% (this COV is largely caused by the COV in Pcv measurement, a value of 10 mmHg can be 9.51 or 10.49 mmHg). Although this 10% is higher than the 6% for Pmsf, after recalibration the Pmsa model analogue may replace Pmsf. It must be emphasized that the correction factor only describes our postoperative cardiac surgery population and will require similar validation in other patient groups.

Study limitations. The number of patients included in the study is relatively low. However, we still found a significant difference between Pmsa and Pmsf. With a larger study population the difference between Pmsf and Parm could have become significant. However, the absolute difference of -1.0 mmHg is not clinically relevant. We included patients with preserved left ventricular function, after relatively simple cardiac surgery, and excluded patients with previous myocardial infarction and/or congestive heart failure (New York Heart Association class 4). These patients are known to have markedly increased vascular tone with an associated decreased proportional unstressed vascular volume. Thus, caution needs to be used when extrapolating the accuracy of these comparisons to other patients groups. During the study, we made no changes in medication. Therefore, we cannot report on the values and comparison of Pmsf, Parm and Pmsa during changes in vasoactive medication, which influences vascular elastance, resistance and conductance properties. A fundamental limitation of the Parm technique is the need to measure arterial pressure from a radial arterial site. In patients with sepsis or on high levels of vasopressors, radial artery compliance may not reflect central arterial compliance, although mean Pa remains accurate.[16] Therefore, in these patients it is not clear if Parm or Pmsa will tract Pmsf. Still, under those conditions, the diagnosis of decreased effective circulating blood volume is rarely an issue.

Conclusions

The equilibrium pressure in the arm during stop-flow (Parm) and inspiratory hold maneuver-derived Pmsf values are interchangeable in mechanically ventilated postoperative cardiac surgery patients. Thus, the mean systemic filling pressure can be simply measured at the bedside by measuring arterial pressure during upper arm stop-flow, without the need of inspiratory hold maneuvers or central venous or pulmonary artery catheters. Furthermore, changes in effective circulatory volume are accurately trended by changes in both Parm and Pmsa.

References

1 Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF, Jr., Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354**:**2564-2575.

2 Huang SJ, Hong WC, Han YY, Chen YS, Wen CS, Tsai YS, Tu YK. Clinical outcome of severe head injury using three different ICP and CPP protocol-driven therapies. *J Clin Neurosci* 2006; 13**:**818-822.

3 Brandstrup B, Tonnesen H, Beier-Holgersen R, Hjortso E, Ording H, Lindorff-Larsen K, Rasmussen MS, Lanng C, Wallin L, Iversen LH, Gramkow CS, Okholm M, Blemmer T, Svendsen PE, Rottensten HH, Thage B, Riis J, Jeppesen IS, Teilum D, Christensen AM, Graungaard B, Pott F. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg* 2003; 238**:**641-648.

4 Guyton AC, Polizo D, Armstrong GG. Mean circulatory filling pressure measured immediately after cessation of heart pumping. *Am J Physiol* 1954; 179**:**261-267.

5 Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, Jansen JR. Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. *Crit Care Med* 2009; 37**:**912-918.

6 Jansen JR, Maas JJ, Pinsky MR. Bedside assessment of mean systemic filling pressure. *Curr Opin Crit Care* 2010; 16**:**231-236.

7 Geerts BF, Maas J, de Wilde RB, Aarts LP, Jansen JR. Arm occlusion pressure is a useful predictor of an increase in cardiac output after fluid loading following cardiac surgery. *Eur J Anaesthesiol* 2011; 28**:**802-806.

8 Anderson RM: *The gross physiology of the cardiovascular system*. Tucson, Arizona: Racquet Press; 1993.

9 Parkin WG, Leaning MS. Therapeutic control of the circulation. *J Clin Monit Comput* 2008; 22**:**391-400.

10 Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. *J Appl Physiol* 1993; 74**:**2566-2573.

11 Jansen JR, Schreuder JJ, Mulier JP, Smith NT, Settels JJ, Wesseling KH. A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. *Br J Anaesth* 2001; 87**:**212-222.

12 de Wilde RB, Schreuder JJ, van den Berg PC, Jansen JR. An evaluation of cardiac output by five arterial pulse contour techniques during cardiac surgery. *Anaesthesia* 2007; 62**:**760-768.

13 Stern DH, Gerson JI, Allen FB, Parker FB. Can we trust the direct radial artery pressure immediately following cardiopulmonary bypass? *Anesthesiology* 1985; 62**:**557-561.

14 Pauca AL, Hudspeth AS, Wallenhaupt SL, Tucker WY, Kon ND, Mills SA, Cordell AR. Radial artery-to-aorta pressure difference after discontinuation of cardiopulmonary bypass. *Anesthesiology* 1989; 70**:**935-941.

15 Rich GF, Lubanski RE, Jr., McLoughlin TM. Differences between aortic and radial artery pressure associated with cardiopulmonary bypass. *Anesthesiology* 1992; 77**:**63-66.

16 Hatib F, Jansen JR, Pinsky MR. Peripheral vascular decoupling in porcine endotoxic shock. *J Appl Physiol* 2011; 111**:**853-860.

17 Betik AC, Luckham VB, Hughson RL. Flow-mediated dilation in human brachial artery after different circulatory occlusion conditions. *Am J Physiol Heart Circ Physiol* 2004; 286**:**H442-H448.

18 Katz SD, Rao R, Berman JW, Schwarz M, Demopoulos L, Bijou R, LeJemtel TH. Pathophysiological correlates of increased serum tumor necrosis factor in patients with congestive heart failure. Relation to nitric oxide-dependent vasodilation in the forearm circulation. *Circulation* 1994; 90**:**12-16.

19 Sumner DS: Volume plethysmography in vascular disease: an overview. In *Noninvasive diagnostic techniques in vascular disease*, edn 3rd. Edited by Berstein EF. St. Louis, MO: CV Mosby; 1985:97-118.

20 Chu AC, St Andrew D. Efficient, inexpensive rapid cuff inflator for venous occlusion plethysmography. *Clin Phys Physiol Meas* 1983; 4**:**339-341.

21 Gomez H, Torres A, Polanco P, Kim HK, Zenker S, Puyana JC, Pinsky MR. Use of non-invasive NIRS during a vascular occlusion test to assess dynamic tissue O(2) saturation response. *Intensive Care Med* 2008; 34**:**1600-1607.

22 Parkin G, Wright C, Bellomo R, Boyce N. Use of a mean systemic filling pressure analogue during the closed-loop control of fluid replacement in continuous hemodiafiltration. *J Crit Care* 1994; 9**:**124-133.

23 Maas JJ, Geerts BF, Jansen JR. Evaluation of mean systemic filling pressure from pulse contour cardiac output and central venous pressure. *J Clin Monit Comput* 2011; 25**:**193-201.

24 Guyton AC, Lindsey AW, Abernathy B, Richardson T. Venous return at various right atrial pressures and the normal venous return curve. *Am J Physiol* 1957; 189**:**609-615.

25 Pinsky MR. Instantaneous venous return curves in an intact canine preparation. *J Appl Physiol* 1984; 56**:**765-771.

26 Greene AS, Shoukas AA. Changes in canine cardiac function and venous return curves by the carotid baroreflex. *Am J Physiol* 1986; 251**:**H288-H296.

27 Versprille A, Jansen JR. Mean systemic filling pressure as a characteristic pressure for venous return. *Pflugers Arch* 1985; 405**:**226-233.

28 Jellinek H, Krenn H, Oczenski W, Veit F, Schwarz S, Fitzgerald RD. Influence of positive airway pressure on the pressure gradient for venous return in humans. *J Appl Physiol* 2000; 88**:**926-932.

29 Schipke JD, Heusch G, Sanii AP, Gams E, Winter J. Static filling pressure in patients during induced ventricular fibrillation. *Am J Physiol Heart Circ Physiol* 2003; 285**:**H2510-H2515.

30 Maas JJ, de Wilde RB, Aarts LP, Pinsky MR, Jansen JR. Determination of vascular waterfall phenomenon by bedside measurement of mean systemic filling pressure and critical closing pressure in the intensive care unit. *Anesth Analg* 2012; 114**:**803-810.

31 Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. *J Clin Monit Comput* 1999; 15**:**85-91.

Chapter 6

Arm occlusion pressure is a useful predictor of an increase in cardiac output after fluid loading following cardiac surgery

Bart F. Geerts[1], Jacinta J. Maas[2], Rob B.P. de Wilde[2], Leon P.H.J. Aarts[1] and Jos R.C. Jansen[2]

[1]Department of Anesthesiology, Leiden University Medical Center, The Netherlands,
[2]Department of Intensive Care Medicine, Leiden University Medical Center, The Netherlands

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Abstract

In pharmacological research, arm occlusion pressure is used to study hemodynamic effects of drugs. However, arm occlusion pressure might be an indicator of static filling pressure of the arm. We hypothesised that arm occlusion pressure can be used to predict fluid loading responsiveness. Twenty-four patients who underwent cardiac surgery were studied during their first 2 hours in the ICU. The lungs were ventilated mechanically and left ventricular function was supported as necessary. Arm occlusion pressure was defined as the radial artery pressure after occluding arterial flow for 35 seconds by a blood pressure inflated to 50 mmHg above systolic blood pressure. The cuff was positioned around the arm in which a radial artery catheter had been inserted. Measurements were performed before (baseline) and after fluid loading (500 ml hydroxyethyl starch 6%). Patients whose cardiac output increased by at least 10% were defined as responders. In responders (n = 17), arm occlusion pressure, mean arterial pressure and central venous pressure increased and stroke volume variation and pulse pressure variation decreased. In non-responders (n = 7), arm occlusion pressure and central venous pressure increased, and pulse pressure variation decreased. Mean arterial pressure, stroke volume variation and heart rate did not change significantly. The area under the curve to predict fluid loading responsiveness for arm occlusion pressure was 0.786 (95% confidence interval 0.567-1.000), at a cut-off of 21.9 mmHg, with sensitivity of 71% and specificity of 88% in predicting fluid loading responsiveness. Prediction of responders with baseline arm occlusion pressure was as good as baseline stroke volume variation and pulse pressure variation. In conclusion, arm occlusion pressure was a good predictor of fluid loading responsiveness in our group of cardiac surgery patients and offers clinical advantages over stroke volume variation and pulse pressure variation.

Introduction

Fluid therapy is an important tool in hemodynamic management of patients with suboptimal tissue perfusion. However, excessive fluid resuscitation can result in general and pulmonary oedema, increasing hospital stay and even mortality.[1] In mechanically ventilated patients with a regular heart rhythm, stroke volume variation (SVV) and pulse pressure variation (PPV) perform well as predictors of a clinically significant increase in cardiac output (CO) after fluid administration (i.e. fluid loading responsiveness).[2,3] In vasoplegic patients, both indicators failed.[4,5] Furthermore, SVV and PPV have never been shown to act as a measure of volume status. Therefore, the search for a measure of volume status and a predictor of fluid loading responsiveness which can be used independent of respiratory settings and heart rhythm continues.[6]

A physiological measure of effective volume status is mean systemic filling pressure: the equilibrium pressure anywhere in the circulation under circulatory arrest. The pressure gradient between static filling pressure and central venous pressure (Pcv) is the driving force for venous return and thus for CO. Consequently, increasing mean systemic filling pressure and thereby the pressure gradient for venous return by fluid expansion should improve CO, assuming a constant resistance to venous return and adequate myocardial function.

In pharmacology research, upper arm occlusion pressure (Parm) has been used to determine the effects of drugs on venous capacitance and arterial resistance.[7] We hypothesised that Parm might function as an indicator of mean filling pressure and volume status of the arm. Mean filling pressure of the arm has never been studied as a predictor of fluid responsiveness. We determined Parm by measuring radial artery pressure 30 seconds after occlusion of arterial flow induced by inflating a cuff around the upper arm. The aim of this study was to explore the value of Parm as a predictor of fluid loading responsiveness. This approach is attractive, as it would provide the clinician with a simple, readily available and robust measurement that can be made at the bedside.

Methods

Twenty-four patients undergoing elective cardiac surgery were included after approval of the institutional ethics committee (P06.149, chairman Prof. Dr. F.C. Breedveld, approval date 5 December 2006) and personal informed consent was obtained. All patients had symptomatic coronary artery or valve disease with preserved ventricular function. Patients with aortic aneurysm, extensive peripheral arterial occlusive disease, postoperative severe arrhythmia, postoperative valve insufficiency or the necessity for artificial pacing or use of a cardiac assist device were excluded.

Prior to surgery, a pulmonary artery catheter (Intellicath; Edwards Lifesciences; Irvine, CA, USA) was inserted to measure thermodilution cardiac output (COtd) and Pcv, and a 20 G radial artery catheter was used to measure radial artery pressure. Anaesthesia was maintained with propofol (2.5 $mg \cdot kg^{-1} \cdot h^{-1}$) and sufentanil (0.06-0.20 $\mu g \cdot kg^{-1} \cdot h^{-1}$). The lungs were mechanically ventilated (Evita 4; Dräger, Lübeck, Germany) in a volume-control mode with standard settings (12 $breaths \cdot min^{-1}$, tidal volume 8-10 $ml \cdot kg^{-1} \cdot min^{-1}$, FiO_2 0.4, positive end-expiratory pressure 5 cmH_2O). During the observation period, the patients were kept in the supine position. The use of sedative and vascular medication remained unchanged. No fluids were administered during the observation period outside the study protocol.

Arterial occlusion in the arm was created with a rapid cuff inflator (Hokanson E20, Bellevue, Washington, USA) connected to compressed air and an upper arm cuff. The cuff was positioned around the same arm as that used to measure radial artery pressure. The cuff pressure was increased stepwise to 50 mmHg above the patients' systolic arterial pressure. The duration of arm occlusion was 35 seconds. Arm occlusion pressure (Parm) was calculated as the average value of the radial artery pressure over 1 second at 30 seconds after the start of arm occlusion.

The radial artery pressure was analysed with the "Modelflow" program (FMS, Amsterdam, the Netherlands) to provide beat-to-beat values of cardiac output (COmf) using the pulse contour CO method, calibrated using the averaged value of three COtd measurements spread equally over the ventilatory cycle.[8] From the beat-to-beat values of "Modelflow", SVV, PPV and heart rate (HR) were determined. SVV and PPV were calculated for 5 ventilatory cycles and their values were averaged. Pcv, mean arterial pressure (Pa), COmf and HR were averaged over 30 second intervals.

The study protocol started within 2 hours after arrival of the patients in the ICU and took approximately 15 minutes. Values of Parm, Pcv, Pa, COmf, SVV and PPV were collected before (baseline) and 2-5 minutes after rapid fluid loading. Volume loading was achieved by using 500 ml 6% hydroxyethyl starch solution (Voluven; Fresenius Kabi, Bad Homburg, Germany). Shortly after the end of the study protocol, sedation was stopped and weaning procedures were started. We observed no adverse events during the study protocol and all patients were discharged from the ICU on the first postoperative day.

Statistical analysis

A formal power analysis was not performed because relevant data were not available from the literature. However, study sample size is similar to those in other fluid loading responsiveness studies. We used a Kolmogorov-Smirnov test and a paired t-test. Patients were classified as responders to fluid loading when the increase in COmf was at least

10%. The 10% cut-off corresponds to more than twice the reported precision of the "Modelflow" method (i.e. twice the SD for repeated measurements).[9,10] Consequently, responders experienced a clinically significant change in CO. Prediction of fluid responsiveness for COmf, Parm, Pa, Pcv, SVV and PPV was tested by calculating the area under the receiver operating characteristic (ROC) curve (AUC) together with the 95% confidence intervals (95% CI). A p-value for the difference between the AUC and the reference value of 0.5 (i.e. prediction of responders and non-responders by chance) was calculated. All values are given as mean ± SD. A p-value of less than 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, Illinois, USA) and MedCalc 9 (MedCalc Inc., Mariakerke, Belgium) software.

Results

Twenty-four patients (19 males) aged 64 ± 10 years with a body surface area of 2.0 ± 0.2 m^2 completed the study protocol. Seventeen underwent coronary artery bypass grafting, and seven also underwent repair of one or two valves. Norepinephrine (0.01-0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was used in 16 patients, dobutamine (1.0-7.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in nine and sodium nitroprusside (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in one. The doses of these drugs were not changed during the observation period. Hemodynamic data were distributed normally. Pooled results of hemodynamic variables at baseline and after administration of 500 ml of fluid are shown in table 6.1. After fluid loading with 500 ml, COmf, Parm, Pa and Pcv increased. HR did not change. PPV and SVV decreased.

The population was divided into responders (n = 17) and non-responders (n = 7) (table 6.1). In the responder group COmf, Pa, Pcv and Parm increased and SVV and PPV decreased after fluid loading. Parm increased from 16 to 22 mmHg. In the non-responder group, fluid loading caused Parm to increase from 24 to 30 mmHg. Pcv also increased, PPV decreased, and COmf, Pa, SVV and HR did not change significantly.

Table 6.1 Changes in hemodynamic parameters at baseline and after fluid loading with 500 ml of colloid

	All patients (n = 24)			Responders (n = 17)			Non-responders (n = 7)		
	Baseline	500 ml	p	Baseline	500 ml	p	Baseline	500 ml	p
COmf ($l \cdot min^{-1}$)	5.2 ± 1.3	6.0 ± 1.4	< 0.001	5.1 ± 1.3	6.2 ± 1.4	< 0.001	5.5 ± 1.3	5.7 ± 1.3	0.148
Parm (mmHg)	18.6 ± 7.7	24.3 ± 8.7	< 0.001	16.2 ± 6.3	22.0 ± 7.6	< 0.001	24.3 ± 8.2	29.9 ± 9.1	< 0.001
Mean Pa (mmHg)	82.3 ± 15.6	90.7 ± 16.1	< 0.001	78.9 ± 9.9	88.9 ± 11.2	< 0.001	90.4 ± 23.6	94.8 ± 25.2	0.056
Pcv (mmHg)	9.0 ± 2.6	11.5 ± 2.9	< 0.001	8.6 ± 2.6	10.9 ± 2.5	< 0.001	9.9 ± 2.5	13.0 ± 3.4	0.004
PPV (%)	13.8 ± 9.0	8.0 ± 7.5	< 0.001	14.8 ± 7.8	8.1 ± 6.6	0.001	11.1 ± 11.5	7.7 ± 10.0	0.011
SVV (%)	15.5 ± 10.5	9.3 ± 9.3	0.001	16.5 ± 10.9	8.5 ± 6.5	< 0.001	13.0 ± 9.9	11.2 ± 14.6	0.627
HR (min^{-1})	83 ± 16	83 ± 14	0.908	83 ± 18	83 ± 16	1.000	81 ± 10	82 ± 11	0.860

CO, cardiac output; Parm, arm occlusion pressure; Pcv, central venous pressure; mean Pa, mean arterial pressure; HR, heart rate.

The statistical results of the ROC curves in predicting fluid responsiveness are shown in table 6.2 and figure 6.1. AUCs for baseline COmf, Pa and Pcv were not significantly different from 0.5, or chance. In addition, the sensitivity and/or specificity were low. The results for Parm, PPV and SVV were significantly different from chance (p-values 0.012, 0.001 and 0.010 respectively) with high sensitivity and specificity for cut-off values of 21.8 mmHg or less, at least 7.2 % and at least 8.8 % respectively, indicating that these are reliable predictors of the effect on CO of fluid loading with 500 ml. There were no significant differences between the AUCs of Parm and PPV (difference = 0.0536, 95%CI -0.198 to 0.305, p = 0.676) or Parm and SVV (difference = 0.0446, 95%CI -0.227 to 0.317, p = 0.748).

Discussion

This is the first study in which Parm has been examined as a predictor of the effect of fluid loading on CO. Baseline Parm was significantly lower in the responder group than in the non-responder group. We consider that Parm is a good predictor of fluid responsiveness in our group of mechanically ventilated patients with preserved ventricular function. Simple measurements of radial artery pressure during upper arm occlusion could help to detect patients whose CO will increase after fluid loading.

Table 6.2 Receiver operating characteristics from baseline values as predictors of increase of cardiac output by more than 10% after fluid loading

	AUC	95% CI Lower	Upper	p	Sensitivity	Specificity	Cut-off
COmf (l•min^{-1})	0.588	0.371	0.783	0.507	35	100	≤ 4.0
Mean Pa (mmHg)	0.588	0.371	0.783	0.507	100	29	≤ 91.0
Pcv (mmHg)	0.687	0.427	0.829	0.259	71	57	≤ 9.0
Parm (mmHg)	0.786	0.572	0.924	0.012	88	71	≤ 21.8
PPV (%)	0.844	0.649	0.962	0.001	77	71	≥ 7.2
SVV (%)	0.746	0.544	0.908	0.010	82	86	≥ 8.8

AUC, area under receiver operating curve; 95% CI, 95% confidence interval; p-value, comparison of AUC with AUC = 0.5; COmf, cardiac output; mean Pa, mean arterial pressure; Pcv, central venous pressure; Parm, stop-flow pressure of the arm; PPV, pulse pressure variation; SVV, stroke volume variation.

In our study, the results from ROC analysis indicate that prediction of fluid loading on CO was identified equally using baseline Parm, PPV and SVV, but that prediction was not possible using baseline COmf, Pa or Pcv. Both SVV and PPV have been reported to perform better as predictors of fluid responsiveness than static pressures (Pa, Pcv and pulmonary artery occlusion pressure).[3,11-14] However, SVV or PPV are influenced by ventilator settings as tidal volume[11,15], respiratory rate[16] and also by cardiac function. In patients with reduced cardiac function, SVV is expected to be smaller because stroke volume is obviously limited and consequently ventilator-induced changes in stroke volume will be reduced.[3,12] Reuter *et al.*[15] showed that SVV could still perform as a predictor of fluid loading responsiveness in patients with reduced cardiac function.

In addition, determination of SVV and PPV is possible only if the patient is fully dependent on mechanical ventilation and has a regular cardiac rhythm. SVV and PPV failed to predict the effects of fluid loading on CO accurately in spontaneously breathing patients[4,5] and in mechanically ventilated patients with tidal volumes less than 8 ml·kg^{-1} body weight.[11] In our study, the lungs were ventilated mechanically with tidal volumes ranging from 7 to 12 ml·kg^{-1} predicted body weight. Thus, for some of our patients SVV and PPV may have been less reliable.

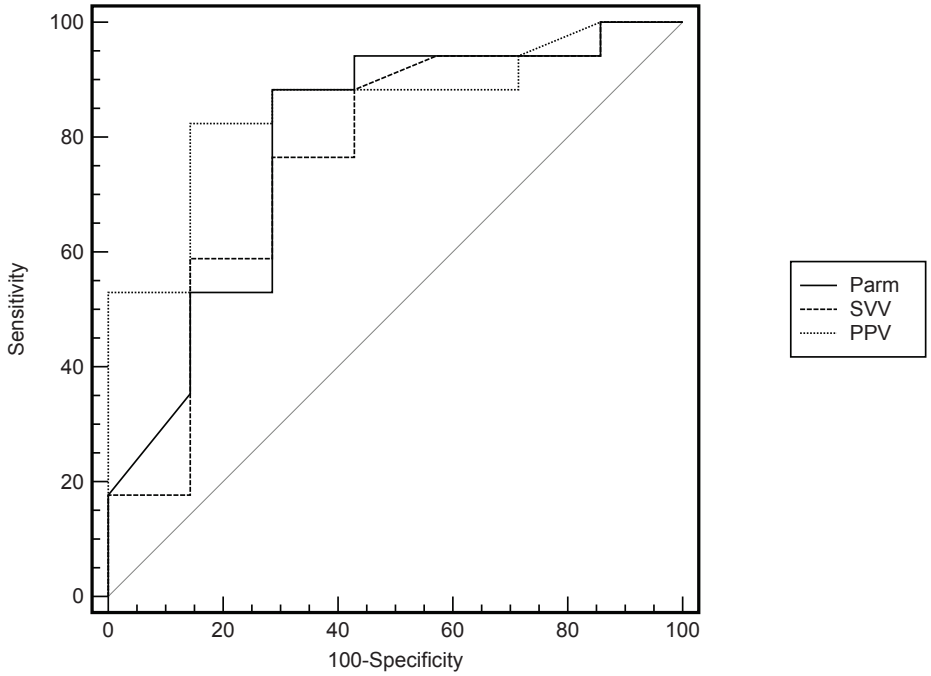

Figure 6.1 Prediction of cardiac output response
Receiver operating characteristic curves comparing the ability of baseline arm occlusion pressure (Parm), pulse pressure variation (PPV) and stroke volume variation (SVV) to discriminate between responders and non-responders. Patients were characterized as responders when cardiac output increased by at least 10% after fluid loading with 500 ml colloid.

In contrast, the Parm technique does not require a specific tidal volume or respiratory rate. To measure Parm with the arm occlusion method, only a peripheral arterial catheter is required. These requirements allow measurement in almost any environment in the operating theatre and ICU. Its application is not limited to sedated and mechanically ventilated patients with a regular heart rhythm. In our study, Parm was a good predictor of fluid loading responsiveness, equal to SVV or PPV in predicting value. However, our study patients were a relatively homogeneous group.

Definition of fluid loading responsiveness

There is no consensus on the amount of fluid or use of measurements to assess fluid loading responsiveness. Fluid amounts between 250 and 1000 ml have been reported.[3-5,17,18] Outcome measures used include CO[4,5,18], stroke volume[17] and stroke volume index.[3] Positive responses have been defined as a change in outcome measure of more than 10%-25%.[3,4,18] We chose a 10% change in pulse contour CO as cut-off

level after fluid loading with 500 ml. The 10% increase in CO was chosen because this increase can be measured accurately with the modified "Modelflow" pulse contour method.[9,10,19,20] This value corresponds with the boundaries used in other studies in which a 10% cut-off was used for 500 ml fluid loading responsiveness.[4,21-23]

Considerations and limitations

The number of patients (n = 24) included in our study is relatively small and the distribution of responders and non-responders is unequal. However, despite this small number of patients, we were able to find highly significant results. Prediction of fluid loading responsiveness by baseline Parm had high sensitivity (71%) and specificity (88%). We theorise that these results can be explained by the similarity between Parm and mean systemic filling pressure. Mean systemic filling pressure is the equilibrium pressure anywhere in the circulation under circulatory arrest, whereas Parm might be seen as the equilibrium pressure of the arm. We hypothesise that mean systemic filling pressure may be largely equal for different vascular compartments of the body because their venous outflow pressures and arterial input pressures are relatively similar. Mean systemic filling pressure is a physiological measure of effective volume status.[24,25] The pressure gradient between mean systemic filling pressure and Pcv is the driving force for venous return and thus for CO. Increasing mean systemic filling pressure and thereby the pressure gradient for venous return by fluid expansion should improve CO, assuming a constant resistance to venous return. If there is hypervolemia or limitation of cardiac function (i.e. the heart operates on the flat part of the Frank-Starling curve) fluid loading will increase Pcv along with mean systemic filling pressure, and venous return will not increase. It is important to stress that we excluded patients with previous myocardial infarction and patients with congestive heart failure (New York Heart Association class 4). Unfortunately, we could not classify our patients because no ejection fraction data were available. Therefore, we must be careful not to extrapolate our results to patients with heart failure. In our patients, a low Parm (< 22 mmHg) predicted fluid loading responsiveness. In the case of cardiac failure or tamponade, Pcv will rise along with Parm during volume administration. This will result in an unchanged pressure gradient for venous return and thus, will fail to induce an improvement in CO. Therefore, we anticipate that our results will be applicable to patients with compromised cardiac function. Rapid increments of Pcv can be seen as a warning of right ventricular limitation.

Conclusions

Arm occlusion pressure can be measured at the bedside. Unlike SVV and PPV, the measurement of Parm is relatively independent of heart rhythm, mechanical or spontaneous breathing, or sedation. Parm is a good predictor of fluid loading responsiveness in cardiac surgery patients with normal ventricular function.

References

1 Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M: A rational approach to perioperative fluid management. *Anesthesiology* 2008; 109**:**723-740.

2 Michard F, Reuter DA: Assessing cardiac preload or fluid responsiveness? It depends on the question we want to answer. *Intensive Care Med* 2003; 29**:**1396.

3 Hofer CK, Muller SM, Furrer L, Klaghofer R, Genoni M, Zollinger A: Stroke volume and pulse pressure variation for prediction of fluid responsiveness in patients undergoing off-pump coronary artery bypass grafting. *Chest* 2005; 128**:**848-854.

4 Perner A, Faber T: Stroke volume variation does not predict fluid responsiveness in patients with septic shock on pressure support ventilation. *Acta Anaesthesiol Scand* 2006; 50**:**1068-1073.

5 Heenen S, De Backer D, Vincent JL: How can the response to volume expansion in patients with spontaneous respiratory movements be predicted? *Crit Care* 2006; 10**:**R102.

6 Magder S: Clinical usefulness of respiratory variations in arterial pressure. *Am J Respir Crit Care Med* 2004; 169**:**151-155.

7 Pang CC: Measurement of body venous tone. *J Pharmacol Toxicol Methods* 2000; 44**:**341-360.

8 Jansen JR, Versprille A: Improvement of cardiac output estimation by the thermodilution method during mechanical ventilation. *Intensive Care Med* 1986; 12**:**71-79.

9 Jansen JR, Schreuder JJ, Mulier JP, Smith NT, Settels JJ, Wesseling KH: A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. *Br J Anaesth* 2001; 87**:**212-222.

10 Critchley LA, Critchley JA: A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. *J Clin Monit Comput* 1999; 15**:**85-91.

11 De Backer D, Heenen S, Piagnerelli M, Koch M, Vincent JL: Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med* 2005; 31**:**517-523.

12 Huang CC, Fu JY, Hu HC, Kao KC, Chen NH, Hsieh MJ, Tsai YH: Prediction of fluid responsiveness in acute respiratory distress syndrome patients ventilated with low tidal volume and high positive end-expiratory pressure. *Crit Care Med* 2008; 36**:**2810-2816.

13 Michard F, Teboul JL: Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation. *Crit Care* 2000; 4**:**282-289.

14 Michard F, Teboul JL: Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest* 2002; 121**:**2000-2008.

15 Reuter DA, Kirchner A, Felbinger TW, Weis FC, Kilger E, Lamm P, Goetz AE: Usefulness of left ventricular stroke volume variation to assess fluid responsiveness in patients with reduced cardiac function. *Crit Care Med* 2003; 31**:**1399-1404.

16 De Backer D, Taccone FS, Holsten R, Ibrahimi F, Vincent JL: Influence of respiratory rate on stroke volume variation in mechanically ventilated patients. *Anesthesiology* 2009; 110**:**1092-1097.

17 Preisman S, Kogan S, Berkenstadt H, Perel A: Predicting fluid responsiveness in patients undergoing

cardiac surgery: functional haemodynamic parameters including the Respiratory Systolic Variation Test and static preload indicators. *Br J Anaesth* 2005; 95**:**746-755.

18 Osman D, Ridel C, Ray P, Monnet X, Anguel N, Richard C, Teboul JL: Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Crit Care Med* 2007; 35**:**64-68.

19 de Wilde RB, Geerts BF, Cui J, van den Berg PC, Jansen JR: Performance of three minimally invasive cardiac output monitoring systems. *Anaesthesia* 2009; 64**:**762-769.

20 de Wilde RB, Schreuder JJ, van den Berg PC, Jansen JR: An evaluation of cardiac output by five arterial pulse contour techniques during cardiac surgery. *Anaesthesia* 2007; 62**:**760-768.

21 Lee JH, Kim JT, Yoon SZ, Lim YJ, Jeon Y, Bahk JH, Kim CS: Evaluation of corrected flow time in oesophageal Doppler as a predictor of fluid responsiveness. *Br J Anaesth* 2007; 99**:**343-348.

22 Wagner JG, Leatherman JW: Right ventricular end-diastolic volume as a predictor of the hemodynamic response to a fluid challenge. *Chest* 1998; 113**:**1048-1054.

23 Solus-Biguenet H, Fleyfel M, Tavernier B, Kipnis E, Onimus J, Robin E, Lebuffe G, Decoene C, Pruvot FR, Vallet B: Non-invasive prediction of fluid responsiveness during major hepatic surgery. *Br J Anaesth* 2006; 97**:**808-816.

24 Guyton AC, Polizo D, Armstrong GG: Mean circulatory filling pressure measured immediately after cessation of heart pumping. *Am J Physiol* 1954; 179**:**261-267.

25 Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, Jansen JR: Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. *Crit Care Med* 2009; 37**:**912-918.

Chapter 7

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

Jacinta J. Maas[1], Michael R. Pinsky[2], Leon P.H.J. Aarts[3] and Jos R.C. Jansen[1]

[1]Department of Intensive Care Medicine, Leiden University Medical Center, The Netherlands,
[2]Department of Critical Care Medicine, University of Pittsburgh, PA, USA,
[3]Department of Anesthesiology, Leiden University Medical Center, The Netherlands

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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.

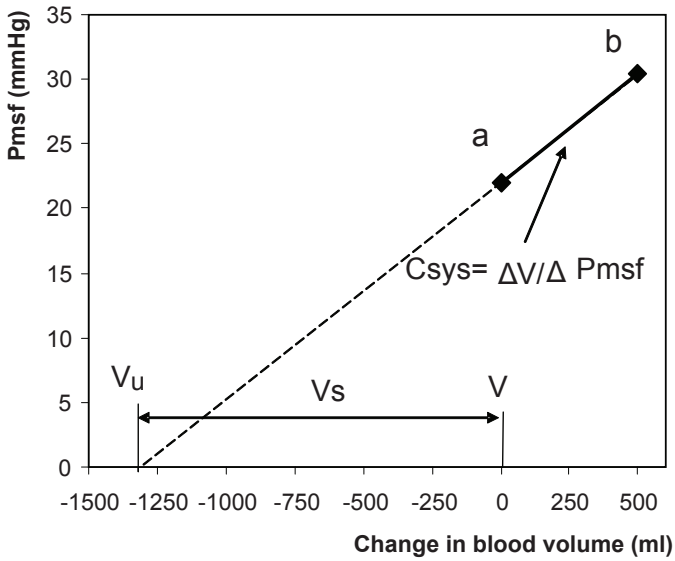

Figure 7.1 Schematic diagram of the determination of systemic compliance and stressed volume
Relationship between change in blood volume and mean systemic filling pressure (Pmsf) for normovolemia (a) and after intravascular volume administration with 500 ml (b). In the figure, systemic compliance (Csys) , 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.

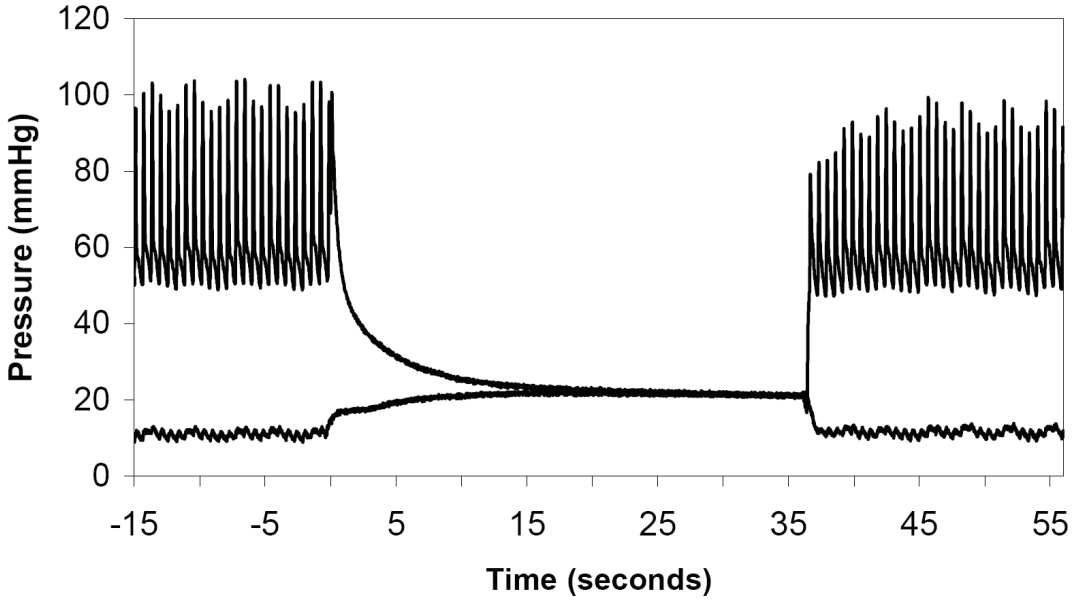

Figure 7.2 Arm occlusion procedure
Representative registration of radial artery pressure and venous pressure before (–15 to 0 seconds), during (0 to 36 seconds) and after the occlusion of the upper arm of a patient. $Pmsf_{arm}$ is the mean arterial pressure 30 seconds after stop-flow. Note the influence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

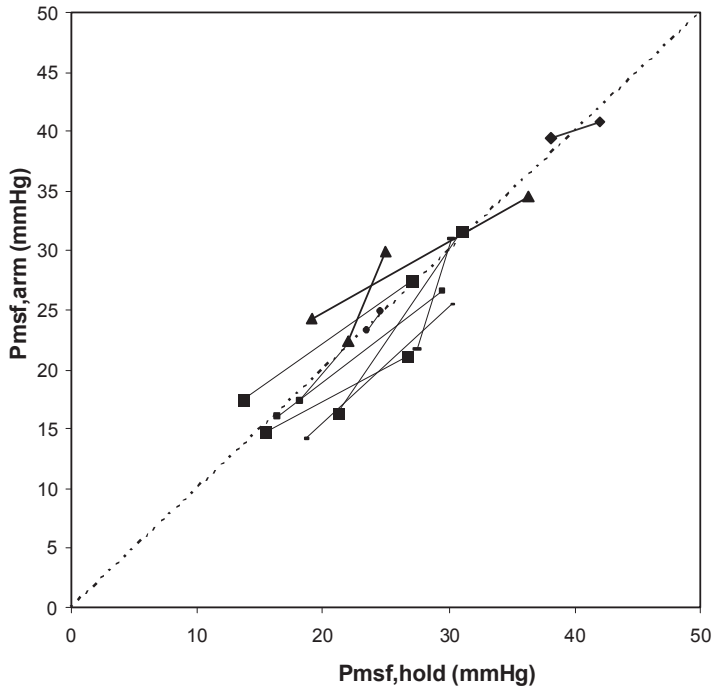

Figure 7.3 Mean systemic filling pressure determined with inspiratory holds and during arm occlusion

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).

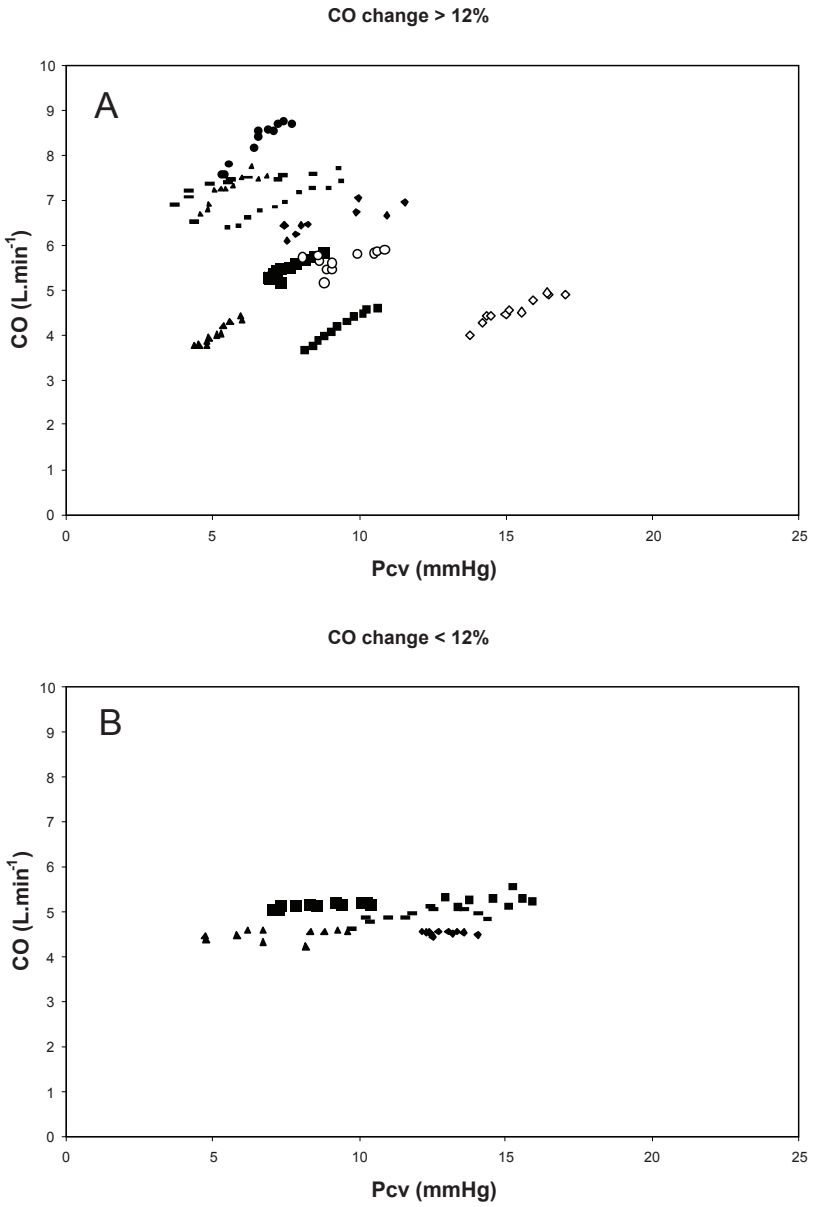

Figure 7.4 Individual cardiac function curves
Individual cardiac function curves for patients with (A) and without (B) a >12% increase in cardiac output (CO) after 500 ml fluid administration. Fluid administration was performed in 10 steps of 50 ml and central venous pressure (Pcv) and CO were measured 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.

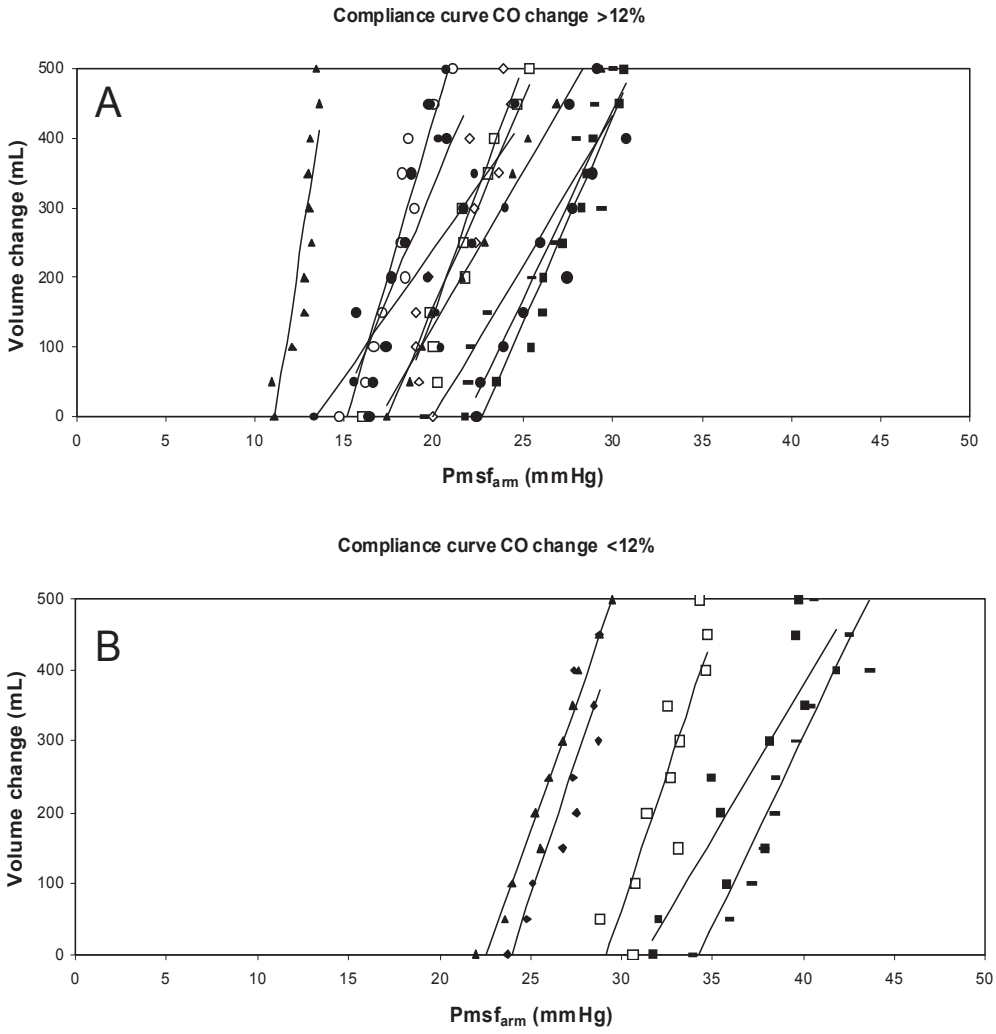

Figure 7.5 Individual volume-pressure curves
Individual volume-pressure curves patients with (A) and without (B) >12% increase in cardiac output (CO) on 500 ml fluid administration. Fluid administration was performed in 10 fluid administration steps of 50 ml and mean systemic filling pressure was measured 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.

References

1 Rothe CF. Mean circulatory filling pressure: its meaning and measurement. *J Appl Physiol* 1993; 74**:**499-509.

2 Magder S, De Varennes B. Clinical death and the measurement of stressed vascular volume. *Crit Care Med* 1998; 26**:**1061-1064.

3 Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, Jansen JR. Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. *Crit Care Med* 2009; 37**:**912-918.

4 Anderson RM: *The gross physiology of the cardiovascular system*. Tucson, Arizona: Racquet Press; 1993.

5 Geerts BF, Maas J, de Wilde RB, Aarts LP, Jansen JR. Arm occlusion pressure is a useful predictor of an increase in cardiac output after fluid loading following cardiac surgery. *Eur J Anaesthesiol* 2011; 28**:**802-806.

6 Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. *J Appl Physiol* 1993; 74**:**2566-2573.

7 Jansen JR, Schreuder JJ, Mulier JP, Smith NT, Settels JJ, Wesseling KH. A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. *Br J Anaesth* 2001; 87**:**212-222.

8 de Vaal JB, de Wilde RB, van den Berg PC, Schreuder JJ, Jansen JR. Less invasive determination of cardiac output from the arterial pressure by aortic diameter-calibrated pulse contour. *Br J Anaesth* 2005; 95**:**326-331.

9 de Wilde RB, Schreuder JJ, van den Berg PC, Jansen JR. An evaluation of cardiac output by five arterial pulse contour techniques during cardiac surgery. *Anaesthesia* 2007; 62**:**760-768.

10 Laboratory values of clinical importance. In *Harrison's Principles of Internal Medicine*, edn 13th. Edited by Isselbacher KJ, Braunwald E, Wilson JD. New York: McGraw-Hill; 1994:2489-2496.

11 Versprille A, Jansen JR. Tidal variation of pulmonary blood flow and blood volume in piglets during mechanical ventilation during hyper-, normo- and hypovolaemia. *Pflugers Arch* 1993; 424**:**255-265.

12 Pinsky MR. Instantaneous venous return curves in an intact canine preparation. *J Appl Physiol* 1984; 56**:**765-771.

13 Chu AC, St Andrew D. Efficient, inexpensive rapid cuff inflator for venous occlusion plethysmography. *Clin Phys Physiol Meas* 1983; 4**:**339-341.

14 Hirakawa S, Ito H, Sahashi T, Takai K, Wada H. Effects of milrinone on systemic capacitance vessels in relation to venous return and right ventricular pump function. *J Cardiovasc Pharmacol* 1992; 19**:**96-101.

15 Lee RW, Gay RG, Lancaster LD, Olajos M, Goldman S. Dog model to study the effects of pharmacologic agents on the peripheral circulation: effects of milrinone. *J Pharmacol Exp Ther* 1987; 240**:**1014-1019.

16 Lee RW, Raya TE, Gay RG, Olajos M, Goldman S. Beta-2 adrenoceptor control of the venous circulation in intact dogs. *J Pharmacol Exp Ther* 1987; 242**:**1138-1143.

17 Pinsky MR, Matuschak GM. Cardiovascular determinants of the hemodynamic response to acute endotoxemia in the dog. *J Crit Care* 1986; 1**:**18-31.

18 Shigemi K, Brunner MJ, Shoukas AA. Alpha- and beta-adrenergic mechanisms in the control of vascular capacitance by the carotid sinus baroreflex system. *Am J Physiol* 1994; 267**:**H201-H210.

19 Greene AS, Shoukas AA. Changes in canine cardiac function and venous return curves by the carotid baroreflex. *Am J Physiol* 1986; 251**:**H288-H296.

20 Caldini P, Permutt S, Waddell JA, Riley RL. Effect of epinephrine on pressure, flow, and volume relationships in the systemic circulation of dogs. *Circ Res* 1974; 34**:**606-623.

21 Shoukas AA, Sagawa K. Control of total systemic vascular capacity by the carotid sinus baroreceptor reflex. *Circ Res* 1973; 33**:**22-33.

22 Ogilvie RI, Zborowska-Sluis D. Effects of nitroglycerin and nitroprusside on vascular capacitance of anesthetized ganglion-blocked dogs. *J Cardiovasc Pharmacol* 1991; 18**:**574-580.

23 Drees JA, Rothe CF. Reflex venoconstriction and capacity vessel pressure-volume relationships in dogs. *Circ Res* 1974; 34**:**360-373.

24 Rose WC, Shoukas AA. Two-port analysis of systemic venous and arterial impedances. *Am J Physiol* 1993; 265**:**H1577-H1587.

25 London GM, Safar ME, Simon AC, Alexandre JM, Levenson JA, Weiss YA. Total effective compliance, cardiac output and fluid volumes in essential hypertension. *Circulation* 1978; 57**:**995-1000.

26 London GM, Safar ME, Weiss YA, Simon CA. Total effective compliance of the vascular bed in essential hypertension. *Am Heart J* 1978; 95**:**325-330.

27 Yamamoto J, Trippodo NC, Ishise S, Frohlich ED. Total vascular pressure-volume relationship in the conscious rat. *Am J Physiol* 1980; 238**:**H823-H828.

28 Lee RW, Lancaster LD, Gay RG, Paquin M, Goldman S. Use of acetylcholine to measure total vascular pressure-volume relationship in dogs. *Am J Physiol* 1988; 254**:**H115-H119.

29 Jacobsohn E, Chorn R, O'Connor M. The role of the vasculature in regulating venous return and cardiac output: historical and graphical approach. *Can J Anaesth* 1997; 44**:**849-867.

Chapter 8

Determination of vascular waterfall phenomenon by bedside measurement of mean systemic filling pressure and critical closing pressure in the ICU

Jacinta J. Maas[1], Rob B.P. de Wilde[1], Leon P.H.J. Aarts[2], Michael R. Pinsky[3], and Jos R.C. Jansen[1]

[1]Department of Intensive Care Medicine, Leiden University Medical Center, The Netherlands,
[2]Department of Anesthesiology, Leiden University Medical Center, The Netherlands,
[3]Department of Critical Care Medicine, University of Pittsburgh, PA, USA

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Abstract

Mean systemic filling pressure (Pmsf) can be determined at the bedside by measuring central venous pressure (Pcv) and cardiac output (CO) during inspiratory hold maneuvers. Critical closing pressure (Pcc) can be determined using the same method measuring arterial pressure (Pa) and CO. If Pcc > Pmsf then a vascular waterfall exists. The purpose of this study was to assess the existence of a waterfall and its implications for the calculation of vascular resistances by determining mean systemic filling pressure (Pmsf) and critical closing pressure (Pcc) at the bedside. In 10 mechanically ventilated postcardiac surgery patients, inspiratory hold maneuvers were performed, transiently increasing Pcv and decreasing Pa and CO to four different steady-state levels. For each patient, values of Pcv and CO were plotted in a venous return curve to determine Pmsf. Similarly, Pcc was determined with a ventricular output curve plotted for Pa and CO. Measurements were performed in each patient before and after volume expansion with 0.5 l colloid and vascular resistances were calculated. For every patient the relationship between the four measurements of Pcv and CO and of Pa and CO was linear. Baseline Pmsf was 18.7 ± 4.0 mmHg and differed significantly from Pcc 45.5 ± 11.1 mmHg; ($p < 0.0001$). The difference of Pcc and Pmsf was 26.8 ± 10.7 mmHg, indicating the presence of a systemic vascular waterfall. Volume expansion increased Pmsf (26.3 ± 3.2 mmHg), Pcc (51.5 ± 9.0 mmHg) and CO (5.5 ± 1.8 to 6.8 ± 1.8 $l \cdot min^{-1}$). Arterial (upstream of Pcc) and venous (downstream of Pmsf) vascular resistance were 8.27 ± 4.45 and 2.75 ± 1.23 $mmHg \cdot min \cdot l^{-1}$; the sum of both (11.01 $mmHg \cdot min \cdot l^{-1}$) was significantly different from total systemic vascular resistance (16.56 ± 8.57 $mmHg \cdot min \cdot l^{-1}$, $p = 0.005$). Arterial resistance was related to total resistance.

In conclusion, vascular pressure gradients in cardiac surgery patients suggest the presence of a vascular waterfall phenomenon, which is not effected by CO. Thus measures of total systemic vascular resistance may become irrelevant in assessing systemic vasomotor tone.

Introduction

In the classical view, cardiac output (CO) is determined by cardiac function (contractility, heart rate), preload, and afterload, despite Guyton's studies on venous return.[1] For short periods, venous return and cardiac output can differ, but averaged over time, venous return must be equal to CO. When the heart is stopped and a large arteriovenous fistula opened, arterial and venous pressures rapidly equilibrate to one pressure, which is called mean systemic filling pressure (Pmsf).[2] Pmsf reflects the mean weighted upstream pressure for venous return to the heart. The difference between Pmsf and right atrial pressure or central venous pressure (Pcv) during steady-state flow represents the pressure gradient for venous return, and if CO is known, one can calculate the resistance to venous return as the ratio of driving pressure to flow. Recently, we demonstrated that it was possible to determine Pmsf at the bedside in mechanically ventilated postcardiac surgery patients with an intact circulation.[3] Applying inspiratory holds of increasing airway pressure levels, Pcv rises and CO declines to a steady-state level (figure 8.1). From the values of Pcv and CO at different airway pressures, a venous return curve can be constructed (figure 8.2). When CO is extrapolated to zero, Pcv will equal Pmsf. Pmsf is in turn determined by stressed blood volume and systemic vascular compliance. Thus, measuring Pmsf allows more insight into variables and mechanisms that control the peripheral circulation in critically ill patients, such as systemic venous resistance (Rvr), stressed and unstressed volume and vascular compliance.[4,5]

During ventricular fibrillation for testing an implantable cardioverter/defibrillator in humans, both Pcv and arterial blood pressure (Pa) were measured and a gap between Pa and Pcv persisted.[6-8] This gap between Pa and Pcv was also found in dogs on cardiac bypass after stopping bypass during 20 seconds.[9] This stop-flow Pa value is termed the arterial critical closing pressure (Pcc). Thus, arterial Pcc is the pressure under which the flow between the arterial and venous side of circulation is stopped despite the persistence of a pressure gradient. Beyond this critical closing locus vascular pressures decrease rapidly to Pmsf. If there is a Pcc to Pmsf pressure gradient, we refer to it as a vascular *waterfall*. Once blood flows over the Pcc edge of the waterfall, the height of the waterfall has no effect on flow. With our technique of inspiratory hold maneuvers to calculate Pmsf as the zero flow intercept of venous pressure, we can also determine Pcc as the zero intercept of Pa. These measurements can be performed at the bedside and in patients with a beating heart and blood flow.[3]

The existence of a vascular waterfall has implications for the calculation of systemic vascular resistance and in our understanding of the determinants of blood flow distribution (10). Traditionally, total systemic vascular resistance is defined as Rsys = [Pa-Pcv]/CO. However, this construct taken from electrical circuit theory of current flowing through a wire presumes a constant pressure decrease from input site to output site, such that increasing output pressure (Pcv) decreases this pressure gradient and thus decreases CO. In the presence of a waterfall (or Starling resistor), there are two separate

pressure gradients, one arterial pressure gradient from the central arterial circuit (Pa) to Pcc and another venous pressure gradient from Pmsf to Pcv. Thus, two separate but in series vascular resistances can be identified, one upstream of Pcc defining arterial resistance (Ra) and one downstream of Pmsf defining Rvr.
The aim of our study was to determine whether there is a Pcc to Pmsf pressure gradient during steady-state flow conditions at the bedside and if so, how changes in CO, due to intravascular volume loading might affect it. We hypothesized that intravascular fluid loading will increase Pmsf and CO but not change Pcc.

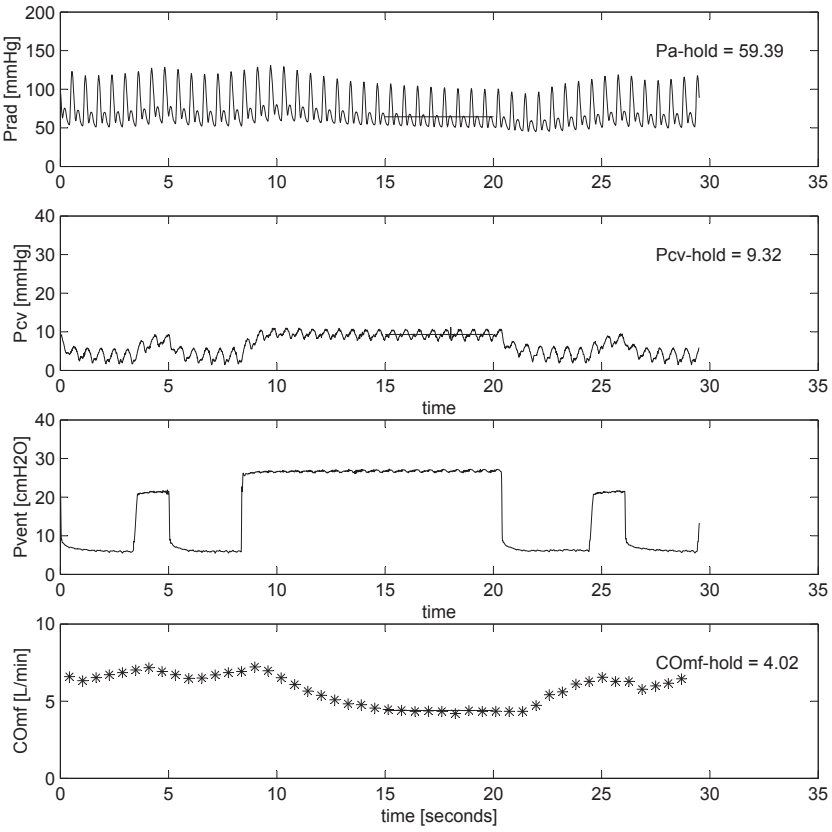

Figure 8.1 Example of an inspiratory hold maneuver
Effects of an inspiratory hold maneuver on arterial pressure (Prad), central venous pressure (Pcv), airway pressure (Pvent) and beat-to-beat cardiac output (COmf). Preceding the hold maneuver the effects of a normal ventilatory cycle are plotted. Note the rapid restoration to baseline (within 4 seconds).

Methods and materials

Patients. Ten postoperative patients after aortic valve replacement, mitral valve surgery, or coronary artery bypass surgery instrumented with a pulmonary artery catheter were included in the study. The study was approved by the University Medical Ethics Committee of Leiden University and the University of Pittsburgh, whereas the study was performed in Leiden University Medical Center. Written informed consent was obtained from the patients. Patients with congestive heart failure (New York Heart Association class 4), postoperative valvular insufficiency, aortic aneurysm or extensive

peripheral arterial vascular disease, postoperative arrhythmia, or intra-aortic balloon counter-pulsation were excluded.
Postoperative anesthesia was maintained with propofol and sufentanil. Patient's lungs were mechanically ventilated (Evita 4 servo ventilator; Dräger, Lübeck, Germany) in synchronized intermittent mandatory ventilation mode with tidal volumes of 6 to 8 $ml \cdot kg^{-1}$ and a respiratory rate of 12 to 14 $breaths \cdot min^{-1}$ to achieve normocapnia (arterial P_{CO2} between 40 and 45 mmHg). A positive end-expiratory pressure of 5 cmH_2O and a fraction of inspired oxygen of 0.4 were applied. During the study period, all patients were hemodynamically stable and no changes in vasoactive medication were made.

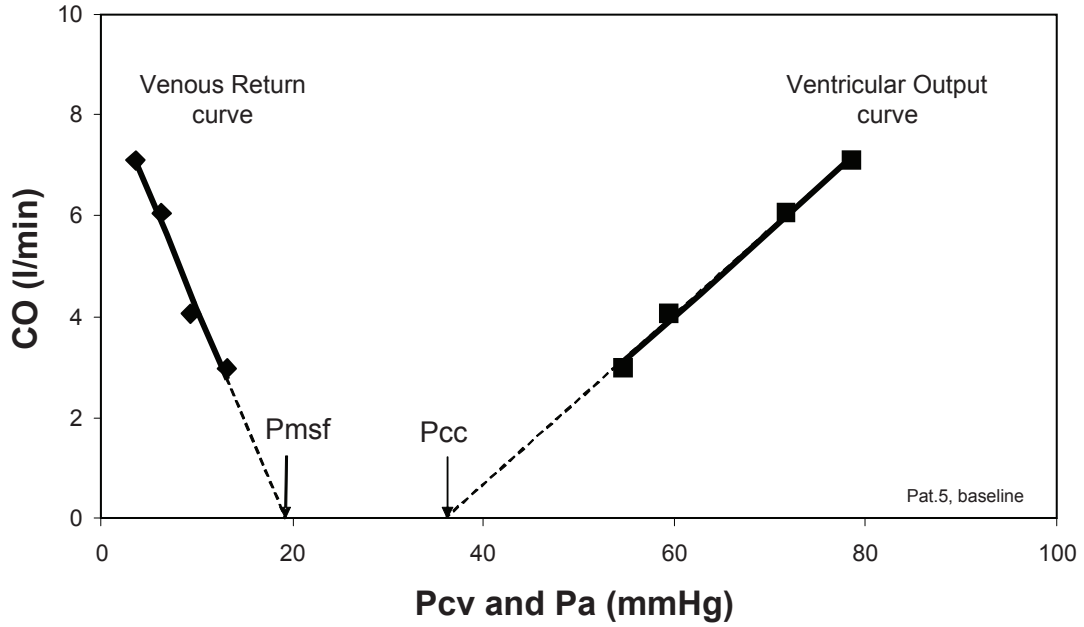

Figure 8.2 Venous return curve and cardiac function curve
Relationship between cardiac output (CO) and central venous pressure (Pcv) in a venous return curve and between CO and arterial blood pressure (Pa) in a ventricular output curve for an individual patient. Extrapolation to the zero flow intercept leads to mean systemic filling pressure (Pmsf) for the venous return curve and to critical closing pressure (Pcc) for the ventricular output curve.

Measurements. Arterial blood pressure was monitored via a 20-gauge, 3.8 cm long fluid-filled radial artery catheter. Pcv was measured with a central venous catheter inserted in the right internal jugular vein (MultiCath 3 venous catheter; Vigon GmbH & Co., Aachen, Germany). Both were connected to pressure transducers (PX600F; Edwards Lifesciences, Irvine, CA) and referenced to the intersection of the anterior axillary line and the fifth intercostal space. Airway pressure was measured at the entrance of the endotracheal tube and balanced at zero level against ambient air. CO was obtained beat-to-beat by Modelflow pulse contour analysis as previously described and validated.[11-13]

Experimental protocol. Within 1 hour after arrival at the intensive care unit, the protocol started and mechanical ventilation was switched from synchronized intermittent mandatory ventilation to airway pressure release ventilation to allow external control

of the ventilator to perform inspiratory hold maneuvers. Respiratory rate, fraction of inspired oxygen, positive end-expiratory pressure, and tidal volumes were kept unchanged. No spontaneous breathing efforts were observed during the study. Pa and Pcv were recorded at a sample frequency of 100 Hz and 0.2 mmHg resolution on computer disk for offline data analysis. We calibrated the pulse contour CO measurements with 3 thermodilution CO measurements equally spread over the ventilatory cycle. During the observation period, no changes were made in ventilatory settings, sedation and vasoactive medication.

Steady-state Pa, Pcv and CO were measured over the last 3 seconds of 12-second inspiratory hold maneuvers at plateau pressures of 5, 15, 25 and 35 cmH_2O, as we previously described.[3] With increasing airway pressure, Pcv increases and CO and Pa decrease to a steady state between 7 and 12 seconds after start of the inspiratory hold (figure 8.1). The resulting values of Pcv were plotted against CO in a venous return curve for the four inspiratory hold procedures and a linear regression line was fitted through these data points (figure 8.2). Similarly, in a ventricular output curve, Pa was plotted against CO for the same inspiratory hold maneuvers (figure 8.2). Measurements were done during baseline conditions and after administration of 500 ml hydroxyethylstarch (130/0.4) over 15 minutes to assess changes in CO, Pcc, and Pmsf after volume expansion for each patient.

Data analysis and statistics. Pmsf was defined as the zero flow intercept of the venous return curve as previously described.[3] Pcc was the extrapolation of Pa to zero flow in the ventricular output curve (figure 8.2). For each patient linear, regressions for the four pairs of Pcv and CO, and of Pa and CO were fitted using a least-squares method. Lilliefors method was used to test for normality. The pairwise differences for Pcc at baseline and after intravascular fluid administration and the pairwise differences for Rsys and the sum of Rvr and Ra, were inconsistent with normal distribution. The other pairwise data were not inconsistent with normal distribution ($p > 0.05$). The differences between Pmsf and Pcc were tested by a paired Student t-test. A significant difference between Pmsf and Pcc was considered consistent with a vascular waterfall. Systemic arterial vascular resistance was defined as Ra = [Pa-Pcc]/CO, and systemic venous vascular resistance as Rvr = [Pmsf-Pcv]/CO. Total systemic vascular resistance was calculated as Rsys = [Pa-Pcv]/CO. The difference between Rsys and the sum of Ra and Rvr, reflecting the hydrostatic energy loss across the vascular waterfall, was tested with a Wilcoxon signed rank test. Linear regression between Ra and Rsys include 95% confidence interval (CI) for bias and slope, together with the Pearson correlation. The changes in CO, Pmsf, Pcc, the gap between Pcc and Pmsf, Ra, Rvr and the slopes of both the venous return and the ventricular output curves induced by intravascular volume expansion were tested by paired Student t-tests or Wilcoxon signed rank test as indicated by the Lilliefors test for normality. Data are presented as mean ± SD. Differences with a $p < 0.05$ were considered significant.

Results

Ten patients were included in the study. Patient characteristics are shown in table 8.1. The data of the venous return and ventricular output curves for all individuals before and after 500 ml intravascular fluid administration are shown in table 8.2. The goodness of fit of these curves through the data obtained from the inspiratory hold maneuvers, given by R^2, is remarkably high. The slopes of the venous return and ventricular output curves as well as the values for Pmsf and Pcc ranged over 2:1 ratios indicating significant different hemodynamic conditions for individual patients.

Table 8.1 Patient Characteristics

No	Gender	Age (years)	Weight (kg)	Length (cm)	Surgery	Inotropics ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	Propofol ($mg \cdot h^{-1}$)	Sufenta ($\mu g \cdot h^{-1}$)
1	M	60	80	172	CABG		300	15
2	M	57	78	169	CABG	Dobu 2	300	15
3	M	79	78	174	AVR	Dobu 5	200	10
4	M	50	90	190	AVR	NPN 0.25	300	15
5	M	80	90	172	CABG	Nor 0.01	200	10
6	F	64	83	167	CABG	Nor 0.04, Dobu 3	200	10
7	M	50	112	183	CABG	Nor 0.06	500	15
8	M	71	73	179	CABG	Nor 0.09, Dobu 4	120	5
9	M	75	95	173	CABG	Nor 0.02	200	10
10	M	56	69	175	MVP+TVP		300	10
mean		64	85	175			259	12
SD		11	12	7			107	3

CABG, coronary artery bypass grafting; AVR, aortic valve replacement; MVP+TVP, mitral and tricuspid valve repair; Dobu, dobutamine; NPN, nitroprusside sodium; Nor, norepinephrine; SD, standard deviation.

Table 8.2 Venous return and ventricular output curves for all individuals before and after 500 ml intravascular fluid administration

	Baseline						After 500 ml fluid loading					
No	Slope Pmsf ($l \cdot min^{-1} \cdot mmHg^{-1}$)	R^2	Pmsf (mmHg)	Slope Pcc ($l \cdot min^{-1} \cdot mmHg^{-1}$)	R^2	Pcc (mmHg)	Slope Pmsf ($l \cdot min^{-1} \cdot mmHg^{-1}$)	R^2	Pmsf (mmHg)	Slope Pcc ($l \cdot min^{-1} \cdot mmHg^{-1}$)	R^2	Pcc (mmHg)
1	-0.548	0.996	15.5	0.145	0.949	38.7	-0.371	0.983	28.7	0.284	0.987	60.6
2	-0.440	0.995	21.2	0.195	0.894	37.3	-0.612	0.999	24.4	0.245	0.995	42.5
3	-0.663	0.989	16.0	0.132	0.997	38.4	-0.469	0.987	27.4	0.168	0.995	45.5
4	-0.198	0.997	19.6	0.054	0.990	66.1	-0.193	0.999	29.0	0.064	0.941	61.8
5	-0.454	0.994	19.2	0.170	0.996	36.4	-0.429	0.988	19.6	0.164	0.987	43.3
6	-0.587	0.937	15.3	0.166	0.997	58.2	-0.482	0.972	24.3	0.138	0.973	62.5
7	-0.565	0.995	14.1	0.130	0.996	38.5	-0.434	0.769	27.8	0.186	0.736	46.4
8	-0.459	0.971	28.0	0.262	0.978	53.8	-0.491	0.985	30.5	0.542	0.977	59.0
9	-0.257	0.997	19.2	0.091	0.956	52.4	-0.373	0.956	24.2	0.169	0.965	53.9
10	-0.211	0.911	18.6	0.055	0.992	35.3	-0.224	0.997	27.0	0.089	0.881	39.5
mean	-0.438	0.978	18.7	0.140	0.974	45.5	-0.408	0.964	26.3	0.205	0.944	51.5
SD	0.164	0.030	4.0	0.064	0.033	11.1	0.125	0.070	3.2	0.135	0.081	9.0

Pmsf, mean systemic filling pressure; Pcc, critical closing pressure; SD, standard deviation.

Baseline measurements. In all patients, a linear relationship between CO and Pcv and between CO and Pa was found, with an averaged slope of -0.438 ± 0.164 ($l \cdot min^{-1} \cdot mmHg^{-1}$) and of 0.140 ± 0.064 ($l \cdot min^{-1} \cdot mmHg^{-1}$), respectively. In table 8.3, the hemodynamic values before and after intravascular volume administration are shown. Baseline mean Pmsf was 18.7 ± 4.0 mmHg and mean Pcc was 45.5 ± 11.1 mmHg. In every patient, a pressure gap between Pcc and Pmsf was observed (range 16.1–46.48 mmHg). The values of Pmsf and Pcc were significantly different ($p < 0.0001$) with a mean difference at baseline of 26.8 ± 10.7 mmHg, indicating the presence of a vascular waterfall. Ignoring the presence of a waterfall, total systemic vascular resistance (Rsys) would have been calculated as 16.56 ± 8.57 $mmHg \cdot min \cdot l^{-1}$. However, considering a waterfall, Ra was 8.27 ± 4.45 $mmHg \cdot min \cdot l^{-1}$, Rvr was 2.75 ± 1.23 $mmHg \cdot min \cdot l^{-1}$, and the sum of Ra and Rvr was 11.01 ± 5.52 $mmHg \cdot min \cdot l^{-1}$, which is significantly different from Rsys ($p = 0.005$) and reflects at least a 30% hydrodynamic energy loss across the vascular waterfall.

Table 8.3 Hemodynamic data of patients during baseline condition and after intravascular volume expansion

	Baseline Mean	SD	Hyper Mean	SD	p
Pa (mmHg)	85.5	15.4	91.4	13.5	0.059
Pcv (mmHg)	4.8	1.8	7.1	2.6	0.011
COmf ($l \bullet min^{-1}$)	5.5	1.8	6.8	1.8	0.010
HR (min^{-1})	91	13	88	10	0.149
SV (ml)	61.5	20.2	78.5	18.7	0.012
PP (mmHg)	61.0	15.0	75.4	15.9	0.001
Pcc (mmHg)	45.5	11.1	51.5	9.0	0.013[a]
Pmsf (mmHg)	18.7	4.0	26.3	3.2	< 0.001
Slope VO ($l \bullet min^{-1} \bullet mmHg^{-1}$)	0.140	0.064	0.205	0.135	0.046
Slope VR ($l \bullet min^{-1} \bullet mmHg^{-1}$)	-0.438	0.164	-0.408	0.125	0.450
Pcc-Pmsf (mmHg)	26.8	10.7	25.2	8.2	0.454
Pmsf-Pcv (mmHg)	13.8	4.0	19.2	3.1	< 0.0001
Rsys ($mmHg \bullet min \bullet l^{-1}$)	16.56	8.57	13.49	5.77	0.028
Ra ($mmHg \bullet min \bullet l^{-1}$)	8.27	4.45	6.54	3.67	0.008
Rvr ($mmHg \bullet min \bullet l^{-1}$)	2.75	1.23	3.00	1.01	0.350

Values are means ± SD; n = 10 patients. Pa, mean arterial pressure; Pcv, central venous pressure; CO, cardiac output; HR, heart rate; SV, stroke volume; PP, pulse pressure (systolic pressure – diastolic pressure); Pcc, critical closing pressure Pmsf, mean systemic filling pressure; VO, ventricular output curve; VR, venous return curve; Rsys, total systemic vascular resistance; Ra, arterial vascular resistance Rv, venous vascular resistance. Statistical comparison, p, paired t-test between baseline and volume expansion; [a] Wilcoxon signed rank test.

Volume loading. Pmsf, Pcv, Pcc and CO increased with intravascular volume administration as did the pressure gradient for venous return (Pmsf-Pcv) (table 8.3). The pressure gradient Pcc-Pmsf did not change significantly with intravascular volume administration. The slope of the ventricular output curve declined ($p = 0.046$) reflecting the decrease in Ra, whereas the slope of the venous return curve and its calculated Rvr

did not change significantly.
We investigated a possible relation between Rsys and Ra, because Rsys and Ra significantly changed whereas Rvr did not change with intravascular fluid administration. The results of individual data are indicated in figure 8.3. The relation between Ra and Rsys (Ra = 0.52(95%CI 0.44-0.62) • Rsys–0.55 (95%CI -2.11 +1.02), Pearson correlation 0.945) appeared highly significant.

Discussion

This study shows that both Pmsf and Pcc can be determined at the bedside in intensive care patients with intact dynamic circulation. The pressure gap of 26.8 ± 10.7 mmHg between Pcc and Pmsf indicates that a waterfall phenomenon is likely to be present. These data are consistent with the findings of several animal studies[14,15] as well as those reported in humans.[6-8] However, the human studies were performed in patients during ventricular fibrillation and total circulatory arrest. The duration of circulatory arrest in humans ranged from 7.5 seconds[7] to 30 seconds.[8] Schipke *et al.*[6] reported a mean Pcc of 24.2 ± 5.3 mmHg during cardiac arrest after 13 ± 2 seconds. Kottenberg-Assenmacher *et al.*[8] found values of Pcc of 26.6 and 23.9 mmHg after 15 and 30 seconds of cardiac arrest. However, using a predictive model on heart beating data, i.e. on the aortic pressure decay, these authors found a significant higher value (53 ± 15.6 mmHg). The Pcc value of 45.5 ± 11.1 mmHg in our study is in the range Kottenberg-Assenmacher *et al.*[8] found on heart beating data, but is substantially higher than values found during cardiac arrest. The discrepancy between heart beating and cardiac arrest values can be explained by a leak in the waterfall. As long as the volume supply exceeds the volume loss, the height of the waterfall will be intact. This is the case in the intact circulation, which was preserved in our study. However, when supply becomes less than the volume loss, as is the case during a cardiac arrest, the drain of arterial blood through those vascular waterfalls with lower local Pcc values will result in a reduction of measured Pcc.

Despite the difference of absolute values of Pcc for the intact circulation versus circulatory arrest, the observed pressure gap of 26.8 mmHg between Pcc and Pmsf in our patients is remarkably similar to the values Jellinek, Schipke and Kottenberg-Assenmacher *et al.* report.[6-8] In animal stop-flow studies, the pressure gap between arterial and venous pressure was already well known and the reason for using a pump or large arteriovenous fistula to move blood from the arterial compartment to the venous compartment to achieve equilibrium pressure during the stop-flow period.[2] The implications of a Pcc significantly greater than Pmsf are that our interpretation of vasomotor tone and vascular resistance must change.

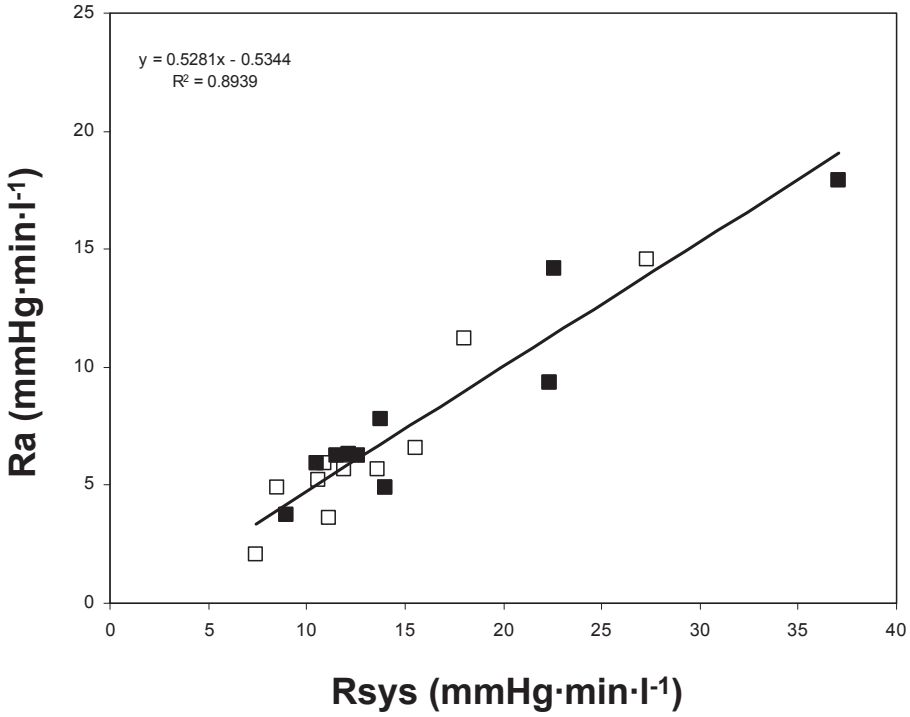

Figure 8.3 Relationship between arterial vascular resistance (Ra) and total systemic vascular resistance (Rsys)
Ra is calculated as (mean arterial pressure - critical closing pressure)/cardiac output. Rsys is calculated as (mean arterial pressure – central venous pressure)/cardiac output. The filled squares represent measurements at baseline, the open squares represent measurements after volume loading.

Vascular resistance. Classically, Rsys is calculated as the ratio of the pressure difference between mean Pa and mean Pcv, and CO. Kottenberg-Assenmacher *et al.*[8] already pointed out that Rsys has to be partitioned into an Ra and an Rvr, or rather the resistance before and after the waterfall. Our study extends their findings. We were able to calculate arterial resistance as Ra = [Pa-Pcc]/CO and venous resistance as Rvr = [Pmsf-Pcv]/CO. Based on our findings, we conclude that Rsys is an entity that does not exist in vascular physiology and calculated Rsys overestimates the sum of Ra and Rvr. In figure 8.4, a dotted line is plotted directly after the waterfall, because it is not known whether the waterfall ends directly in vascular lacunae (where Pmsf is located). Furthermore, we have no information about the presence of parallel blood streams to the waterfall. However, if the clinician at the bedside wants to understand if arterial tone is increased, decreased, or normal, and how it changes in response to time and treatment, then he or she needs to measure CO, Pa and Pcc. Ra can be calculated directly from CO, Pa, and Pcc (figure 8.3). Measurement of Pcc and Pmsf and calculation of Ra and Rvr allows us to understand physiology and the point of action of vasoactive medication and in future could guide the clinician in the hemodynamic treatment of critically ill patients.

Influence of volume expansion. The response to volume loading is an increase in Pmsf, while a stable value of Pcc is expected. With the analogy of a lake filled by a waterfall,

adding volume will increase the filling pressure below the waterfall, but the pressure at the edge of the waterfall would not be changed. Surprisingly, Pcc did increase after volume expansion, although less than Pmsf did. We do not have an explanation for this finding. Importantly, there was an increase in both Pmsf and the pressure gradient for venous return with intravascular volume expansion, resulting in an increase in CO. Resistance to venous return did not change with fluid expansion in our study. Although we do not have a solid explanation for the decrease in Ra with intravascular volume administration, vascular stress-relaxation associated with increased flow and baroreceptors-induced decreased sympathetic tone are potential mechanisms for this phenomenon. We saw only a minor decrease in heart rate after intravascular volume administration, whereas pulse pressure (systolic blood pressure - diastolic blood pressure) increased less (24%) than stroke volume increased (30%). These finding are also consistent with baroreceptors-induced arterial vasodilation.

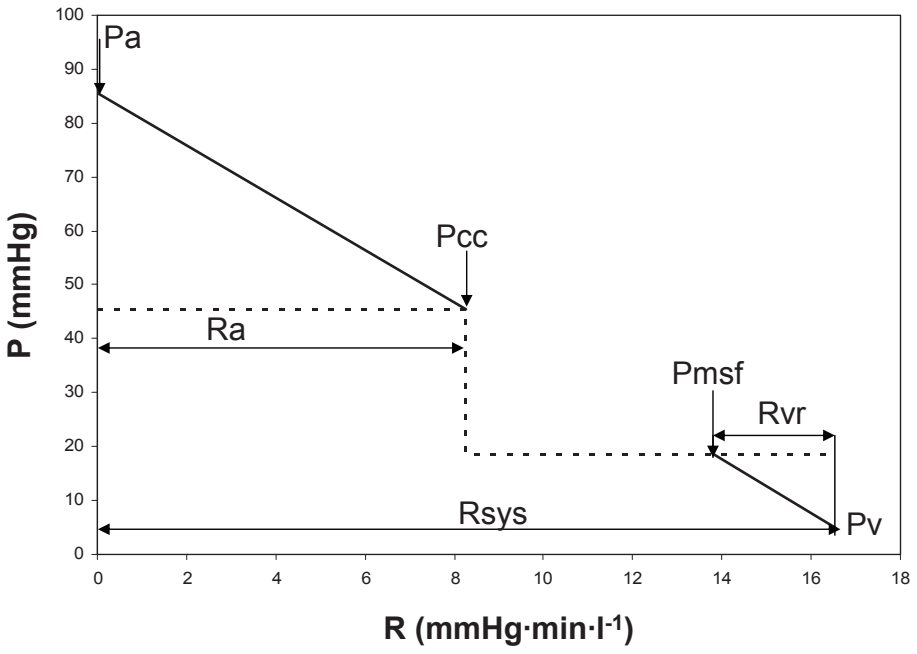

Figure 8.4 Schematic graph of the pressure trend from arterial blood pressure (Pa) to critical closing pressure (Pcc), mean systemic filling pressure (Pmsf) to venous pressure (Pv)
The pressure drop between Pcc and Pmsf (the vascular waterfall) shows that total systemic vascular resistance (Rsys) does not exist. Instead vascular resistance can be divided in a resistance upstream of the waterfall (arterial resistance Ra) and downstream (venous resistance Rvr). The dotted line between the waterfall and Pmsf indicates that it is unknown how close to the waterfall Pmsf is located.

Methodological issues. For the inspiratory hold method to define vascular state, several assumptions are made. First, a steady state in which venous return equals CO must be created. Figure 8.1 demonstrates that during an inspiratory hold, a plateau in Pcv, Pa, and CO is reached during the last seconds of the inspiratory pause. Second, measurements must be done before autonomic reflexes occur. We did not observe any change in heart rate, Pcv, or Pa during the last seconds of the inspiratory hold. This might be caused by

the use of propofol and sufentanil, which can depress baroreceptor reflexes.[16-18] Third, a linear relationship between CO and Pcv and between CO and Pa is needed to be able to extrapolate to the point of zero flow. The presence of such linear relations was, indeed, shown by Guyton[1], in several animal studies[19-22] and in our study in humans.[3] Before concluding that there is a waterfall phenomenon, other possible explanations for the pressure gap between Pcc and Pmsf need to be addressed. An underestimation of Pmsf by our method is unlikely. On the contrary, the positive intrathoracic pressure in theory can increase effective circulatory volume by squeezing blood from the liver and the pulmonary vessels.[23] An overestimation or underestimation of Pcc could be possible, because of the extrapolation of the CO-Pa curve beyond the data range (figure 8.2). However, during the inspiratory holds of 35 cmH_2O in some patients cardiac output reached very low values during a few seconds, almost abolishing the need for extrapolation. However, none of these potential arguments explain the large pressure gap between Pcc and Pmsf of 26.8 mmHg.

Waterfalls, where are they located and what is their function? The exact location of the vascular waterfall is not known, but generally an arteriolar or precapillary locus is assumed.[10,24] In all animal studies, critical closing pressures higher than venous pressures were found.[25,26] From stop-flow experiments in animals, such local Pcc to venous pressure gaps were reported for brain[27,28], kidneys[29], and coronaries.[8] Importantly, the organ-specific Pcc values are often different, reflecting organ specific vascular flow control.
Why are there vascular waterfalls,and what is their purpose? First, because different organs may have different Pcc values, with the heart and the brain probably having lower Pcc values than muscle, kidney, and gut, they allow for vital organ perfusion at lower Pa values. Furthermore, vital organ perfusion is maintained transiently during stop-flow conditions. After cardiac arrest, arterial blood pressure will be reduced to Pcc. Because Pcv slowly increases to the level of Pmsf, a pressure gradient (between Pcc and Pmsf) will be preserved for some time. Thus, at least temporarily some flow and perfusion pressure is maintained to the brain and heart. Indeed, during ventricular fibrillation in pigs, flow in the left carotid artery was preserved at a low level for minutes.[30] Second, and perhaps more importantly, short-lasting changes in Pcv induced by intrathoracic pressure changes (by inspiration, coughing, or Valsalva maneuvers) will only affect the downstream portion of the waterfall, thereby maintaining the stability of circulatory flow from the arteries into the organs. Only after some time, will an increase in Pcv decrease venous return and thus CO.[24]

Limitations. Although the size of the study group was small, the gap between Pmsf and Pcc was large in every patient during baseline conditions and following intravascular volume expansion. Because only cardiac surgery patients with relative intact ventricular function were included, these conclusions may not carry the same magnitude of inter-

relation in patients with impaired ventricular function. The small size of the study population did not allow conclusion on subgroups as responders and nonresponders to the intravascular fluid administration as all our subjects increased CO in response to intravascular volume administration.

Conclusions

With our bedside measurement of Pcc and Pmsf, we showed that there is a systemic vascular waterfall in cardiac surgery patients, and the practitioner is now able to estimate Ra and Rvr separately. The vascular waterfall is not affected by intravascular fluid administration. Furthermore, because of this vascular waterfall, in excess of 25 mmHg, estimations of vasomotor tone using calculations of systemic vascular resistance will both overestimate actual vasomotor tone and may not accurately represent changes in vasomotor tone.

References

1 Guyton AC. Determination of cardiac output by equating venous return curves with cardiac response curves. *Physiol Rev* 1955; 35:123-129.

2 Guyton AC, Polizo D, Armstrong GG. Mean circulatory filling pressure measured immediately after cessation of heart pumping. *Am J Physiol* 1954; 179:261-267.

3 Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, Jansen JR. Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. *Crit Care Med* 2009; 37:912-918.

4 Rothe CF. Mean circulatory filling pressure: its meaning and measurement. *J Appl Physiol* 1993; 74:499-509.

5 Peters J, Mack GW, Lister G. The importance of the peripheral circulation in critical illnesses. *Intensive Care Med* 2001; 27:1446-1458.

6 Schipke JD, Heusch G, Sanii AP, Gams E, Winter J. Static filling pressure in patients during induced ventricular fibrillation. *Am J Physiol Heart Circ Physiol* 2003; 285:H2510-H2515.

7 Jellinek H, Krenn H, Oczenski W, Veit F, Schwarz S, Fitzgerald RD. Influence of positive airway pressure on the pressure gradient for venous return in humans. *J Appl Physiol* 2000; 88:926-932.

8 Kottenberg-Assenmacher E, Aleksic I, Eckholt M, Lehmann N, Peters J. Critical closing pressure as the arterial downstream pressure with the heart beating and during circulatory arrest. *Anesthesiology* 2009; 110:370-379.

9 Sylvester JT, Gilbert RD, Traystman RJ, Permutt S. Effects of hypoxia on the closing pressure of the canine systemic arterial circulation. *Circ Res* 1981; 49:980-987.

10 Permutt S, Riley RL. Hemodynamics of collapsible vessels with tone: the vascular waterfall. *J Appl Physiol* 1963; 18:924-932.

11 Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. *J Appl Physiol* 1993; 74:2566-2573.

12 Jansen JR, Schreuder JJ, Mulier JP, Smith NT, Settels JJ, Wesseling KH. A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. *Br J Anaesth* 2001; 87:212-222.

13 de Wilde RB, Schreuder JJ, van den Berg PC, Jansen JR. An evaluation of cardiac output by five arterial pulse contour techniques during cardiac surgery. *Anaesthesia* 2007; 62:760-768.

14 Samar RE, Coleman TG. Mean circulatory pressure and vascular compliances in the spontaneously hypertensive rat. *Am J Physiol* 1979; 237:H584-H589.

15 Yamamoto J, Trippodo NC, Ishise S, Frohlich ED. Total vascular pressure-volume relationship in the conscious rat. *Am J Physiol* 1980; 238:H823-H828.

16 Ebert TJ. Sympathetic and hemodynamic effects of moderate and deep sedation with propofol in humans. *Anesthesiology* 2005; 103:20-24.

17 Sato M, Tanaka M, Umehara S, Nishikawa T. Baroreflex control of heart rate during and after propofol

infusion in humans. *Br J Anaesth* 2005; 94:577-581.

18 Lennander O, Henriksson BA, Martner J, Biber B. Effects of fentanyl, nitrous oxide, or both, on baroreceptor reflex regulation in the cat. *Br J Anaesth* 1996; 77:399-403.

19 Pinsky MR. Instantaneous venous return curves in an intact canine preparation. *J Appl Physiol* 1984; 56:765-771.

20 Versprille A, Jansen JR. Mean systemic filling pressure as a characteristic pressure for venous return. *Pflugers Arch* 1985; 405:226-233.

21 Den Hartog EA, Versprille A, Jansen JR. Systemic filling pressure in intact circulation determined on basis of aortic vs. central venous pressure relationships. *Am J Physiol* 1994; 267:H2255-H2258.

22 Uemura K, Sugimachi M, Kawada T, Kamiya A, Jin Y, Kashihara K, Sunagawa K. A novel framework of circulatory equilibrium. *Am J Physiol Heart Circ Physiol* 2004; 286:H2376-H2385.

23 van den Berg PC, Jansen JR, Pinsky MR. Effect of positive pressure on venous return in volume-loaded cardiac surgical patients. *J Appl Physiol* 2002; 92:1223-1231.

24 Magder S. Starling resistor versus compliance. Which explains the zero-flow pressure of a dynamic arterial pressure-flow relation? *Circ Res* 1990; 67:209-220.

25 Bellamy RF. Diastolic coronary artery pressure-flow relations in the dog. *Circ Res* 1978; 43:92-101.

26 Burton AC. On the physical equilibrium of small blood vessels. *Am J Physiol* 1951; 164:319-329.

27 Aaslid R, Lash SR, Bardy GH, Gild WH, Newell DW. Dynamic pressure--flow velocity relationships in the human cerebral circulation. *Stroke* 2003; 34:1645-1649.

28 Weyland A, Buhre W, Grund S, Ludwig H, Kazmaier S, Weyland W, Sonntag H. Cerebrovascular tone rather than intracranial pressure determines the effective downstream pressure of the cerebral circulation in the absence of intracranial hypertension. *J Neurosurg Anesthesiol* 2000; 12:210-216.

29 Ehrlich W, Baer RW, Paidipaty BB, Randazzo R. Instantaneous renal arterial pressure-flow relations in anesthetized dogs. *Am J Physiol* 1984; 246:H702-H709.

30 Steen S, Liao Q, Pierre L, Paskevicius A, Sjoberg T. The critical importance of minimal delay between chest compressions and subsequent defibrillation: a haemodynamic explanation. *Resuscitation* 2003;58:249-258.

Chapter 9

Partitioning the resistances along the vascular tree: effects of dobutamine and hypovolemia in piglets with an intact circulation

Bart F. Geerts[1], Jacinta J. Maas[2], Rob B.P. de Wilde[2], Leon P.H.J. Aarts[1], Michael R. Pinsky[3] and Jos R.C. Jansen[2]

[1]Department of Anesthesiology, Leiden University Medical Center, The Netherlands,
[2]Department of Intensive Care Medicine, Leiden University Medical Center, The Netherlands,
[3]Department of Critical Care Medicine, University of Pittsburgh, PA, USA

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Abstract

We present a new physiological model that discriminated between changes in the systemic arterial and venous circulation. To test our model, we studied the effects of dobutamine and hypovolemia in intact pentobarbital-anesthetized piglets. Aorta pressure (Pao), central venous pressure (Pcv), mean systemic filling pressure (Pmsf) and cardiac output (CO), were measured in 10 piglets, before, during and after dobutamine infusion (6 $\mu g \cdot kg^{-1} \cdot min^{-1}$), as well as during hypovolemia (-10 $ml \cdot kg^{-1}$), and after fluid resuscitation to normovolemia. Venous (Rvr) and total systemic (Rsys) resistance were determined from Pao, Pcv, Pmsf and CO. The quotient of Rvr/Rsys was used to determine the predominant location of vascular changes (i.e. vasoconstriction or dilatation on either venous or arterial side). Administration of dobutamine increased heart rate and CO, whereas it decreased Pmsf, Rsys, Rvr and Rvr/Rsys. The decrease in Rvr was significantly greater than Rsys. Pao and Pcv did not change. Hypovolemia decreased CO, Pcv, Pmsf, Rvr and Rvr/Rsys, but kept Rsys constant and increased heart rate. In conclusion, hypovolemia and dobutamine differentially alter Pmsf, Rsys, Rvr and Rvr/Rsys ratio. The increase in CO during dobutamine infusion was attributed to the combined increased cardiac function and decreased Rvr. The decrease in CO with hypovolemia was due to a decrease Pmsf but was partly compensated for by a decrease in Rvr tending to preserve venous return and thus CO.

Introduction

The hemodynamic effects of therapeutic interventions have been extensively studied on isolated arterial, venous or heart models either in vitro or in vivo. Although, intact circulation models have been used before, they are often limited to only one study characteristic; i.e. heart function, venous capacitance, (un)stressed volume, vascular compliance, mean systemic filling pressure or venous resistance.[1] None of these models is applicable in ICU patients and none was used to determine the coherent characteristics of the venous and arterial vasculature and heart function. Since arteries, veins and heart operate in concert, we developed an integrated in vivo model, applicable in patients, based on Guytonian Physiology.

We modelled the systemic circulation with one resistor upstream (Ra) and one resistor downstream (Rvr) of mean systemic filling pressure (Pmsf) (figure 9.1). At the site where the pressure is equal to Pmsf the large blood volume is indicated by a capacitor.[2-4] This site contains about 70% of total blood volume and has been reported to correspond with the location of the capillaries and post-capillary venules.[5] Resistance over the total systemic circulation (Rsys) and over the venous system (Rvr) can be calculated from aortic pressure (Pao), central venous pressure (Pcv) and cardiac output (CO) values as (Pao-Pcv)/CO and Rvr by (Pmsf-Pcv)/CO, respectively (figure 9.1). Rsys reflects both arterial and venous resistance: Rsys = Ra + Rvr. So, Ra = Rsys - Rvr.

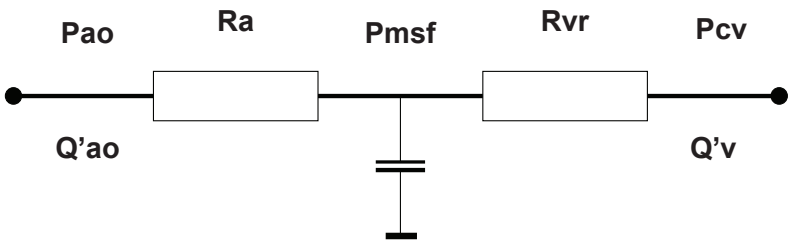

Figure 9.1 Circulation model

The circulation model to compute the resistances up-streams (Ra) and down-streams (Rvr) of mean systemic filling pressure (Pmsf). The sum of Ra and Rvr is equal to total systemic resistance (Rsys). Aortic pressure (Pao) and central venous pressure (Pcv) are measured. Q'ao is the flow in the aorta (cardiac output); Q'v is the venous return. Mean systemic filling pressure is determined with inspiratory hold maneuvers.

In this study we used a hemodynamic condition of hypovolemia as well as dobutamine as a known cardiovascular stimulant to test our model in an intact anesthetized piglet model. In the vasculature, Ruffolo and colleagues[6] presumed that with dobutamine, the β_2 mediated effects are counterbalanced by the α_1 activity leading to a decreased total peripheral vascular resistance by a reduction of sympathetic tone and arterial vasodilatation. However, since local vascular effects may differ owing to local differences in receptor expression which varies in arteries and veins, one may see

either local vasodilatation or vasoconstriction. Presently, no intact-circulation model exists to study differences in systemic arterial and venous resistance. Since we recently validated a bedside technique to estimate mean systemic filling pressure (Pmsf)[7], we are now able to determine the venous resistance in patients. Thus, examining both total blood flow and the ratio of the systemic to venous resistance one can quantify the effect of different hemodynamic conditions and vasoactive agents on total systemic vascular resistance and venous resistance.

The aim of our study was to determine the reproducibility of Pmsf, Rsys and Rvr in our intact in vivo piglet model and, secondly, we tested our model during dobutamine and hypovolemia. We hypothesized that dobutamine would increase CO by the combined actions of increasing inotropy, arterial vasodilation, with less evident venodilation. Furthermore, we expected both hypovolemia and dobutamine to decrease Pmsf and hypovolemia to not change in the site of Pmsf, i.e. the ratio Rvr/Rsys to be constant.

Methods and materials

All experiments were performed according to the ''Guide for Care and Use of Laboratory Animals'' published by the US National Institutes of Health and were approved by the local Animal Care Committee.

Surgery

Ten Yorkshire piglets were anesthetized with 30 $mg \cdot kg^{-1}$ sodium pentobarbital intra-peritoneally, followed by a continuous infusion of 9.0 $mg \cdot kg^{-1} \cdot h^{-1}$. After tracheostomy, the animals were ventilated at a rate of 10 breaths per min at an I:E-ratio of 2.4:3.6 and with a tidal volume adjusted to maintain arterial pCO_2 of approximately 40 mmHg, while a positive end-expiratory pressure of 2 cmH_2O was applied. PCO_2, airway pressure and airflow were measured in the tracheal cannula. The animals were placed in a supine position on a thermo-controlled operating table (38° C). A catheter was inserted through the right common carotid artery into the aortic arch to measure Pao and to sample arterial blood. Two other catheters were inserted through the right external jugular vein. A pulmonary artery catheter was inserted to measure pulmonary artery pressure, to measure thermodilution cardiac output (COtd) and to sample mixed venous blood. A quadruple-lumen catheter was inserted into the superior vena cava to measure Pcv and to infuse sodium pentobarbital and pancuronium bromide (Organon N.V., Boxtel, the Netherlands). The catheters for vascular pressure measurements were kept patent by an infusion of saline with 2.5 IE Heparin ml^{-1} at 3 $ml \cdot h^{-1}$. The bladder was cannulated trans-abdominally to check urine loss in order to maintain water balance. After an intercostal thoracotomy in the second left intercostal space, an electromagnetic flow probe (type transflow 601, model 400, Skalar, Delft, The Netherlands) was placed within the pericardium around the ascendant part of the aortic arch to measure aortic blood flow. Two suction catheters, one dorsal and one ventral, were inserted into the

left pleural space. The thorax was closed airtight and both air and fluids were evacuated for 1-2 minutes with -10 cmH_2O suction while applying a PEEP of 10 cmH_2O. After surgery and while on continuous pentobarbital infusion, the animals were paralyzed with an intravenous infusion of pancuronium bromide (0.3 $mg \cdot kg^{-1} \cdot h^{-1}$), after a loading dose of 0.1 $mg \cdot kg^{-1}$ in 3 min.

Measurements

The electrocardiogram (ECG), Pao, pulmonary artery pressure (Ppa), Pcv, flow probe signal and ventilatory pressure (Pvent) flow were simultaneously recorded. Zero level of blood pressures was chosen at the level of the tricuspid valves, indicated by the pulmonary artery catheter during lateral-to-lateral radiography. The airway pressure transducer was balanced at zero level against ambient air. During the observation periods, ECG, blood flow and pressure signals were sampled in real time for 30-s periods at 250 Hz. The mean of four thermodilution cardiac output measurements equally distributed of the ventilatory cycle was used to obtain the value of COtd.[8,9] Areas under the aortic blood flow curves were analyzed online and calibrated by COtd to estimate beat-to-beat cardiac output (COem). After the surgical procedure the animals were ventilated at a rate of 10 min^{-1} with an inflation time of 2.4 s and an expiration time of 3.6 s. Tidal volume was readjusted to an end-expiratory pCO_2 of approximately 5.33 kPa (40 mmHg), usually corresponding with a slightly higher arterial pCO_2. The ventilatory settings were kept constant during the observation periods.

We determined Pmsf using inspiratory pause procedures as previously described.[5,10,11] Briefly, during inflation of the lungs venous capacitance is loaded due to an increase in Pcv, which leads to a transient reduction in venous return, in right ventricular output and consequently in left ventricular output (figure 9.2). To avoid transient effects on the relationship between venous return and Pcv, we measured Pcv and (CO) during short periods of end-inspiratory steady state following these initial non-steady state conditions. CO and Pcv are determined over the final 5 seconds for a set of seven 12-second inspiratory hold procedures at seven randomly applied tidal volumes between 25 and 300 ml. The inspiratory hold maneuvers are separated by 5-min intervals to re-establish the initial hemodynamic steady state. From the steady-state values of Pcv and CO measured by an electromagnetic flow probe (COem) during the seven inspiratory pause periods a venous return curve was constructed by fitting a linear regression line according to the method of least square means through these data points (figure 9.3). Pmsf is defined as the extrapolation of this linear regression to zero flow.[5,10,11]

Protocol

To eliminate the effects of surgery, opening of the pericardium, and applying mechanical ventilation on the hemodynamic measurements, the piglets were allowed to stabilize for 60 to 120 minutes after surgery. Data collection started once heart rate (HR), mean Pao and Pcv were stable for at least 15 minutes. After stabilization, baseline-1

measurements were performed. Next, continuous dobutamine infusion was started with 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and hemodynamic measurements were performed after 30 minutes. The dobutamine infusion was stopped and after 30 minutes baseline-2 measurements were obtained. The observations were continued 15 minutes after bleeding the animals with 10 $ml \cdot kg^{-1}$. The observations ended with baseline-3 measurements 15 minutes after giving back the withdrawn 10 $ml \cdot kg^{-1}$ blood.

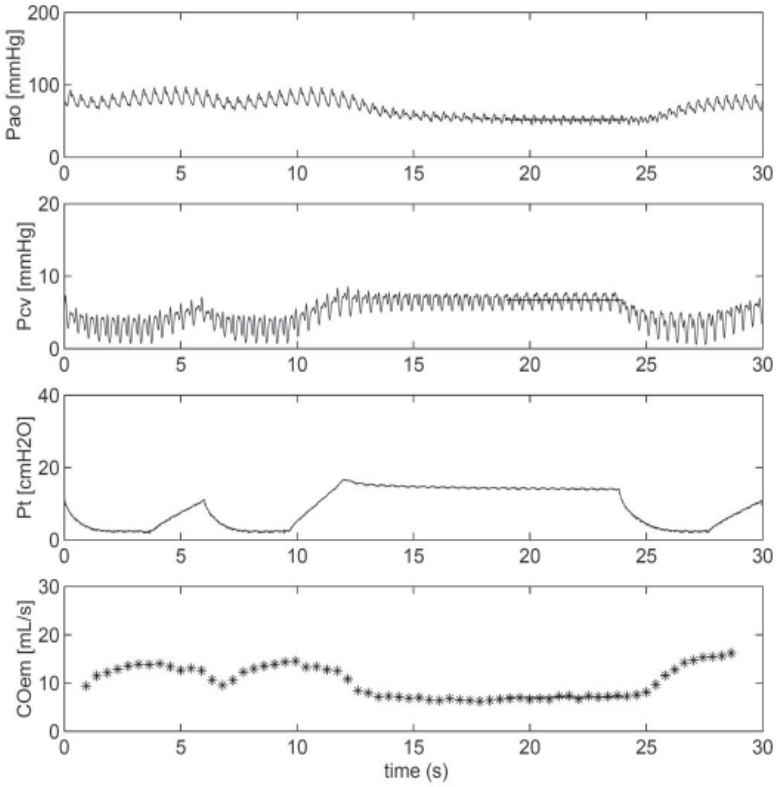

Figure 9.2 Example of an inspiratory hold maneuver
Effects of an inspiratory hold maneuver on aortic pressure (Pao), central venous pressure (Pcv), airway pressure (Pt) and beat-to-beat cardiac output (COem). Preceding the hold maneuver the effects of a normal ventilatory cycle are plotted.

Data analysis and statistics

We fitted the set of seven data points of Pcv and COem by linear regression for each condition to define the venous return curve. We defined Pmsf as the extrapolation of this linear regression to zero flow (figure 9.3), assuming that airway pressure does not affect Pmsf. We have previously validated this extrapolation in piglets.[5,10,11] Total systemic vascular resistance (Rsys) was calculated as the ratio of the pressure difference between mean Pa and mean Pcv and COtd (Rsys = (Pa - Pcv)/COtd). 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 COtd (Rvr = (Pmsf-Pcv)/COtd). 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. After confirming a normal distribution of data with the Kolmogorov-Smirnov test, differences in parameters during baseline and interventions were analyzed using paired t-tests. Repeatability was calculated from the three baseline conditions using Bland-Altman analysis. Hereto, for each animal the mean and difference of the values of baseline-1 and 2 and of baseline-2 and 3 was determined. The upper and lower limits of agreement were calculated as bias ± 2SD. The coefficient of variation (COV) was calculated as 100% x (SD/mean). Effects of time on our data set were calculated by comparing baseline values. Changes induced by the interventions with dobutamine and hypovolemia were compared to the mean of the baseline values before and after the interventions to eliminate time effect. All values are given as mean ± SD. A p-value < 0.05 was considered statistically significant.

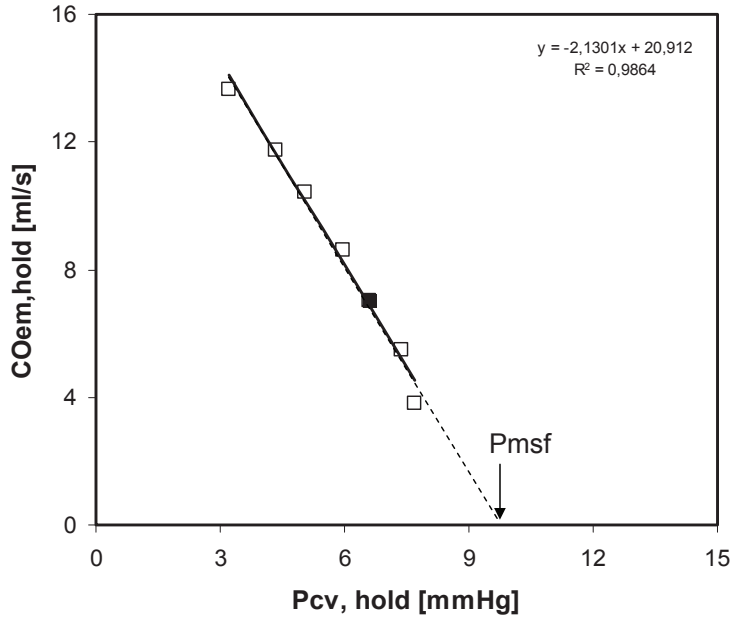

Figure 9.3 Venous return curve for an individual animal
The relationship between venous return (COem) and central venous pressure (Pcv) is plotted. Mean system filling pressure (Pmsf) is indicated by extrapolating the curve to COem = zero.

Results

Ten 8–10 week old piglets (all females) bodyweight of 10.3 ± 0.7 kg were studied. Pooled data are shown in table 9.1. A Kolmogorov-Smirnov test indicated normal distribution of all data. In 10 animals baseline-1, dobutamine, and baseline-2 data were obtained, in only 8 animals we were able to study the effects of bleeding by 10 ml·kg^{-1}.

Repeatability

Bland-Altman analyses for repeated measurements of the main derived variables Pmsf, Pvr, Rsys, Rvr and Rvr/Rsys are given in table 9.2. A remarkable low percentage coefficient of variation of 3.8% was found for Pmsf. The percentage coefficient of variation increases with the number of variables incorporated in the calculation and was highest for Rvr/Rsys.

Table 9.1 Pooled results for 10 piglets at start (Baseline-1), 30 minutes after the start of 6 µg•kg^{-1}• min^{-1} IV dobutamine infusion (Dobutamine), 30 minutes after stopping the dobutamine infusion (Baseline-2), 15 minutes after bleeding 10 ml/kg (Hypovolemia) and 15 minutes after reestablishing normovolemia (Baseline-3)

	Baseline-1	Dobutamine	Baseline-2	Hypovolemia	Baseline-3
Pao (mmHg)	88.10 ± 17.24	87.51 ± 9.37	82.56 ± 17.02	83.05 ± 14.46	86.83 ± 18.30
Ppa (mmHg)	15.52 ± 3.51	19.77 ± 6.99	19.74 ± 7.39	17.10 ± 6.51	18.96 ± 5.97
Pcv (mmHg)	4.09 ± 1.33	4.10 ± 1.03	4.62 ± 1.38	3.75 ± 1.71 †	4.69 ± 1.47
HR (min^{-1})	146 ± 42	215 ± 33 ‡	152 ± 42	175 ± 47 ‡	150 ± 45
COtd (ml•s^{-1})	24.15 ± 3.70	33.64 ± 3.94 ‡	24.53 ± 5.38	22.69 ± 3.87 †	24.57 ± 4.64
Pmsf (mmHg)	13.59 ± 1.04	12.02 ± 1.27 †	14.10 ± 1.37	10.94 ± 1.81 ‡	4.85 ± 1.28
Pvr (mmHg)	10.71 ± 1.21	7.88 ± 1.12 *	9.50 ± 1.72	7.19 ± 1.66 ‡	0.15 ± 1.75
Rvr (mmHg•s•ml^{-1})	0.401 ± 0.095	0.237 ± 0.037 ‡	0.406 ± 0.126	0.327 ± 0.104 †	0.465 ± 0.085
Rsys (mmHg•s•ml^{-1})	3.474 ± 0.424	2.507 ± 0.271 ‡	3.379 ± 0.322	3.496 ± 0.352	3.359 ± 0.455
Rvr/Rsys	0.117 ± 0.031	0.096 ± 0.019 †	0.127 ± 0.037	0.095 ± 0.035 †	0.129 ± 0.039
Hb (g•dl-1)	9.56 ± 1.02	10.34 ± 1.22 †	9.73 ± 0.99	9.67 ± 0.89	9.71 ± 1.05

Aorta pressure (Pao), pulmonary artery pressure (Ppa), central venous pressure (Pcv), heart rate (HR), cardiac output with thermodilution (COtd), mean systemic filling pressure (Pmsf), pressure gradient for venous return (Pvr), venous flow resistance (Rvr),systemic flow resistance (Rsys), location of Pmsf (Rvr/Rsys), and hemoglobin (Hb).
** $p < 0.05$, † $p < 0.01$ and ‡ $p < 0.001$ to the average of the baseline value before and after the intervention.*

Interventions

The infusion of 6 µg·kg^{-1}·min^{-1} dobutamine increased HR and COtd and decreased Pmsf, Pvr, Rvr, Rsys and Rvr/Rsys ratio. Whereas Pao, Ppa and Pcv did not change during the study. The decrease of Rvr during dobutamine was larger than the decrease in Rsys, 52% and 28% respectively. Recovery baseline condition after dobutamine (baseline-2) did not show any significant changes from the initial baseline values (baseline-1), except for HR which decreased after dobutamine infusion was stopped but still was elevated compared to baseline-1. Bleeding the animals with 10 ml·kg^{-1} showed a decrease in Pcv, Pmsf, Pvr, Rvr and Rvr/Rsys. Recovery to baseline condition after bleeding (baseline-3) did not show any significant changes from baseline values before bleeding (baseline-2). Surprisingly, hemoglobin (Hb) increased during continuous dobutamine infusion and returned to baseline-1 values 30 minutes after the infusion was stopped. Hemoglobin did not change by bleeding.

Discussion

Our data support the feasibility to estimate Pmsf, Rsys and Rvr. The discrimination between arterial and venous resistance is possible because we can estimate Pmsf accurately. Our data on vascular resistance clearly show that although both arterial and venous components of vascular resistance decrease, the primary peripheral vascular effects of dobutamine in the healthy animal model was to induce more venodilation than arterial dilation. Bleeding the animals showed Pmsf, Pcv, COtd and surprisingly Rvr to decrease and Pao and Rsys to be constant. Evidently, there is some compensation for the loss of venous return by adaptation of Rvr.

Table 9.2 Bland-Altman results for repeated measurements of mean systemic filling pressure (Pmsf), gradient for venous return (Pvr), systemic vascular resistance (Rsys), the resistance for venous return (Rvr) from Pmsf to central venous pressure and the quotient Rvr/Rsys as a location of Pmsf in the circulation. Data of baseline-1, baseline-2 and baseline-3 are used (n = 18)

	Mean	Bias	SD	COV (%)	Limits of agreement	
					Lower	Upper
Pmsf (mmHg)	14.17	-0.55	0.54	3.8	-1.63	0.53
Pvr (mmHg)	9.64	-0.18	0.78	8.1	-1.74	1.38
Rsys (mmHg•s•ml^{-1})	3.422	0.078	0.348	10.0	-0.618	0.774
Rvr (mmHg•s•ml^{-1})	0.415	-0.023	0.059	14.2	-0.141	0.095
Rvr/Rsys	0.12	0.01	0.02	16.7	-0.03	0.05

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.

Repeatability

Comparison of baseline-1, -2 and -3 showed no differences, except for the observation of heart rate HR during baseline-2. Therefore, we conclude for stable observation periods in our animals. We determined the precision of the main derived variables, i.e. Pmsf, Pvr, Rsys and Rvr, by Bland-Altman analysis of repeated measurements (table 9.2). Although, Pmsf is determined by extrapolation of the venous return curve to COem is equal to zero (figure 9.3), the coefficient of variation appeared to be surprisingly low (3.8%). With the low coefficient of variation for Pmsf, Rvr and Rsys changes by the intervention with dobutamine and hypovolemia can be monitored with precision. Therefore, we consider the data as presented in table 9.1 as reliable.

Our estimated Pmsf values (11-15 mmHg) are in agreement with those described in highly instrumented animals, which are in dogs 7-12.5 mmHg[12-17], rats 7-9 mmHg[18,19], pigs 10-12 mmHg[5,10,11], and as high as 20-30 mmHg in conscious calves implanted with an artificial heart.[20] Furthermore, we report a baseline Pmsf value of 19 mmHg in cardiovascular surgical patients.[7]

How can our data be explained? In a non-controlled circulation a decrease in effective blood volume (i.e. a change from stressed to unstressed volume) will be reflected by a decrease in Pmsf.[21] If dobutamine caused arterial vasodilation such that the number of perfused capillaries increased, then unstressed volume should also increase, decreasing Pmsf for a constant blood volume. The greater number of draining venous conduits would also decrease the resistance to venous return. We found that dobutamine decreased Pmsf without altering Pcv, decreasing the pressure gradient for venous return. Despite this decrease in pressure gradient, cardiac output was increased. Thus, the decrease in Rvr was more than inversely proportional to the increase in cardiac output or cardiac output would have remained constant. A decrease in Rvr may be caused by four mechanisms; (1) a decrease of the length of the vascular bed between the sites were the pressure is equal to Pmsf and right atrium, (2) an increase in cross

section of the vascular bed, (3) a decrease in blood viscosity or (4) a combination of the three mechanisms. As we measure an increase in Hb during dobutamine infusion a decrease in viscosity is very unlikely. Thus, the observed decrease in Pmsf combined with the increased COtd requires that Rvr decrease due to an increase in the venous flow cross-sectional area, presumably due to dobutamine-induced increased parallel vascular blood flow.

The changes in Pao, Pcv, COtd, Rsys and Rvr are illustrated schematically in figure 9.4, in which flow resistance is projected on the x-axis. We have used this graphical model to analyze two different stationary conditions in circulation, i.e. baseline condition and during infusion of dobutamine. The numeric data for this model are taken from table 9.1, columns baseline-1 and dobutamine. The lines between Pao and Pcv represent the pressure gradient (Psys) over Rsys and between Pmsf and Pcv; the pressure gradient (Pvr) for venous return over Rvr. The slope of the lines represent blood flow, i.e. COtd = Psys/Rsys = Pv/Rvr. During dobutamine infusion the Pao-Pcv difference was equal to baseline. However, COtd increased and both Rsys and Rvr decreased significantly. The fall in Rvr due to dobutamine was larger than the fall in Rsys, 52% and 28% respectively. From this difference in response to dobutamine we conclude that the primary peripheral vascular effect of dobutamine is on the venous side of the circulation as shown in figure 9.4. The larger decrease on the venous side can be explained mainly by the decrease in Pmsf due to dobutamine. If we had observed no change in Pao, Pcv or Pmsf despite an increase in COtd, then Rvr must have changed proportional to Rsys, which is described by the intersection of dashed Pao-Pcv dobutamine line and solid Pmsf line. Importantly, our method to determine Pmsf has recently also been validated in mechanically ventilated patients[7], thus this approach can now to applied to humans as well. In addition, we confirmed the well-known positive inotropic effect of dobutamine as manifest by the increase in HR and stroke volume despite an unchanged Pcv and Pao. It is unclear from our data which factor plays a greater role in increasing COtd, increasing inotropy or decreasing Rvr.

In our animals hypovolemia caused Pmsf, Pcv, COtd and surprisingly Rvr to decrease and Pao and Rsys to be constant. The gradient for venous return, Pvr = Pmsf - Pcv, decreased with 27%, so with a constant resistance for venous return, Rvr, we expected a decrease in CO of the same order (CO = Pvr/Rvr). However, Rvr decreased by 16% leading to a decrease in COtd with only 9%. Thus, there appears to be compensation for the loss of venous return by adaptation of Rvr, manifested by the significant increase in heart rate. Potentially, this occurred by shifting blood away from the splanchnic circulation with its higher Rvr to other systemic vascular circuits, as we have previously shown[22], but our study does not allow us to confirm this speculation. However, since we observed that the location at which Pmsf exists (Rvr/Rsys) shifted more into the direction of the venous site of the circulation, suggests that such a redistribution of blood flow did occur.

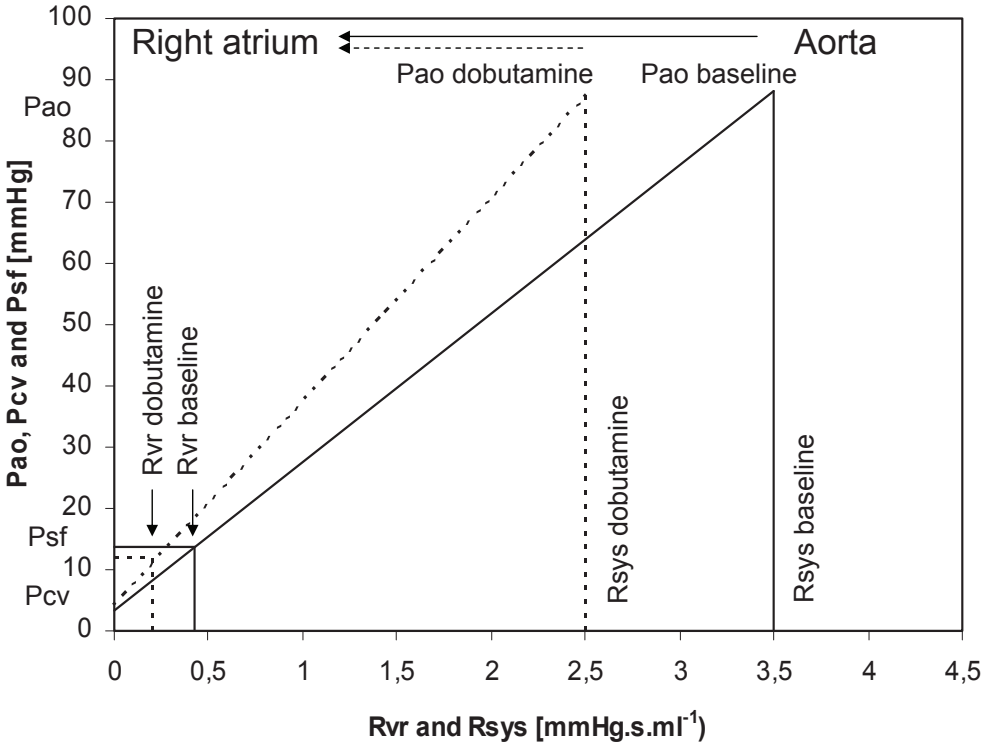

Figure 9.4 Conceptual model of the systemic circulation.
Horizontally, the linear projection of vascular flow resistance (Rsys) between aortic valves (at the right) and right atrium (at the left) is plotted. In this linear projection the aorta takes about 2%, the arterioles about 55%, the remaining arterial system about 15% and the rest is distributed between capillaries and the venous system. The resistance (Rvr) down-streams mean systemic filling pressure (Psf) and central venous pressure (Pcv) is indicated. Vertically, aortic pressure (Pao), central venous pressure (Pcv) and mean systemic filling pressure for baseline condition and during infusion of dobutamine are plotted. The values of table 9.2 are used to construct the model. Further explanation is given in the text.

Limitations

Some limitations apply to our model. The technical set-up with a flow probe around the aorta is not general applicable in humans. A reliable less invasive beat-to-beat determination of cardiac output by trans-oesophageal ultrasound or arterial pulse contour allow similar studies to be done in humans.[7]

We measured only Pao and Pcv and calculated Pmsf. Pmsf is a lumped variable of all the vascular beds. Thus, it is not clear, which specific or general vascular beds were affected by dobutamine infusion or hypovolemia. The difference in local adrenergic receptor (subtype) expression and overall expression of the receptors vary between different vascular beds and between species. Although the circulation of the pig bares macroscopic resemblance to the human physiology, a direct extrapolation of the results is precarious. This, however, also applies for previous studies.[1,6] Clearly, future human studies using less invasive means will need to be done to validate these findings in patient with normal vascular responsiveness and disease.

Conclusions

The use of our in vivo animal model to assess the hemodynamic effects on Pmsf, Rsys, Rvr and Rvr/Rsys of a cardiovascular drug and of hypovolemia was successfully tested. The discrimination between arterial and venous resistance is possible because we can estimate Pmsf accurately. The higher cardiac output seen during dobutamine infusion was attributed to the combined increased cardiac function and decreased venous flow resistance despite a decrease in Pmsf. Hypovolemia decreases as expected Pmsf but this decrease was partly compensated for by a decrease in Rvr to preserve venous return and thus cardiac output.

References

1 Pang CC. Autonomic control of the venous system in health and disease: effects of drugs. *Pharmacol Ther* 2001; 90**:**179-230.

2 Gelman S. Venous function and central venous pressure: a physiologic story. *Anesthesiology* 2008; 108**:**735-748.

3 Magder S, De Varennes B. Clinical death and the measurement of stressed vascular volume. *Crit Care Med* 1998; 26**:**1061-1064.

4 Peters J, Mack GW, Lister G. The importance of the peripheral circulation in critical illnesses. *Intensive Care Med* 2001; 27**:**1446-1458.

5 Versprille A, Jansen JR. Mean systemic filling pressure as a characteristic pressure for venous return. *Pflugers Arch* 1985; 405**:**226-233.

6 Ruffolo RR, Jr. The pharmacology of dobutamine. *Am J Med Sci* 1987; 294**:**244-248.

7 Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, Jansen JR. Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. *Crit Care Med* 2009; 37**:**912-918.

8 Jansen JR, Schreuder JJ, Bogaard JM, van Rooyen W, Versprille A. Thermodilution technique for measurement of cardiac output during artificial ventilation. *J Appl Physiol* 1981; 51**:**584-591.

9 Jansen JR, Schreuder JJ, Settels JJ, Kloek JJ, Versprille A. An adequate strategy for the thermodilution technique in patients during mechanical ventilation. *Intensive Care Med* 1990; 16**:**422-425.

10 Den Hartog EA, Versprille A, Jansen JR. Systemic filling pressure in intact circulation determined on basis of aortic vs. central venous pressure relationships. *Am J Physiol* 1994; 267**:**H2255-H2258.

11 Hiesmayr M, Jansen JR, Versprille A. Effects of endotoxin infusion on mean systemic filling pressure and flow resistance to venous return. *Pflugers Arch* 1996; 431**:**741-747.

12 Guyton AC. Determination of cardiac output by equating venous return curves with cardiac response curves. *Physiol Rev* 1955; 35**:**123-129.

13 Guyton AC, Lindsey AW, Abernathy B, Richardson T. Venous return at various right atrial pressures and the normal venous return curve. *Am J Physiol* 1957; 189**:**609-615.

14 Pinsky MR. Instantaneous venous return curves in an intact canine preparation. *J Appl Physiol* 1984; 56**:**765-771.

15 Greene AS, Shoukas AA. Changes in canine cardiac function and venous return curves by the carotid baroreflex. *Am J Physiol* 1986; 251**:**H288-H296.

16 Lee RW, Lancaster LD, Gay RG, Paquin M, Goldman S. Use of acetylcholine to measure total vascular pressure-volume relationship in dogs. *Am J Physiol* 1988; 254**:**H115-H119.

17 Fessler HE, Brower RG, Wise RA, Permutt S. Effects of positive end-expiratory pressure on the canine venous return curve. *Am Rev Respir Dis* 1992; 146**:**4-10.

18 Samar RE, Coleman TG. Mean circulatory pressure and vascular compliances in the spontaneously hypertensive rat. *Am J Physiol* 1979; 237**:**H584-H589.

19 Yamamoto J, Trippodo NC, Ishise S, Frohlich ED. Total vascular pressure-volume relationship in the conscious rat. *Am J Physiol* 1980; 238**:**H823-H828.

20 Honda T, Fuqua JM, Edmonds CH, Hibbs CW, Akutsu T. Applications of total artificial heart for studies of circulatory physiology; measurement of resistance to venous return in postoperative awake calves. Preliminary report. *Ann Biomed Eng* 1976; 4**:**271-279.

21 Prather JW, Taylor AE, Guyton AC. Effect of blood volume, mean circulatory pressure, and stress relaxation on cardiac output. *Am J Physiol* 1969; 216**:**467-472.

22 Schlichtig R, Klions HA, Kramer DJ, Nemoto EM. Hepatic dysoxia commences during O2 supply dependence. *J Appl Physiol* 1992; 72**:**1499-1505.

Chapter 10

Cardiac output response to norepinephrine in postoperative cardiac surgery patients: interpretation with venous return and cardiac function curves

Jacinta J. Maas[1], Michael R. Pinsky[2], Rob B.P. de Wilde[1], Evert de Jonge[1] and Jos R.C. Jansen[1]

[1]Department of Intensive Care Medicine, Leiden University Medical Center, The Netherlands,
[2]Department of Critical Care Medicine, University of Pittsburgh, PA, USA

Critical Care Medicine in press

Abstract

Norepinephrine can either increase or decrease cardiac output, but the determinants have not been studied in ICU patients. The aim of the study was to explain these effects with the use of Guytonian venous return and cardiac function curves. In sixteen mechanically ventilated postoperative cardiac surgery patients inspiratory holds were performed at baseline-1, during increased norepinephrine infusion and baseline-2 conditions. We determined mean arterial pressure, central venous pressure, cardiac output, stroke volume variation and mean systemic filling pressure, resistance for venous return and systemic vascular resistance. Increasing norepinephrine by 0.04 ± 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$ increased mean arterial pressure 20 mmHg in all patients. Cardiac output decreased in 10 and increased in 6 patients. In all patients mean systemic filling pressure, systemic vascular resistance and resistance for venous return increased and stroke volume variation decreased. Resistance to venous return and systemic vascular resistance increased more ($p = 0.019$ and $p = 0.002$) in the patients with a cardiac output decrease. Heart rate decreased in the patients with a decline in cardiac output and was unchanged in the patients with a cardiac output increase. Baseline stroke volume variation was higher in those in whom cardiac output increased (14.4 ± 4.2 versus 9.1 ± 2.4%, $p = 0.012$). Stroke volume variation > 8.7% predicted the increase in cardiac output to norepinephrine (ROC AUC 0.900). In conclusion, the change in cardiac output induced by norepinephrine is determined by the balance between volume recruitment (as determined by mean systemic filling pressure) and change in resistance for venous return and baseline heart function. Furthermore, the response of cardiac output on norepinephrine can be predicted by baseline stroke volume variation.

Introduction

Norepinephrine (NE) is the vasopressor of choice in septic shock[1] because of its ability to maintain vasomotor tone, but it is also recommended as treatment for resistant cardiogenic shock.[2,3] However, the effect of NE on cardiac output (CO) is highly variable. Both increases and decreases in CO can be seen in response to NE in patients with both septic shock[4-10] and without.[11,12] Cardiovascular mechanisms used to explain these effects include increases in cardiac contractility, cardiac preload, coronary perfusion and afterload[5,13,14] as recently described in humans with septic shock.[10]

Central to these arguments is that changes in effective circulating blood and venous return occur independent of changes in contractility. Potentially, the final CO change in response to NE must be determined by the balance between the increased preload effects of increasing peripheral vasomotor tone versus the increased afterload effect of increasing mean arterial pressure (Pa). Furthermore, the resistance to venous return (Rvr) may also be increased by NE owing to venoconstriction. But until now no studies have been done in humans that describe the effects of NE based on effective circulating blood volume (by measurements of mean systemic filling pressure (Pmsf)), Rvr, total systemic resistance (Rsys), and the intersection of venous return and cardiac function curves. Recently, we showed that it is possible to measure Pmsf and Rvr at the bedside in intensive care patients.[15] Furthermore, using the same measurement techniques, we described the hemodynamic effects of dobutamine in piglets.[16]

The aim of the study was to determine the effects of NE on the determinants of the CO change and to explain these effects with the use of Guytonian venous return and cardiac function curves. We hypothesized that NE could increase CO by increasing effective circulating volume by recruitment from venous capacitance vessels (increase in Pmsf) or decrease CO by either an increase in venous resistance decreasing venous return or an increase in left ventricular afterload (increase in Rsys).

Materials and methods

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 16 patients planned for elective coronary artery bypass surgery or mitral valvuloplasty. All patients signed informed consent on the day before surgery. Patients with previous myocardial infarction, left ventricular ejection fraction < 45%, aortic insufficiency, 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 ICU. Sedation was maintained with propofol (3.2 $mg \cdot kg^{-1} \cdot h^{-1}$) and sufentanil (0.17 $\mu g \cdot kg^{-1} \cdot h^{-1}$). The patients were mechanically ventilated in airway pressure release ventilation mode (Evita 4, Dräger AG, Lübeck, Germany) adjusted to achieve normocapnia (arterial pCO_2 between 40 and 45 mmHg) with tidal volumes of 7.3 ± 1.3

$ml \cdot kg^{-1}$, a respiratory rate of $12 \cdot min^{-1}$ and 5 cmH_2O positive end-expiratory pressure. All patients were in sinus rhythm. Hemodynamic stability was achieved using fluids ($60\ ml \cdot hour^{-1}$) and catecholamines. During the study interval, no changes were made in vasoactive drug therapy, except for the protocolized increase in NE dosage, and all patients were hemodynamically stable. Every patient experienced full recovery from anesthesia within 8 hours after surgery and was discharged from intensive care unit on the first postoperative day.

Physiological monitoring. Pa was measured with a radial artery catheter and central venous pressure (Pcv) was measured with a venous catheter inserted in the right internal jugular vein. Both catheters were connected to a pressure transducer (PX600F, Edwards Lifesciences, Irvine, Califormia, USA). Zero levels of blood pressures were referenced to the intersection of the anterior axillary line and the fifth intercostal space. Airway pressure 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. Beat-to-beat CO, stroke volume and stroke volume variation (SVV) were obtained by Modelflow pulse contour analysis (Modelflow, FMS, Amsterdam, The Netherlands) as previously described and validated by us.[17-20] Modelflow was calibrated with the averaged result of three measurements with the bolus lithium indicator dilution method (LiDCO Ltd, Cambridge, UK) at the beginning of the protocol. For the lithium dilution method an injection of lithium chloride (0.3 mmol) is given in the central venous catheter, and the resulting arterial lithium-time curve is recorded by withdrawing blood past a lithium sensor attached to the patient's radial artery line. Pressures were recorded online using a data acquisition program on a personal computer.

Determination of Pmsf. Previously we described the bedside determination of Pmsf in detail.[15] Summarizing, we measured steady-state Pa, Pcv and CO over the final 3 seconds for a set of four inspiratory holds of 12 seconds at airway plateau pressures of 5, 15, 25 and 35 cm H_2O. The inspiratory hold maneuvers were separated by 1-minute intervals to reestablish the initial hemodynamic steady state. During these inspiratory holds, when airway pressure increased, Pcv increased concomitantly, whereas CO and Pa decreased with a delay of three to four beats resulting in a plateau between 7 and 12 seconds after start of the inflation. Next, a venous return curve was constructed by plotting the values of the four pairs of Pcv and CO against each other. Pmsf was defined as the Pcv after fitting a linear line through these data points and extrapolating CO to zero (figure 10.1).

Protocol. After stabilization of the patient in the intensive care unit, series of baseline-1 measurements were done of Pa, Pcv, CO and Pmsf. Next, continuous NE infusion rate was increased to induce a 20 mmHg increase in Pa and after 15 minutes the series of measurements were repeated. The observation period ended with baseline-2

measurements 15 minutes after returning to a NE infusion rate equal to baseline-1 condition.

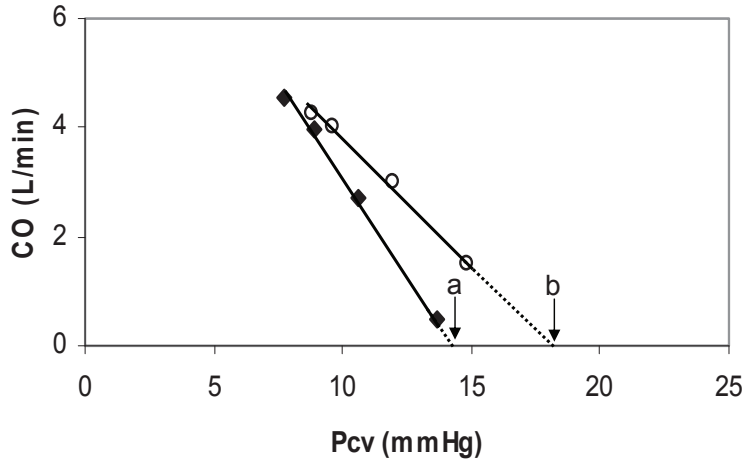

Figure 10.1 Example of a venous return curve
Venous return curve plotted for 1 patient after 4 inspiratory hold maneuvers. At increasing values of airway pressure, central venous pressure (Pcv) increases and cardiac output (CO) decreases. Mean systemic filling pressure (Pmsf) is the value of Pcv, when cardiac output is extrapolated to zero (marked with an arrow). Measurements were performed during baseline conditions (closed diamonds, straight line, Pmsf indicated by a) and after norepinephrine dosage increase (open circles, dotted line, Pmsf indicated by b).

Data analysis and statistics. The venous return data (Pcv versus CO) were fitted using a least-squares method. The extrapolation of the regression line to zero CO determines Pmsf. Total vascular systemic resistance was calculated as the ratio of the pressure difference between Pa and Pcv and CO (Rsys = (Pa-Pcv)/CO). The resistance downstream of Pmsf was taken to reflect resistance for venous return and calculated as the ratio of the pressure difference between Pmsf and Pcv and CO (Rvr = (Pmsf-Pcv)/CO). The pressure gradient for venous return (Pvr) was defined as the pressure difference between Pmsf and Pcv. After confirming a normal distribution of data with the Kolmogorov-Smirnov test, differences in parameters during baseline condition (mean of baseline-1 and baseline-2) and the condition with increased NE infusion rate were analyzed using paired t-tests. SVV as predictor of the NE-induced change in CO was analyzed using a receiver operating characteristic curve. The precision of the receiver operating characteristic analysis for the area under the curve, sensitivity, specificity and cut-off values are reported as 95% confidence intervals. All values are given as mean ± SD. A p-value < 0.05 was considered statistically significant.

Results

Sixteen patients were included in the study with a mean age of 64 ± 11 years, mean weight 90 ± 17 kg, and mean length 176 ± 8 cm. All patients underwent coronary artery bypass surgery, except one patient who had a mitral valvuloplasty. All patients had low dosages of NE (0.04 ± 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$) at baseline. Except for dobutamine

which was given to one patient in low dosage (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$), no other vasoactive medication was given.
Table 10.1 shows the pooled results of baseline measurements before (baseline-1), during increased NE infusion rate and after return to original NE dose (baseline-2). There were no significant differences in hemodynamic values between baseline-1 and baseline-2. An average increase in NE dosage of 0.04 ± 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$ induced an increase of Pa with 19.7 ± 8.7 mmHg. Increasing NE resulted in a decrease in CO in 10 patients and an increase in CO in 6 patients (table 10.1). In the patients with a CO decrease, NE was increased from 0.04 ± 0.04 to 0.09 ± 0.06 $\mu g \cdot kg^{-1} \cdot min^{-1}$; in the patients with a CO increase, NE was increased from 0.04 ± 0.04 to 0.08 ± 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The dose of NE during baseline conditions as well as the dose during NE increase did not differ between both groups. The 10 patients that decreased CO on NE had a significantly higher rise in Pcv, Rsys and Rvr during NE (p-values 0.042, 0.002 and 0.019 respectively) compared to the 6 patients that increased CO on NE. Furthermore, these 10 patients had a decline in HR ($p = 0.002$) and a stable stroke volume, while the group of 6 patients with an increase in CO had a stable HR and an increase in stroke volume ($p = 0.001$). The patients with a CO decrease during NE had at baseline a significant lower SVV ($p = 0.012$) as well as a lower SVV during NE ($p = 0.001$) compared to the patients with a CO increase during NE.

When predicting CO response to NE based on SVV, a receiver operating characteristic curve with an area under the curve of 0.900 (95% CI 0.647-0.987, $p = 0.0001$) was found and a cut-off SVV value of 8.7% with a sensitivity and specificity of 100% and 70%, respectively.

Discussion

Our study shows that NE-induced increases in arterial pressure can be associated with either an increase or a decrease in CO in stable postoperative cardiac surgery patients depending on baseline ventricular responsiveness. Those patients with a greater baseline SVV increased their CO in response to a NE-induced increase in arterial pressure.
The physiologic explanation for these divergent CO responses in a group of otherwise similar patients rests in the differential effects NE had on venous return and ventricular function between these two subgroups of patients. To illustrate this point, we plotted venous return curves (based on the inspiratory hold maneuvers) and an estimation of a cardiac function curve for both CO-increasing and CO-decreasing patients (figure 10.2A and B). We used SVV as a measure of the steepness of the cardiac function curve.[21] Because the heart can only pump into the arteries that which it receives and the heart has minimal reservoir capacity venous return matches CO very closely over a few heart beats.[22] Thus, the intersection of the cardiac function and venous return curves at the time of study reflects steady-state CO and its change if either of these relations varies. These points are expanded upon below.

Table 10.1 Pooled results for 16 patients at start (Baseline-1), after increasing norepinephrine dosage (NE) and 15 minutes after decreasing the norepinephrine infusion to original dosage (Baseline-2).

All Patients (n = 16)

	Baseline-1	NE	Baseline-2	p
Pa (mmHg)	81.60 ± 10.16	101.85 ± 9.81	82.80 ± 13.60	< 0.001
HR (min^{-1})	74.4 ± 14.0	70.1 ± 13.8	75.7 ± 14.1	0.003
CO ($l•min^{-1}$)	4.30 ± 0.78	4.09 ± 0.67	4.44 ± 0.80	0.043
SV (ml)	59.4 ± 13.3	60.4 ± 15.2	60.7 ± 15.6	0.825
Pcv (mmHg)	7.61 ± 2.07	8.55 ± 2.35	7.58 ± 2.13	< 0.001
Pmsf (mmHg)	21.44 ± 6.12	27.57 ± 7.39	21.98 ± 5.34	< 0.001
Pvr (mmHg)	13.60 ± 5.66	19.02 ± 6.20	14.26 ± 5.16	0.001
Rvr ($mmHg•min•l^{-1}$)	3.14 ± 0.94	4.72 ± 1.64	3.22 ± 0.99	< 0.001
Rsys ($mmHg•min•l^{-1}$)	17.42 ± 3.88	23.31 ± 4.09	17.35 ± 4.27	< 0.001
Rvr/Rsys	19.0 ± 7.9	20.4 ± 6.6	19.2 ± 6.9	0.305
SVV (%)	11.1 ± 4.0	7.9 ± 4.3	11.0 ± 4.7	< 0.001

Patients with CO increase after NE Group A (n = 6)

	Baseline-1	NE	Baseline-2	p
Pa (mmHg)	81.65 ± 13.67	98.41 ± 10.68	85.14 ± 19.27	0.010
HR (min^{-1})	73.2 ± 17.0	72.7 ± 16.1 [h.]	73.0 ± 16.1	0.419
CO ($l•min^{-1}$)	4.06 ± 0.93	4.31 ± 0.86 [d.]	4.16 ± 0.80	0.004
SV (ml)	57.5 ± 16.9	61.4 ± 16.8	59.2 ± 17.1	0.001
Pcv (mmHg)	7.57 ± 2.30	8.03 ± 2.68 [e.]	7.37 ± 2.25	0.064
Pmsf (mmHg)	19.80 ± 5.27	23.57 ± 4.62	19.22 ± 4.40	0.014
Pvr (mmHg)	12.23 ± 4.36	15.55 ± 4.34	11.85 ± 4.02	0.024
Rvr ($mmHg•min•l^{-1}$)	2.97 ± 0.57	3.58 ± 0.64 [c., f.]	2.82 ± 0.73	0.026
Rsys ($mmHg•min•l^{-1}$)	18.83 ± 5.01	21.54 ± 4.36 [g.]	18.97 ± 5.07	0.022
Rvr/Rsys	16.7 ± 6.0	17.1 ± 4.3	15.2 ± 3.4	0.355
SVV (%)	14.4 ± 4.2 [a.]	11.9 ± 2.7 [b.]	14.9 ± 3.7	0.009

Patients with CO decrease after NE Group B (n = 10)

	Baseline-1	NE	Baseline-2	p
Pa (mmHg)	82.52 ± 8.10	103.91 ± 9.19	82.22 ± 9.21	< 0.001
HR (min^{-1})	75.1 ± 12.8	68.6 ± 12.9 [h.]	77.3 ± 13.4	0.002
CO ($l•min^{-1}$)	4.46 ± 0.64	3.96 ± 0.52 [d.]	4.61 ± 0.74	0.002
SV (ml)	60.5 ± 11.6	59.8 ± 15.1	61.6 ± 15.5	0.558
Pcv (mmHg)	7.57 ± 1.93	8.86 ± 2.22 [e.]	7.65 ± 2.06	< 0.001
Pmsf (mmHg)	22.40 ± 6.11	29.97 ± 7.88	23.51 ± 4.94	0.005
Pvr (mmHg)	14.77 ± 5.52	21.10 ± 6.38	15.86 ± 4.54	0.010
Rvr ($mmHg•min•l^{-1}$)	3.29 ± 1.00	5.41 ± 1.68 [c., f.]	3.48 ± 0.93	0.001
Rsys ($mmHg•min•l^{-1}$)	16.67 ± 2.34	24.37 ± 3.74 [g.]	16.49 ± 2.96	< 0.001
Rvr/Rsys	20.3 ± 7.8	22.3 ± 7.2	21.5 ± 6.4	0.478
SVV (%)	9.1 ± 2.4 [a.]	5.3 ± 2.9 [b.]	8.7 ± 3.6	< 0.001

NE, norepinephrine; Pa, mean arterial blood pressure; HR, heart rate; CO, cardiac output; SV, stroke volume; Pcv, central venous, pressure; Pmsf mean systemic filling pressure; Pvr, pressure gradient for venous return; Rvr, resistance to venous return; Rsys, systemic vascular resistance; Rvr/Rsys, location of Pmsf; SVV, stroke volume variation.

Comparing mean baseline value between Group A and B: [a.] $p = 0.012$. Comparing norepinephrine values between Group A and B:[b.] $p = 0.001$; [c.] $p = 0.009$. Comparing change in value induced by norepinephrine between Group A and B: [d.] $p < 0.001$; [e.] $p = 0.042$; [f.] $p = 0.019$; [g.] $p = 0.002$; [h.] $p = 0.003$

Cardiac output increase by norepinephrine. In 6 patients CO increased during NE. We schematically constructed an averaged venous return curve and a cardiac function curve for these patients (figure 10.2A) based on the average values of Pcv, Pmsf and CO (table 10.1). Two mechanisms determine the change in the venous return curve during NE: an increase in effective circulating blood volume as manifest by an increased Pmsf and an increase in Rvr. How can Pmsf increase during NE? This can occur due to a decrease in systemic vascular compliance or a decrease in systemic vascular unstressed volume. Changes in systemic vascular compliance in response to low dose NE are minimal; however, decreases in unstressed volume are more likely owing to blood flow redistribution away from high unstressed volume vascular beds.[23] Unstressed volume is the blood volume that is required to fill the circulatory system without causing intravascular pressure and stressed volume (the volume that stretches the vascular system to create the intravascular pressure, Pmsf).[23] Thus, as Pmsf increased during NE without a change in total blood volume, the increase in Pmsf is the result of a volume shift from the unstressed to the stressed compartment (figure 10.2A shift from point *a* to *b*). This recruitment of volume from unstressed to stressed volume can be the result of an increased arteriolar resistance to those parts of the circulation with a high proportions of unstressed volume (e.g. splanchnic circulation)[24] or a selective increase in venous smooth muscle tone.

An increase in venous smooth muscle tone will not only decrease unstressed volume, but also diminish the cross-sectional area of the venous vessels and increase Rvr, which will be manifest by the lower slope of the venous return curve during increased NE compared to baseline condition (figure 10.2A, point *c*). The increase in Pmsf with NE while Pcv was constant results in an increased Pvr. Although both Pvr and Rvr increased, the ratio (which defines venous return) increased during NE. Because venous return and cardiac output must be equal over time, the intersection of the venous return curve and the heart function curve determines cardiac output (figure 10.2A, points *a* and *c*). The heart function curve has to fit through these data points if there is no change in heart function.

The decrease in SVV from baseline to NE (14.4% to 11.9%) indicated that the patients shifted to a less steep part of their cardiac function curve. This change in ventricular responsiveness could have been due to either the increased filling or the impaired output owing to the associated increased afterload. Since CO increased in these patients, the most likely primary mechanism for the decrease in SVV is an increase in preload (an increase in venous return), resembling volume expansion, which, in this case, is achieved by recruitment of volume from the unstressed to the stressed compartment. Thus, in our patients who increased CO on NE, the likely working mechanism of NE is recruitment of intravascular volume resulting in an increase in Pmsf, which has a stronger effect than the associated increase in Rvr and left ventricular afterload (increased Pa).

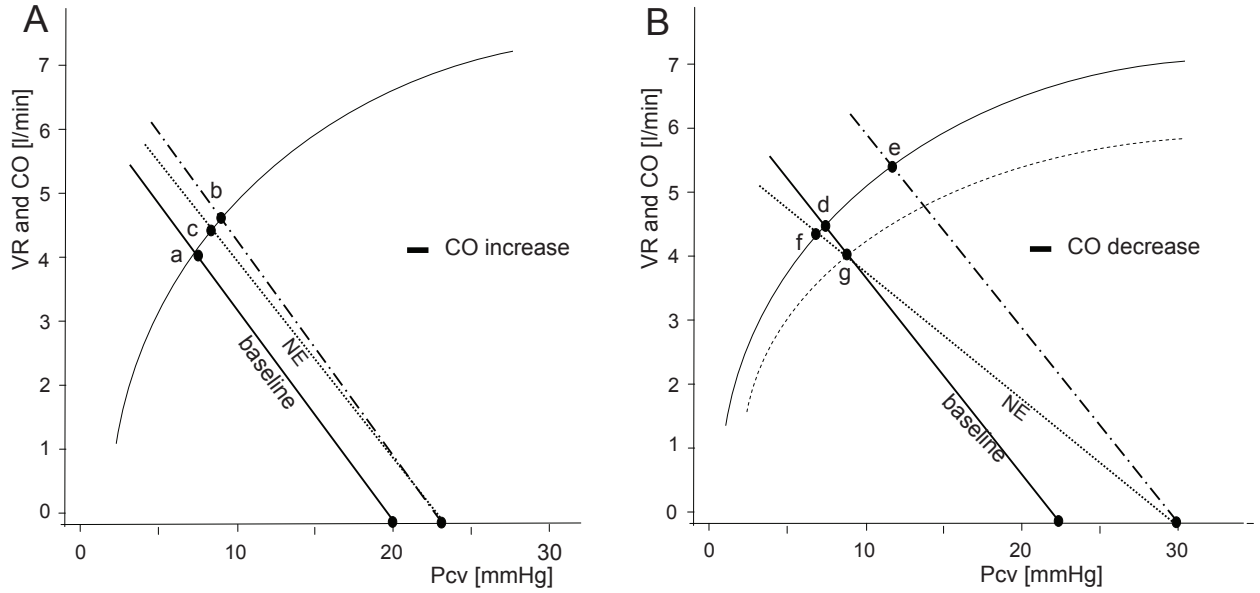

Figure 10.2 Effects of norepinephrine explained with venous return and cardiac output curves
Venous return (VR) curve and cardiac output (CO) curve constructed from average values of central venous pressure (Pcv), mean systemic filling pressure (Pmsf) and CO for patients who increased CO (A) and decreased CO (B) after norepinephrine (NE) dose increase. The dots are the mean values derived from table 2 for the CO-increasing and the CO-decreasing group.
Panel A: a. indicates working point of the circulation during baseline condition; b. indicates volume effect of generalized venoconstriction on CO by NE; c. indicates additional effect of venoconstriction on resistance to venous return (Rvr).
Panel B: d. indicates working point of the circulation during baseline condition; e. indicates volume effect of generalized venoconstriction on CO by NE; f. indicates additional effect of venoconstriction on Rvr; g. indicates effect of decreased heart function.

Such vasopressor-induced recruitment of blood volume from the unstressed compartment was previously described in dogs given α-adrenoceptor agonists (methoxamine hydrochloride and UK 14304-18).[25] Similarly, in pigs with normal cardiac function, NE indeed shifted the venous return curve to the right (and increased Pmsf), without affecting Rvr, which increased venous return and thus CO.[13] Recently, an increase in cardiac preload (defined as left ventricular end-diastolic area) was found in septic shock patients when NE infusion was started or infusion rate increased.[5,10] It is not clear from those studies if the increased end-diastolic volume was due to increased venous return, cardiac dilation due to increased afterload or both. Potentially, in sepsis, the unstressed volume could act as a reservoir, from which blood volume can be recruited. Considering the marked vasodilation and excess blood flow often seen in resuscitated patients in septic shock, this assumption seems reasonable. Monnet *et al*.[10] also suggested that in states where vasoconstriction is predominant, such as cardiogenic and hypovolemic shock, NE would not alter preload significantly and thus could have different effects on CO. Indeed, NE infusion was associated with an unchanged CO in other studies in cardiogenic shock[11,26], in head trauma and in septic patients.[12] The latter two studies gave no individual patient data. Thus, it remains speculative if CO was indeed stable

in these patient groups or that their study group also consisted of both CO-increasing and CO-decreasing patients.

Cardiac output decrease by norepinephrine. In the remaining 10 patients in our study NE caused CO to decrease. In figure 10.2B we indicate at least three mechanisms determining the change in venous return or cardiac output with NE. These include the same two as for the other group, namely an increase in Pmsf (shift from point *d* to *e*) and Rvr (shift to point *f*), plus specifically for this group a decrement in the heart function curve (shift to point *g*). As in the increased CO with NE group, the increase in Pmsf is probably caused by same mechanisms, namely an increase in effective blood volume by recruitment of blood from unstressed to stressed volume concomitant with an increased Rvr. Importantly, the slope of the venous return curve (Rvr) changes significantly more with NE in the CO decrease group as compared to the CO increase group. Despite the increase in Pmsf in the CO decrease group (point *e*), venous return decreased because of larger rise in Rvr (i.e. the flattening of the slope of the venous return curve, point *f*) resulted in a decrement in the ratio of Pvr to Rvr and since venous return = Pvr/Rvr, these changes explain the resultant CO decrease.

Plotting the cardiac function curve and the intersection with the venous return curve revealed the third mechanism for the effects of NE on CO. Because Pmsf and Pcv both increased with NE, a shift of the working point downward to the steeper part on the same cardiac function curve cannot be the explanation for the decrease in CO in these patients. Also, the decrease in SVV is inconsistent with this explanation. The fall in CO can only be explained by a decrement in the cardiac function curve, as manifest by a less steep slope and reaching a lower plateau than it had at baseline (figure 10.2B, dashed heart function curve, point *g*). Thus, in patients that decrease CO on NE, the negative impact of increased left ventricular afterload becomes the dominant process. That initial baseline SVV, a measure of ventricular responsiveness, also identified these patients from those whose CO increased, not only supports this mechanism but also suggests that simple bedside measures can be used to predict the response to NE-induced increased vasomotor tone on CO. Others have reported similar findings. Desjars *et al*.[7] observed a fall in CO in septic patients in response to a NE-induced increased Pa. Similarly CO decreased in hypotensive septic shock patients given nitric oxide synthase inhibition to raise Pa[27] and in patients with cardiogenic shock where the decrease was attributed to mitral valve insufficiency.[11]
Importantly, in our patients who decreased CO with NE, they also displayed HR reduction. This finding resulted in a stroke volume unchanged. HR changes in response to NE have been reported before but the changes are variable. No decrease in HR was reported in septic shock patients treated with NE.[5,8,10,28,29] In fact, HR increased during NE infusion in both septic shock patients[29] and septic pigs.[13] Still other studies demonstrated a NE-induced reduction in HR in healthy humans[30-32], normal and

hypertensive subjects[33] and in several animal studies.[14,34-36] The HR reduction in all these studies was attributed to a baroreceptor-mediated central sympathetic withdrawal triggered by the NE-induced increased blood pressure.[34,36] However, such baroreceptor-induced change in HR is accompanied by vasodilation of veins and arterioles.[37] Thus a decrease in vascular resistance might also be expected. Presumably, the NE-induced increased vascular smooth muscle tone overrides the decrement in sympathetic tone because Pa increased. Still, it is difficult to explain why our subjects who decreased their CO in response to NE also manifest this HR reduction because the increase in Pa was similar to that of the other sub-group whose CO increased similarly. Another possible explanation is a chemoreceptor-mediated response, but this mechanism is more effective in hypotensive than in hypertensive states.[37] Direct stretch of the right atrium by an increase in stressed volume (the Bainbridge reflex) cannot explain the HR reduction, because it induces the opposite effect.[37] Finally, if anything, any direct effect of NE should be an increase in HR due to direct beta adrenergic receptor stimulation.

The differential effects of NE on CO in our study, together with an increase in Pa, are remarkably similar to those reported earlier for the hemodynamic response to aortic cross clamping prior to aortic aneurysm repair. The immediate effect of abdominal aortic cross clamping is to increase Pa. However, in those subjects with preserved ventricular pump function the decreased vascular bed perfusion reduces unstressed volume increasing both Pmsf and CO, whereas in those with impaired ventricular pump function, although Pmsf also increases the increased afterload results in a decrement in CO.[38]

Clinical implications of our study. In a hypotensive patient, maintenance of organ perfusion pressure while still sustaining an adequate CO is critical. Thus, the clinician has the choice between fluid loading and vasoactive medication. Our study allows an insight in the mechanisms by which NE may alter CO. In some patients administration of NE mimics the effect of fluid loading on CO and in others the CO declines because a disproportional increase in Rvr reduces venous return and because of decreased contractile reserve. Our data further suggests that in postoperative cardiac surgery patients a SVV > 8.7% is associated with an increased CO in response to NE. In the hypotensive critically ill patient the clinician can therefore choose either fluid loading, administration of NE, or both to attempt to restore cardiovascular sufficiency, depending on the fluid responsiveness of the patient. Importantly, not only does a SVV < 8.7% in our study predict that NE will decrease CO but also that this is associated with a decrease in HR and cardiac function. In these patients, if one must simultaneously increase Pa and CO, the addition of an inotropic agent, like dobutamine, could be indicated. In pigs we showed that dobutamine decreases Pcv by an increase in cardiac function, leading to an increase in the pressure gradient for venous return. Together with a decrease in Rvr this results in an increase in CO.[16] Although further study in patients with more diverse

clinical conditions, like trauma and sepsis, needs to be done before such a simplified approach can be assumed to universally inform clinical decision-making, the approach we describe above can be used in studying those populations as well.
From a clinical perspective, increasing CO is not always the goal of resuscitation. In the hyperdynamic hypotensive patient, restoration of Pa, in order to improve vital organ perfusion pressure, despite a reduction in CO, is often an acceptable strategy. Finally, avoidance of peripheral edema is another potential goal of balanced resuscitation. In that regard, both NE and fluid loading increase Pmsf, and thus the hydrostatic pressure in the capillaries and venules, increasing the potential for peripheral edema formation. Accordingly, using NE to avoid peripheral edema is not supported by the results of these studies. Theoretically, NE may have possible salutary effect on capillary filtration coefficient, if arterial vasoconstriction decreases capillary pressure. Furthermore, NE-induced vasoconstriction might lead to reduced blood flow through some capillary beds all together, reducing global capillary filtration pressure. However, these effects of NE on peripheral edema formation are beyond the scope of this study.

Limitations and assumptions. We only studied 16 patients, though their responses were very specific and the data reached statistical significance. Thus, we doubt that increasing the number of study patients would reduce the differences found. Still some of the differences in calculated parameters may have reached statistical significance with a larger patient cohort, although the directional changes would unlikely reverse. In this study population, a change in NE dose was not clinically indicated, as the patients had adequate CO and blood pressure. Restoring blood pressure in a previously hypotensive patient may result in different responses than those observed in our normotensive patients. However, no human study has been previously reported of the effects of NE on Pmsf and resistance to venous return. For this explorative study, we therefore chose a stable group of highly instrumented patients to describe the effects of NE. Future studies will need to examine the effect of NE on CO during hypotension due to sepsis, hypovolemia and impaired ventricular function and after volume resuscitation.

Pmsf measured with the inspiratory hold technique has not been validated by comparing it with Pmsf by total circulatory stop-flow.[39] However, Pinsky[40] in intact canine showed Pmsf by ventilatory maneuvers to be equal to Pmsf by total circulatory stop-flow. We[41] recently showed in pigs that flow measured with a flow probe around the pulmonary artery, with a flow probe around the aorta and with Modelflow pulse contour were interchangeable. Furthermore, we found that estimations of Pmsf with the inspiratory hold technique using a flow probe around the aorta and pulse contour Modelflow method were interchangeable. We did not recalibrate the Modelflow after increasing NE dose because in a previous multicenter study[18] in cardiac surgery patients, we showed that a single calibration of Modelflow was adequate and that vasoactive drugs did not affect the ability to track changes in CO thus induced.

We assumed venous compliance to be constant during baseline and NE conditions. There are no human studies examining the effect of NE on venous compliance, but NE infusion in cats did not alter venous compliance.[42]
Our patients were mechanically ventilated without spontaneous breathing efforts and they had regular heart rates, all prerequisites for a reliable estimation of the venous return curves, Pmsf, CO and SVV. These prerequisite conditions make our analysis not directly applicable to other patient groups.

Conclusions

NE-induced increased Pa can either increase or decrease CO. The effect of NE on CO is a balance between increasing effective circulatory blood volume, venoconstriction and increased left ventricular afterload in stable postoperative cardiac surgery patients. Larger SVV correlates with increasing CO in response to NE.

References

1 Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36**:**296-327.

2 Levy B, Perez P, Perny J, Thivilier C, Gerard A. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. *Crit Care Med* 2011; 39**:**450-455.

3 De BD, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent JL. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010; 362**:**779-789.

4 Martin C, Viviand X, Arnaud S, Vialet R, Rougnon T. Effects of norepinephrine plus dobutamine or norepinephrine alone on left ventricular performance of septic shock patients. *Crit Care Med* 1999; 27**:**1708-1713.

5 Hamzaoui O, Georger JF, Monnet X, Ksouri H, Maizel J, Richard C, Teboul JL. Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension. *Crit Care* 2010; 14**:**R142.

6 Lauzier F, Levy B, Lamarre P, Lesur O. Vasopressin or norepinephrine in early hyperdynamic septic shock: a randomized clinical trial. *Intensive Care Med* 2006; 32**:**1782-1789.

7 Desjars P, Pinaud M, Potel G, Tasseau F, Touze MD. A reappraisal of norepinephrine therapy in human septic shock. *Crit Care Med* 1987; 15**:**134-137.

8 Sakka SG, Kozieras J, Thuemer O, van Hout N. Measurement of cardiac output: a comparison between transpulmonary thermodilution and uncalibrated pulse contour analysis. *Br J Anaesth* 2007; 99**:**337-342.

9 Monnet X, Anguel N, Naudin B, Jabot J, Richard C, Teboul JL. Arterial pressure-based cardiac output in septic patients: different accuracy of pulse contour and uncalibrated pressure waveform devices. *Crit Care* 2010; 14**:**R109.

10 Monnet X, Jabot J, Maizel J, Richard C, Teboul JL. Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients (R3). *Crit Care Med* 2011; 39**:**689-694.

11 Rokyta R, Jr., Tesarova J, Pechman V, Gajdos P, Krouzecky A. The effects of short-term norepinephrine up-titration on hemodynamics in cardiogenic shock. *Physiol Res* 2010; 59**:**373-378.

12 Albanese J, Leone M, Garnier F, Bourgoin A, Antonini F, Martin C. Renal effects of norepinephrine in septic and nonseptic patients. *Chest* 2004; 126**:**534-539.

13 Datta P, Magder S. Hemodynamic response to norepinephrine with and without inhibition of nitric oxide synthase in porcine endotoxemia. *Am J Respir Crit Care Med* 1999; 160**:**1987-1993.

14 Pang CC, Tabrizchi R. The effects of noradrenaline, B-HT 920, methoxamine, angiotensin II and vasopressin on mean circulatory filling pressure in conscious rats. *Br J Pharmacol* 1986; 89**:**389-394.

15 Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, Jansen JR. Assessment of venous return curve and

mean systemic filling pressure in postoperative cardiac surgery patients. *Crit Care Med* 2009; 37**:**912-918.

16 Geerts BF, Maas JJ, Aarts LP, Pinsky MR, Jansen JR. Partitioning the resistances along the vascular tree: effects of dobutamine and hypovolemia in piglets with an intact circulation. *J Clin Monit Comput* 2010; 24**:**377-384.

17 Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. *J Appl Physiol* 1993; 74**:**2566-2573.

18 Jansen JR, Schreuder JJ, Mulier JP, Smith NT, Settels JJ, Wesseling KH. A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. *Br J Anaesth* 2001; 87**:**212-222.

19 de Vaal JB, de Wilde RB, van den Berg PC, Schreuder JJ, Jansen JR. Less invasive determination of cardiac output from the arterial pressure by aortic diameter-calibrated pulse contour. *Br J Anaesth* 2005; 95**:**326-331.

20 de Wilde RB, Schreuder JJ, van den Berg PC, Jansen JR. An evaluation of cardiac output by five arterial pulse contour techniques during cardiac surgery. *Anaesthesia* 2007; 62**:**760-768.

21 Michard F. Stroke volume variation: from applied physiology to improved outcomes. *Crit Care Med* 2011; 39**:**402-403.

22 Jansen JR, Maas JJ, Pinsky MR. Bedside assessment of mean systemic filling pressure. *Curr Opin Crit Care* 2010; 16**:**231-236.

23 Rothe CF. Mean circulatory filling pressure: its meaning and measurement. *J Appl Physiol* 1993; 74**:**499-509.

24 Caldini P, Permutt S, Waddell JA, Riley RL. Effect of epinephrine on pressure, flow, and volume relationships in the systemic circulation of dogs. *Circ Res* 1974; 34**:**606-623.

25 Appleton CP, Lee RW, Martin GV, Olajos M, Goldman S. Alpha 1- and alpha 2-adrenoceptor stimulation: changes in venous capacitance in intact dogs. *Am J Physiol* 1986; 250**:**H1071-H1078.

26 Martin C, Papazian L, Perrin G, Saux P, Gouin F. Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? *Chest* 1993; 103**:**1826-1831.

27 Lopez A, Lorente JA, Steingrub J, Bakker J, McLuckie A, Willatts S, Brockway M, Anzueto A, Holzapfel L, Breen D, Silverman MS, Takala J, Donaldson J, Arneson C, Grove G, Grossman S, Grover R. Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. *Crit Care Med* 2004; 32**:**21-30.

28 Rauch H, Muller M, Fleischer F, Bauer H, Martin E, Bottiger BW. Pulse contour analysis versus thermodilution in cardiac surgery patients. *Acta Anaesthesiol Scand* 2002; 46**:**424-429.

29 Dubin A, Pozo MO, Casabella CA, Palizas F, Jr., Murias G, Moseinco MC, Kanoore Edul VS, Palizas F, Estenssoro E, Ince C. Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: a prospective study. *Crit Care* 2009; 13**:**R92.

30 Hoogenberg K, Smit AJ, Girbes AR. Effects of low-dose dopamine on renal and systemic hemodynamics during incremental norepinephrine infusion in healthy volunteers. *Crit Care Med* 1998; 26**:**260-265.

31 Richer M, Robert S, Lebel M. Renal hemodynamics during norepinephrine and low-dose dopamine infusions in man. *Crit Care Med* 1996; 24**:**1150-1156.

32 Pickkers P, Jansen Van Rosendaal AJ, Van Der Hoeven JG, Smits P. Activation of the ATP-dependent potassium channel attenuates norepinephrine-induced vasoconstriction in the human forearm. *Shock* 2004; 22**:**320-325.

33 Manger WM, Frohlich ED, Gifford RW, Dustan HP. Norepinephrine infusion in normal subjects and patients with essential or renal hypertension: effect on blood pressure, heart rate, and plasma catecholamine concentrations. *J Clin Pharmacol* 1976; 16**:**129-141.

34 Hollis AR, Ousey JC, Palmer L, Stephen JO, Stoneham SJ, Boston RC, Corley KT. Effects of norepinephrine and combined norepinephrine and fenoldopam infusion on systemic hemodynamics and indices of renal function in normotensive neonatal foals. *J Vet Intern Med* 2008; 22**:**1210-1215.

35 Nouira S, Elatrous S, Dimassi S, Besbes L, Boukef R, Mohamed B, Abroug F. Effects of norepinephrine on static and dynamic preload indicators in experimental hemorrhagic shock. *Crit Care Med* 2005; 33**:**2339-2343.

36 Karzai W, Reilly JM, Hoffman WD, Cunnion RE, Danner RL, Banks SM, Parrillo JE, Natanson C. Hemodynamic effects of dopamine, norepinephrine, and fluids in a dog model of sepsis. *Am J Physiol* 1995; 268**:**H692-H702.

37 Guyton AC, Hall JE: Nervous regulation of the circulation, and rapid control of arterial pressure. In *Textbook of medical physiology*, edn 10. Edited by Schmitt W, Gruliow R. Philadelphia: W.B. Saunders Company; 2000:184-194.

38 Stene JK, Burns B, Permutt S, Caldini P, Shanoff M. Increased cardiac output following occlusion of the descending thoracic aorta in dogs. *Am J Physiol* 1982; 243**:**R152-R158.

39 Bar-Yosef S. Physiology of the circulation--an old-new vocabulary. *Crit Care Med* 2009; 37**:**1143-1144.

40 Pinsky MR. Instantaneous venous return curves in an intact canine preparation. *J Appl Physiol* 1984; 56**:**765-771.

41 Maas JJ, Geerts BF, Jansen JR. Evaluation of mean systemic filling pressure from pulse contour cardiac output and central venous pressure. *J Clin Monit Comput* 2011; 25**:**193-201.

42 Greenway CV, Seaman KL, Innes IR. Norepinephrine on venous compliance and unstressed volume in cat liver. *Am J Physiol* 1985; 248**:**H468-H476.

Chapter 11

Final considerations and clinical implications

Jacinta J. Maas and Jos R.C. Jansen

Department of Intensive Care Medicine, Leiden University Medical Center, The Netherlands

Final considerations and clinical implications

The critical care physician has several therapeutic options in hemodynamically unstable patients. Fluid resuscitation can restore effective circulating volume and thereby increase venous return (VR), cardiac output (CO) and consequently oxygen delivery to vital organs. However, too vigorous fluid administration can induce general and pulmonary edema which can lead to prolonged hospitalization[1,2] and even increased mortality.[3] Several vasoactive drugs are available: vasopressors, positive inotropic agents, vasodilators et cetera. The clinician has to decide frequently which strategy to use. Several tools are available to help the clinician in this decision-making, e.g. blood pressure, cardiac output, ventilator-induced variation in stroke volume or pulse pressure and echocardiography.

Volume status and fluid responsiveness

In order to decide either to give fluid loading or medication, ideally one would like to know the exact volume status of a patient. In this respect, it is important to recognize that volume status and fluid responsiveness are not the same.[4] In the following examples this principle is illustrated. In figure 11.1 a normovolemic (panel A) and a hypovolemic patient (panel B) are depicted. The areas of unstressed volume (Vu) and stressed volume (Vs) are smaller in the hypovolemic patient and mean systemic filling pressure (Pmsf) is lower. Obviously with volume resuscitation, the normovolemic condition (panel A) can be restored in the hypovolemic patient. When treated with a vasoconstrictive agent, Pmsf is restored, volume is shifted from the unstressed to the stressed compartment and VR is augmented, but the patient still remains hypovolemic (panel C).

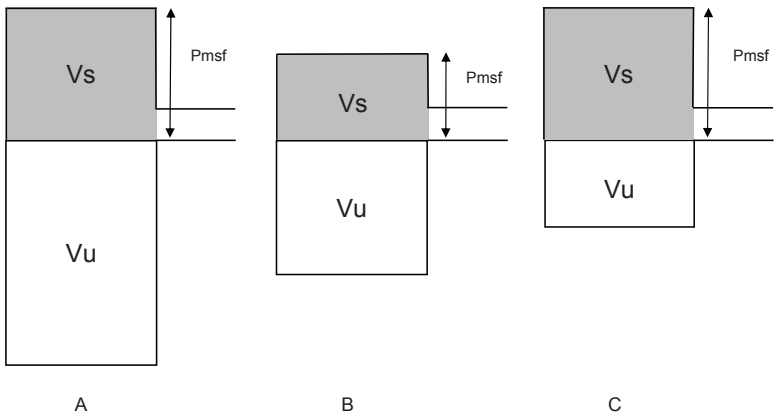

Figure 11.1 Schematic representation of intravascular volumes during normovolemia and hypovolemia

Panel A: normovolemia, with total blood volume divided into unstressed volume (Vu) and stressed volume (Vs). Mean systemic filling pressure (Pmsf) is the pressure in the compartment of Vs

Panel B: hypovolemia, with a reduced area of Vu and Vs, and a decline in Pmsf

Panel C: hypovolemia with administration of venoconstrictive medication. Note that the sum of the areas of Vu and Vs are equal to panel B. Volume has shifted from Vu to Vs. Pmsf is restored by venoconstriction.

Figure 11.2 shows a normovolemic (panel A) and a septic patient (B). In the septic patient volume has shifted from the stressed to the unstressed compartment due to vasodilation and Pmsf is substantially lower. Subsequently, the pressure gradient for venous return will be lower, which compromises VR. The septic patient is actually normovolemic, because the sum of areas A and B are equal to panel A. However, the septic patient is fluid responsive, just like the hypovolemic patient, and volume resuscitation will restore Pmsf. Consequently VR is corrected (panel C). Though, volume resuscitation will increase total blood volume substantially (seen as the larger sum of areas in panel C). During recovery this extra volume again has to be excreted. Another approach could be to restore venous tone with a vasoconstrictive agent. This will also restore Pmsf and VR (to panel A), without the cost of volume loading. In conclusion, both patients are fluid responsive, but the patient in figure 11.1 is hypovolemic and the patient in figure 11.2 is normovolemic. Therefore a measure of volume status complementing fluid responsiveness parameters is clinically valuable.

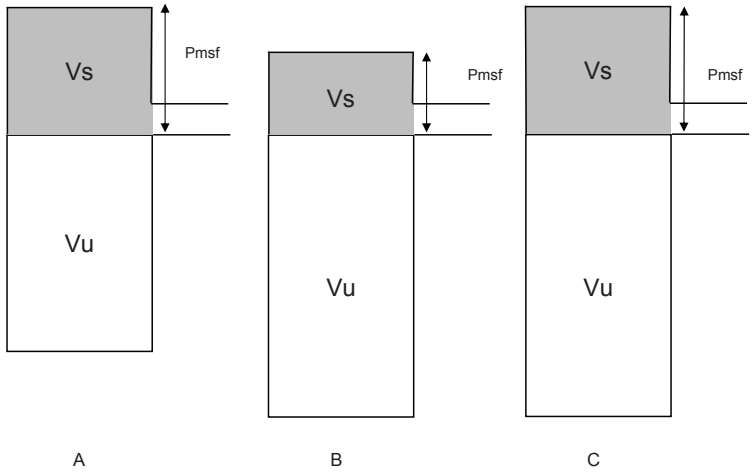

Figure 11.2 Schematic representation of intravascular volumes during sepsis
Panel A: normovolemia, with total blood volume divided into unstressed volume (Vu) and stressed volume (Vs). Mean systemic filling pressure (Pmsf) is the pressure in the compartment of Vs
Panel B: distributive shock, volume has shifted from Vs to Vu due to vasodilation and Pmsf is reduced.
Panel C: distributive shock after volume resuscitation, restoring Pmsf. Note that the sum of the areas Vu and Vs is enlarged.

The intravascular volume contains Vs and Vu. Vs is the most informative of these two volumes, because it represents the effective circulating blood volume. Vs generates Pmsf and consequently contributes to the pressure gradient for venous return. Vu can be seen as the reservoir from which volume can be recruited, but Vu does not take active part in the circulation. Magder and De Varennes[5] succeeded in measuring Vs in the operating room during hypothermic circulatory arrest for major vascular surgery by stopping the cardiac bypass pump and passively draining blood in a reservoir and found a stressed volume of 1290 ± 296 ml. Obviously this technique does not lend itself for use in the ICU.

Mean systemic filling pressure

Pmsf, which is the pressure that exists in the stressed volume compartment, could be a measure of Vs if we assume a constant systemic compliance (Csys). Indeed Vs = Pmsf • Csys. In this thesis we showed that it is feasible to determine Pmsf in ventilated ICU patients with the use of inspiratory holds.[6] However, the technique of measuring Pmsf and Vs with the inspiratory hold method is too time-consuming for a practical application in the ICU.

Pmsf should theoretically be measured anywhere in the circulation, therefore the arm occlusion technique (Parm) could offer a solution. This interesting technique of creating a stop-flow in the arm was already proposed by Anderson.[7] Parm can be measured relatively simple with only an upper arm cuff and a radial artery pressure measurement. We explored if Parm could be used as a measure for Pmsf. Although representing only a part of the body and thus being only a contributing factor to Pmsf, we found acceptable bias and limits of agreement (Chapter 5). Therefore, we concluded that Parm could serve as a substitute for Pmsf. With measurements of Parm after volume loading steps we showed that the possibility to estimate Vs (Chapter 7). With multiple volume steps of 50 ml a volume-pressure curve could be made, from which Vs could be calculated (figure 11.3). We showed that compliance did not change during the volume loading steps. In addition, we found that patients who had an increase in CO after fluid loading had a significantly smaller Vs than patients who did not increase CO. Thus patients on the steep part of the cardiac function curve had a smaller Vs than patients on the flat part of the cardiac function curve. We need to emphasize that we included only postoperative cardiac surgery patients and excluded patients with impaired heart function. Therefore, further research has to be done to investigate this technique in other clinical conditions such as cardiac failure and septic shock. In septic shock, vasodilation reduces Pmsf and Parm with unchanged total blood volume (figure 11.2). In figure 11.3 is schematically depicted how Vs is reduced in sepsis, implying an increase in Vu.

Could Pmsf serve as a predictor of fluid responsiveness as well? Pmsf assessed with the inspiratory hold method can only be determined in mechanically ventilated patients, which is the same limitation other predictors of volume responsiveness (stroke volume variation (SVV), pulse pressure variation (PPV)) have. We showed that Parm performs as good as SVV as predictor of CO response to fluid loading (Chapter 6). Importantly, Parm can be determined in all patients, including spontaneously breathing patients and even in patients with irregular heart rate.

Venous return

Besides being a measure of stressed volume, Pmsf is the driving force for venous return. Assessment of Pmsf allows the physician to construct venous return curves, to assess resistance to venous return and estimate vascular compliance (Chapter 7). As

Guyton[8] showed, the venous return curve can be combined with a cardiac function curve. The intersection of both curves represents the working point of the circulation. The knowledge of the specific effects of vasoactive medication based on venous return curves and cardiac function curves in groups of patients, may guide the clinician in therapeutic actions in an individual patient.

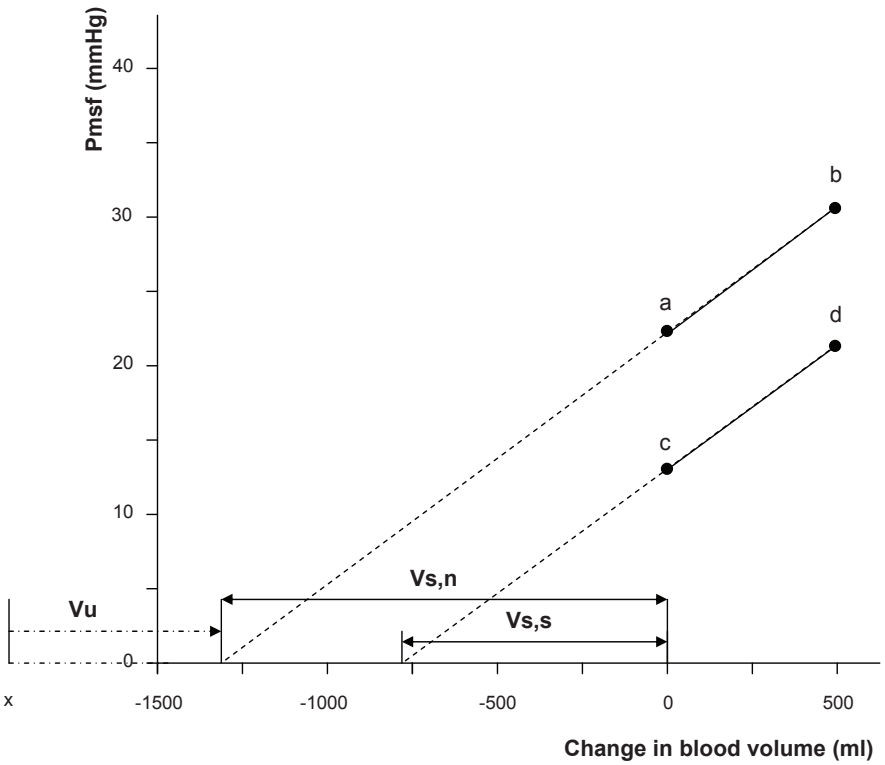

Figure 11.3 Determination of stressed volume
Relationship between change in blood volume and mean systemic filling pressure (Pmsf) for a non-septic patient at normovolemia (a) and after volume loading with 500 ml (b). In the figure stressed volume (Vs,n) is indicated. Removal of 1300 ml blood in this patient will lead to a Pmsf of 0, what rests in the circulation is unstressed volume. Thus Vs,n is 1300 ml. Sepsis is characterized by lower Pmsf at baseline (c) and after volume loading (d). Assuming a constant compliance, extrapolation leads to a stressed volume (Vs,s) of 800 ml, which is lower than Vs,n. As total blood volume is unchanged, unstressed volume increases in the septic patient.

The ability to assess resistance to venous return (Rvr) separately from total systemic vascular resistance (Rsys) allows specifying the hemodynamic effects of vasoactive medication. The question whether vasoactive medication affects the venous or the arterial side of the vascular system or both in ICU patients, can now be answered. In this thesis we showed that a positive inotropic agent as dobutamine predominantly decreases Rvr and to a lesser extent Rsys in pigs (Chapter 9). Besides increasing cardiac contractility, which is well known, dobutamine increases venous return due to the increase in the pressure gradient for venous return and the decrement in Rvr.
There may be differences in effects between different species. Thus the question if the same effects of dobutamine apply to humans, could be answered with use of the

inspiratory hold method in future studies.
Even within one species, humans, vasoactive medication can have opposite effects. In postoperative cardiac surgery patients, norepinephrine increased CO in some patients, while in other patients CO decreased (Chapter 10). We unraveled the different working mechanisms using venous return curves and cardiac function curves. The patients who increased CO increased venous return by recruitment of volume from the unstressed compartment. The patients with a CO decrease showed a significant larger increase in Rvr and Rsys during administration of norepinephrine. Furthermore we showed that the response to norepinephrine could be predicted with SVV measurement. In addition, a reduction in heart rate seemed to indicate a decline in CO in response to norepinephrine. By increasing Pmsf, norepinephrine potentially can induce edema similar to fluid loading. We concluded that our model with venous return and cardiac function curves makes it possible to investigate the effects of other vasoactive agents in different ICU patients with different pathophysiologic and pharmacologic conditions and possibly even predict these effects.
Rvr is an intriguing parameter, which is important for control of venous return and which can be manipulated with medication. The combination of norepinephrine and dobutamine is frequently used in the ICU. Our studies with norepinephrine (increasing stressed volume, but also increasing Rvr and with a variable effect on CO) and dobutamine (increasing contractility as well as decreasing Rvr) provide a rationale for this combination. Future studies addressing the hemodynamic effects of other vasoactive medication (in terms of venous return and cardiac function curves), could provide further insight in choosing the appropriate agent, e.g. targeting Rvr, and could present other combinations e.g. vasopressin and nitroglycerin.

Critical closing pressure and vascular waterfall

With the measurement of critical closing pressure (extrapolating arterial pressure at zero flow, Pcc), which exceeded Pmsf, we confirmed the presence of a vascular waterfall (Chapter 8). The presence of this vascular waterfall allows a temporary preservation of flow to vital organs in case of cardiac arrest.[9] When cardiac arrest continues, blood volume will leak from the arterial side of the vascular system to the venous side, because of the pressure gradient from Pcc tot Pmsf. Ultimately intravascular pressure will equilibrate to one pressure and flow will cease. The existence of a vascular waterfall has implications for calculation of vascular resistances. Arterial resistance should be calculated separately from Rvr. This further extends the model to characterize effects of medication.

Limitations

Because the application of inspiratory holds is necessary for the determination of Pmsf, Pcc and venous return, this technique is limited to mechanically ventilated patients. The

technique, we used in our studies, is as yet not available and suitable for routine clinical use, because it is time-consuming to execute the measurements. It takes approximately 4 minutes to apply the inspiratory holds, and the subsequent analysis again takes several minutes. However, it could be possible to incorporate measurement and analysis into a computer program, providing the clinician with an extra set of hemodynamic variables, as Pmsf, Pcc, Rvr and Ra.
For the assessment of Vs we assumed compliance to remain constant. We observed a constant compliance in the range of the measurements. We have no information about compliance beyond this range. Though, the values we observed were concordant with the values Magder and De Varennes[5] measured during cardiac arrest. Also for the study on norepinephrine, we assumed an unchanged compliance, which was confirmed in an animal study.[10] Further studies regarding compliance will be of value.

In conclusion, study of the venous side of the circulation broadens the clinician's horizon beyond fluid responsiveness and cardiac function. Measurement of Pmsf and Pcc adds to the understanding of the physiology and pathophysiology of hemodynamics and the effects of medication. Future studies to the effects of vasoactive medication with the inspiratory hold technique, will advance our knowledge and help the clinician in choosing the appropriate interventions (medication or fluid strategy) in the treatment of ICU patients.

References

1 Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF, Jr., Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354**:**2564-2575.

2 Mitchell JP, Schuller D, Calandrino FS, Schuster DP. Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. *Am Rev Respir Dis* 1992; 145**:**990-998.

3 Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011; 39**:**259-265.

4 Vincent JL, Weil MH. Fluid challenge revisited. *Crit Care Med* 2006; 34**:**1333-1337.

5 Magder S, De Varennes B. Clinical death and the measurement of stressed vascular volume. *Crit Care Med* 1998; 26**:**1061-1064.

6 Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, Jansen JR. Assessment of venous return curve and mean systemic filling pressure in operative cardiac surgery patients. *Crit Care Med* 2009; 37**:**912-918.

7 Anderson RM: *The gross physiology of the cardiovascular system*. Tucson, Arizona: Racquet Press; 1993.

8 Guyton AC, Hall JE: Cardiac output, venous return, and their regulation. In *Textbook of medical physiology*, edn 10. Edited by Schmitt W, Gruliow R. Philadelphia: W.B. Saunders Company; 2000:210-222.

9 Magder S. Starling resistor versus compliance. Which explains the zero-flow pressure of a dynamic arterial pressure-flow relation? *Circ Res* 1990; 67**:**209-220.

10 Greenway CV, Seaman KL, Innes IR. Norepinephrine on venous compliance and unstressed volume in cat liver. *Am J Physiol* 1985; 248**:**H468-H476.

Chapter 12

Summary/Samenvatting

Summary

The circulation is a circuit, in which blood flows to the heart (venous return), to be pumped by the heart (via the lungs) to the aorta (cardiac output). Starling placed the heart centrally in the circulation with the cardiac function curve. Consequently, analysis regarding cardiac output (CO) mostly concerns with preload, heart rate, contractility and afterload. The heart can be the limiting factor in the circulation, for example after myocardial infarction. However, when cardiac function is intact, CO is determined by venous return (VR). After all, the heart can only pump out, that which it receives and has very limited storing possibilities. Only for short periods of time CO can differ from VR after an intervention, but eventually CO and VR must reach a new equilibrium.
Mean systemic filling pressure (Pmsf) is the pressure in the vascular system during cardiac arrest and is determined by intravascular stressed volume and venous vasomotor tone. Guyton was the first to construct a VR curve by controlling right atrial pressure and measuring CO. When right atrial pressure was increased, VR and CO declined until zero flow was reached. At the point of zero flow right atrial pressure was equal to Pmsf. The pressure gradient between Pmsf and right atrial pressure or central venous pressure (Pcv) is the driving force for VR. The other determinant for VR is the resistance to venous return (Rvr).

In this thesis measurement of Pmsf and Guytonian analysis of venous return curve is taken from the animal laboratory to the intensive care unit (ICU).

Chapter 1
This chapter focuses on the importance of the VR curve for the circulation and its historic background. Pmsf is determined by intravascular stressed volume and venous vasomotor tone and is thus a measure of volume status. The intravascular volume can be divided in stressed volume and unstressed volume. Volume can be shifted between the stressed compartment and the unstressed compartment by changes in venous vasomotor tone. In the VR curve, Pmsf is the zero intercept on the x-axis. The slope of the VR curve is determined by Rvr, which in turn is influenced by venodilation or venoconstriction, but mostly changed by redistribution of blood in the vascular system. Several clinical conditions in the ICU patient are analyzed using the combined VR curve and cardiac function curve. Compensation mechanisms and possible therapeutic actions are derived from these curves. Until recently Pmsf could only be measured during circulatory arrest. We describe a method to asses Pmsf by constructing a VR curve with the inspiratory hold method, which was used in several studies in the following chapters.

Chapter 2
This chapter focuses on VR physiology and the construction of VR curves with the inspiratory hold method in mechanically ventilated patients. With an inspiratory hold

maneuver a steady state with an increased Pcv and a reduced CO is induced. Applying several inspiratory holds at different airway pressure levels, the corresponding Pcv and CO values can be plotted into a VR curve. From these VR curves the clinician can obtain at the bedside not only Pmsf, but also the derived parameters: Rvr (slope of VR curve), systemic compliance (changes in Pmsf after volume expansion) and stressed volume (from a Pmsf-volume curve). This technique opens the door for future studies of the determinants of VR and the control of CO in different patient populations, different pathophysiologic conditions and under different pharmacologic conditions. In the future cardiovascular therapy can be based on assumptions derived by venous return physiology and can be directed by measuring Pmsf, Rvr, stressed volume and systemic compliance in a fashion like the way we now measure CO and arterial pressure.

Chapter 3

In this study we investigated if Pmsf could be measured at the bedside using the inspiratory hold method in 12 postoperative cardiac surgery patients. We measured Pcv and CO (pulse contour analysis) during 4 inspiratory holds at different airway pressures. We constructed VR curves and determined Pmsf. Measurements were performed during 3 volume states: normovolemia (baseline), relative hypovolemia by placing the patients in 30˚ head-up position and relative hypervolemia by volume loading with 500 ml colloid. The VR curve was linear for all measurements and the slope was unaltered by volume status. As expected, Pmsf increased with volume loading and decreased when a relative hypovolemic state was created. Mean baseline compliance was 0.98 $ml \cdot mmHg^{-1} \cdot kg^{-1}$ en mean stressed volume was 1677 ml. We conclude that Pmsf can be determined in ICU patients with an intact circulation, making serial measures of circulatory compliance and stressed volume feasible.

Chapter 4

The aim of this study was to validate the assumptions made in our study in Chapter 3. These assumptions were: a. Pmsf can be determined with CO measurements using the pulse contour method and b. 4 inspiratory holds at different pressure levels are sufficient to determine Pmsf. CO was measured in 10 piglets with a flow probe around the pulmonary artery (COr), with a flow probe around the aorta (COl) and with pulse contour method from aortic pressure (COpc). Seven inspiratory holds were applied with different airway pressures. We showed that COr equaled COl equaled COpc at the end of the inspiratory holds. Pmsf obtained with COl and with COpc were interchangeable and the small coefficient of variation confirmed a good repeatability. Pmsf can thus be determined with use of pulse contour method. Furthermore we showed that Pmsf can be correctly estimated with 4, 3 and even 2 inspiratory holds. Consequently this study supports the assumptions made in the study described in Chapter 3.

Chapter 5

In this study we compared the level of agreement of three methods to measure Pmsf: 1. Pmsf determined with inspiratory hold maneuvers, 2. stop-flow pressure estimated in a model analogue of the circulation (Pmsa) and 3. arm equilibrium pressure during a 30 second stop-flow in the arm (Parm). In eleven postoperative cardiac surgery patients measurements were performed in supine position, rotating the bed to 30° head-up tilt (HUT) and after fluid loading (500 ml colloid). Mean Pmsf, Parm and Pmsa across all three states were 20.9 ± 5.6 mmHg, 19.8 ± 5.7 mmHg and 15.9 ± 4.9 mmHg, respectively. Bland-Altman analysis for the difference between Parm and Pmsf showed a non-significant bias of -1.0 ± 3.08 mmHg and limits of agreement of -7.3 and 5.2 mmHg. For the difference between Pmsf and Pmsa we found a bias of -6.0 ± 3.1 mmHg ($p < 0.001$) and limits of agreement of -12.4 and 0.3 mmHg. Changes in Pmsf and Parm and in Pmsf and Pmsa were fully concordant in response to HUT and volume loading. We conclude that Parm and Pmsf are interchangeable. Changes in effective circulatory volume are tracked well by changes in Parm and Pmsa.

Chapter 6

Pmsf is the equilibrium pressure anywhere in the circulation under circulatory arrest and it could theoretically be measured at any site in the circulation. Furthermore, Pmsf is a measure of effective circulating volume. In this study we explored if the pressure in the arm under stop-flow conditions, which can be seen as the equilibrium pressure of the arm, can be used as a predictor of fluid responsiveness. Arm occlusion pressure (Parm) was defined as the radial artery pressure after applying an upper-arm stop-flow for 35 seconds with a cuff at a pressure 50 mmHg above patients' systolic blood pressure. Measurements were performed before and after fluid loading (500 ml colloid). In 24 patients after cardiac surgery, Parm was compared to SVV and PPV as a predictor of fluid responsiveness. Patients whose CO increased by at least 10% were defined as the responders. The study population was divided into responders (n = 17) and non-responders (n = 7). The area under the curve to predict fluid loading responsiveness for Parm was 0.786 (95% CI: 0.567-1.000). For Parm < 21.9 mmHg sensitivity was 71% and specificity was 88% to predict fluid loading responsiveness. Prediction of responders with Parm was not different from that of SVV and PVV. We conclude that Parm is a good predictor of fluid loading responsiveness in cardiac surgery patients with normal ventricular function.

Chapter 7

In this study we explored the value of Pmsf measured in the arm ($Pmsf_{arm}$) for determination of vascular compliance and stressed volume. Hereto in 15 postoperative cardiac surgery patients 10 sequential infusions of 50 ml colloid were administered. After each fluid loading step $Pmsf_{arm}$, Pcv and CO were obtained. The $Pmsf_{arm}$-volume curve was linear, indicating a stable vascular compliance. Stressed volume could be

determined by extrapolating the $Pmsf_{arm}$-volume curve to zero pressure intercept. Stressed volume was estimated to be 1265 ± 541 ml (28.5 ± 15% predicted total blood volume). Cardiac function curves were plotted with the Pcv and CO values after each volume loading step. Patients who increased CO with > 12% after 500 ml fluid loading were described as fluid responsive. Fluid responding patients were on the steep part of the cardiac function curve and non-responding patients were on the flat part of the curve. From these results we conclude that systemic vascular compliance, stressed volume and cardiac function curves can be determined at the bedside and may be used to characterize patients hemodynamically.

Chapter 8

During cardiac arrest a pressure gap persisted between venous pressure (i.e. Pmsf) and arterial pressure (Pa). The plateau to which Pa declines is called arterial critical closing pressure (Pcc). In this study we explored the feasibility of determining Pcc with the inspiratory hold method. In 10 postoperative cardiac surgery patients CO, Pcv and Pa were obtained with inspiratory holds at 4 increasing airway pressures. The pairs of CO and Pa can be plotted in a ventricular output curve. Pcc was the value of Pa when flow was extrapolated to zero. Arterial resistance (Ra) was calculated as the ratio of Pa-Pcc and CO, while Rvr was the ratio of Pmsf-Pcv and CO. Pcc exceeded Pmsf in all cases, with an average pressure gap of 26.8 mmHg. We conclude that vascular pressure gradients in cardiac surgery patients suggest the presence of a vascular waterfall phenomenon. Furthermore, vascular resistance can now be divided into arterial (Ra) and venous resistance (Rvr). Ra is closely related to total systemic vascular resistance (Rsys).

Chapter 9

In this study we explored the hemodynamic effects of dobutamine and hypovolemia with a physiological model, which incorporated the VR curve, Pmsf, Rvr and Rsys. In 10 piglets measurements were performed before, during and after dobutamine infusion and during hypovolemia and after fluid resuscitation. Dobutamine increased CO and heart rate, but decreased Pmsf, Rsys and Rvr. The decrease in Rvr was significantly greater than the decrease in Rsys. Hypovolemia decreased CO, Pcv, Pmsf and Rvr, while heart rate increased. We conclude that the increase in CO during dobutamine infusion is due to the combined increased cardiac function and decreased Rvr. The decrease in CO with hypovolemia is attributed to a decreased Pmsf, but is partly compensated for by a decrease in Rvr tending to preserve VR and thus CO.

Chapter 10

In this study we explored the effects of norepinephrine on CO with use of VR curves and cardiac function curves. In 16 postoperative cardiac surgery patients, on low dose of norepinephrine, we measured Pmsf, Pcv, heart rate, stroke volume variation (SVV)

and CO before, during and after increased norepinephrine infusion. In 10 patients CO decreased and in 6 patients CO increased. In all patients Pmsf, Rsys and Rvr increased and SVV decreased. In the patients with a decline in CO, Rvr and Rsys increased more than in the patients who increased CO. Heart rate decreased in the patients with a decrease in CO and was unchanged in the patients with a CO increase. Baseline SVV was higher in the patients who increased CO and a SVV value > 8.7% predicted the increase in CO to norepinephrine (area under the curve of 0.900). We conclude that norepinephrine can increase CO by recruiting volume from the unstressed compartment, while the decrease in CO is attributed to a decrease in VR due to an increase in Rvr and possibly a decrease of heart function. The change in CO induced by norepinephrine is determined by the balance between volume recruitment (as determined by Pmsf) and the change in Rvr and heart function. Furthermore the response of CO to norepinephrine can be predicted by baseline SVV.

Chapter 11

This chapter focuses on the difference between volume status and fluid responsiveness. The clinical implications of VR curves, Pmsf and Pcc are explored. Finally limitations and suggestions for further research are discussed.

Nederlandse samenvatting

De bloedsomloop is een gesloten system, waarin bloed naar het hart stroomt (veneuze terugvloed), waarna het door het hart (via de longen) naar de aorta wordt gepompt (hartminuutvolume). Starling plaatste het hart centraal in de bloedsomloop met de hartfunctiecurve. Daarom staan in het onderzoek naar hartminuutvolume (cardiac output, CO) voorbelasting, hartfrequentie, contractiliteit en nabelasting van het hart op de voorgrond. Het hart kan de beperkende factor in de bloedsomloop zijn, bijvoorbeeld na een myocardinfarct. Als de hartfunctie echter intact is, wordt de CO bepaald door de veneuze terugvloed. Het hart kan immers alleen datgene uitpompen, dat het ontvangt en heeft weinig opslagruimte voor bloed. De CO kan na een interventie alleen kortdurend afwijken van de veneuze terugvloed, maar uiteindelijk zal er een nieuw evenwicht ontstaan tussen CO en veneuze terugvloed. De statische vullingsdruk (Pmsf) is de druk die ontstaat in het vasculaire systeem bij een hartstilstand en wordt bepaald door het circulerend bloedvolume en de veneuze vaattonus. Guyton liet als eerste zien hoe een veneuze terugvloedcurve kon worden geconstrueerd door de rechter atrium druk te veranderen en de CO te meten. Bij verhoging van de rechter atrium druk namen de veneuze terugvloed en de CO af, totdat uiteindelijk een CO van nul werd bereikt. Bij een CO en veneuze terugvloed van nul werd de rechter atriumdruk gelijk aan de Pmsf. Het drukverschil tussen Pmsf en de rechter atrium druk of de centraal veneuze druk (Pcv) is de drijvende kracht voor veneuze terugvloed. De andere determinant voor de veneuze terugvloed is de weerstand voor veneuze terugvloed (Rvr).

In dit proefschrift wordt het meten van de statische vullingsdruk (Pmsf) en de analyse van de curve van de veneuze terugvloed naar het hart beschreven. We maken hierin de stap van het dierexperimentele laboratorium naar de intensive care.

Hoofdstuk 1

Dit hoofdstuk beschrijft het belang van de veneuze terugvloed voor de circulatie. De geschiedenis van het bepalen van de veneuze terugvloed en de Pmsf wordt kort beschreven. Pmsf wordt bepaald door het actief circulerend bloedvolume en de veneuze vaattonus en is dus een maat voor de volumetoestand. Het intravasculaire bloedvolume bestaat uit twee compartimenten: een compartiment met een bloedvolume, dat druk veroorzaakt in de bloedvaten (stressed volume, Vs) en een compartiment met een bloedvolume, dat de bloedvaten vult zonder druk op te bouwen (unstressed volume, Vu). Bloed kan verplaatst worden van het ene naar het andere compartiment door de veneuze vaattonus te veranderen. In de veneuze terugvloedcurve is Pmsf het snijpunt met de x-as, bij een CO van nul. De hellingshoek van de curve wordt bepaald door de weerstand voor veneuze terugvloed, die op zijn beurt wordt beïnvloed door veneuze dilatatie of constrictie, maar vooral door redistributie van bloed in het vasculaire systeem. Met behulp van de veneuze terugvloedcurve en de hartfunctiecurve worden relevante klinische ziektebeelden op de intensive care met compensatiemechanismen en behandelingsmogelijkheden beschreven. Tot voor kort kon de Pmsf alleen gemeten worden tijdens een circulatiestilstand. Wij beschrijven een methode om Pmsf te bepalen door een veneuze terugvloedcurve te maken met behulp van metingen van Pcv en CO tijdens inademingspauzes. Deze methode wordt in verschillende onderzoeken in de volgende hoofdstukken gebruikt.

Hoofdstuk 2

In dit hoofdstuk beschrijven we de fysiologie van de veneuze terugvloed en het maken van een veneuze terugvloedcurve met behulp van inademingspauzes bij beademde patiënten. Tijdens een inademingspauze wordt een stationaire toestand bereikt met een verhoging van de Pcv en een verlaging van de CO. Nadat meerdere inademingspauzes met verschillende luchtwegdrukken zijn gegeven, wordt met de gemeten waarden van Pcv en CO een veneuze terugvloedcurve gemaakt. Uit deze veneuze terugvloedcurve kan de clinicus aan het bed niet alleen de Pmsf bepalen, maar ook afgeleide parameters: weerstand voor veneuze terugvloed (Rvr, helling van de curve), compliantie van de bloedsomloop (verandering in Pmsf na vloeistoftoediening) en actief circulerend volume (Vs, uit een Pmsf-volume curve). Deze techniek maakt het mogelijk onderzoek te doen naar de determinanten van de veneuze terugvloed en naar de beïnvloeding van de CO bij verschillende patiëntengroepen, verschillende pathofysiologische toestanden en bij verschillende farmacologische condities. In de toekomst zal de cardiovasculaire behandeling gebaseerd zijn op aannames, gestoeld op de fysiologie van de veneuze

terugvloed, en gestuurd worden door het meten van Pmsf, Rvr, actief circulerend volume en compliantie, zoals wij nu de CO en arteriële bloeddruk meten.

Hoofdstuk 3

In dit hoofdstuk onderzoeken we bij 12 mechanisch beademde, postoperatieve, cardiochirurgische patiënten of Pmsf op de intensive care kan worden bepaald met gebruik van de methode met inademingspauzes. Tijdens 4 inademingspauzes met verschillende luchtwegdrukken werd de bij-behorende Pcv en CO (drukgolfmethode) gemeten. Hiermee werd een veneuze terugvloedcurve gemaakt, waaruit de Pmsf werd berekend. Deze metingen werden gedaan tijdens 3 vullingstoestanden: normale vulling (basistoestand), relatieve ondervulling (door de patiënten in 30˚ hoofd-omhoog positie te plaatsen) en relatieve overvulling (500 ml colloid toediening). Er was een linaire relatie tussen Pcv en CO en de hellingshoek hiervan werd niet beïnvloed door de vullingstoestand. Zoals verwacht steeg de Pmsf na volumetoediening en daalde de Pmsf in de toestand van relatieve ondervulling. De gemiddelde compliantie van de bloedsomloop in basistoestand was 0.98 $ml \cdot mmHg^{-1} \cdot kg^{-1}$ en het gemiddeld effectief circulerend volume was 1677 ml. Wij concluderen dat Pmsf gemeten kan worden bij IC-patiënten met een intacte bloedsomloop door gebruik te maken van inademingspauzes met het beademingsapparaat. Deze procedure maakt het mogelijk de compliantie van de bloedsomloop en het effectief circulerend volume te volgen bij beademde patiënten.

Hoofdstuk 4

Het doel van dit onderzoek was om de aannames te valideren, die gemaakt werden in het onderzoek uit Hoofdstuk 3. Deze aannames waren a. dat de Pmsf kon worden bepaald met behulp van CO metingen met de drukgolfmethode en b. dat 4 inademingspauzes met verschillende luchtwegdrukken voldoende waren voor de bepaling van de Pmsf. Bij 10 biggen werd de CO bepaald door de stroomsnelheid te meten in de arteria pulmonalis (COr) en in de aorta (COl) en met een drukgolfmethode van de druk in de aorta (COpc). Er werden 7 inademingspauzes met verschillende drukken gegeven. We toonden aan dat aan het eind van een inademingspauze de COr gelijk was aan de COl, die weer gelijk was aan de COpc. De Pmsf verkregen met COl en met COpc waren uitwisselbaar en de lage variatiecoëfficiënt wees op een goede herhaalbaarheid. De Pmsf kan dus bepaald worden met behulp van de drukgolfmethode. Vervolgens lieten we zien dat de Pmsf correct kon worden bepaald met 4, 3 of zelfs 2 inademingspauzes. Dit onderzoek vormt daarmee een ondersteuning voor de aannames, die in het onderzoek in Hoofdstuk 3 gedaan werden.

Hoofdstuk 5

In dit onderzoek werden 3 manieren om de Pmsf te meten vergeleken: 1. Pmsf met de methode met inademingspauzes , 2. de druk berekend met een model van de circulatie

(Pmsa) en 3. equilibratiedruk tijdens een lokale circulatiestilstand van 30 seconden in de arm (Parm). Deze metingen werden bij 11 postoperatieve hartchirurgie patiënten gedaan in rugligging, in een 30˚ hoofd-omhoog positie en na 500 ml colloid toediening. De gemiddelde waarden van Pmsf, Pmsa en Parm over de 3 toestanden waren 20.9 ± 5.6 mmHg, 19.8 ± 5.7 mmHg en 15.9 ± 4.9 mmHg. Een Bland-Altman analyse voor Parm en Pmsf liet een niet significant systematisch verschil zien van -1.0 ± 3.08 mmHg en grenzen van overeenkomst van of -7.3 en 5.2 mmHg. Voor Pmsf en Pmsa vonden we een systematisch verschil -6.0 ± 3.1 mmHg ($p < 0.001$) en grenzen van overeenkomst van -12.4 en 0.3 mmHg. De interventies (hoofd-omhoog en colloid toediening) induceerden veranderingen in Pmsf en Parm, en in Pmsf en Pmsa, die volledig concordant waren. We concluderen dat Parm en Pmsf inwisselbaar zijn en dat veranderingen in effectief circulerend volume goed worden gevolgd door veranderingen in Parm en Pmsa.

Hoofdstuk 6

Pmsf is de druk die ontstaat in de bloedvaten tijdens een hartstilstand na het vormen van een nieuw evenwicht en kan dus theoretisch gezien op elke plaats in de bloedsomloop worden gemeten. Pmsf is tevens een maat voor het effectief circulerend volume. We onderzochten of de druk in de arm (Parm), gemeten tijdens een lokale circulatiestilstand, een maat is voor Pmsf en of Parm gebruikt kan worden als een voorspeller voor vloeistofresponsiviteit. Met een manchet om de bovenarm, opgeblazen tot 50 mmHg boven de systolische bloeddruk van de patiënt gedurende 35 seconden, werd een lokale circulatiestilstand verkregen. Parm werd gedefinieerd als de druk in de arteria radialis 30 seconden na het induceren van een circulatiestilstand in de arm. De metingen werden verricht voor en na de toediening van volume (500 ml colloid). De Parm werd bij 24 patiënten na cardiochirurgie als voorspeller van vloeistofresponsiviteit vergeleken met slagvolumevariatie (SVV) en polsdrukvariatie (PPV). Patiënten met een stijging in CO van 10% of meer werden geclassificeerd als responders.
De onderzoekspopulatie werd verdeeld in patiënten met vloeistofresponsiviteit (n = 17) en patiënten zonder vloeistofresponsiviteit (n = 7). De oppervlakte onder de voorspellingscurve voor Parm was 0.786 (95% betrouwbaarheidsinterval 0.567-1.000). Een Parm < 21.9 mmHg had een sensitiviteit van 71% en een specificiteit van 88% om vloeistofresponsiviteit te voorspellen. Hiermee lijkt Parm een goede voospeller van vloeistofresponsiviteit bij cardiochirurgische patiënten met een goede ventrikelfunctie.

Hoofdstuk 7

In dit hoofdstuk onderzochten wij de waarde van Pmsf gemeten in de arm ($Pmsf_{arm}$) voor de bepaling van de compliantie van de bloedsomloop en het effectief circulerend volume. Daarvoor kregen 15 postoperatieve cardiochirurgische patiënten 10 opeenvolgende hoeveelheden van 50 ml colloid toegediend. Na elke vullingsstap werden $Pmsf_{arm}$, Pcv en CO bepaald. Er was een linaire relatie tussen $Pmsf_{arm}$ en volume, wijzend

op een constante compliantie. Het effectief circulerend volume kon worden bepaald door extrapolatie van de $Pmsf_{arm}$-volume curve naar een druk van 0. Het effectief circulerend volume werd geschat op 1265 ± 541 ml (28.5 ± 15% van voorspeld totaal bloed volume). Met behulp van de waarden van Pcv en CO na elke vullingsstap werd tevens een hartfunctiecurve gemaakt. Patiënten, bij wie de CO > 12 % steeg op 500 ml vulling, werden vloeistof-responders genoemd. Vloeistof-responders bevonden zich op een steil deel van de hartfunctiecurve, terwijl de patiënten, die niet vloeistofresponsief waren, zich op een vlak deel van de hartfunctiecurve bevonden. Uit dit onderzoek concluderen we dat de compliantie van de bloedsomloop, het actief circulerend volume en hartfunctiecurves bij intensive care patiënten kunnen worden bepaald en gebruikt om patiënten hemodynamisch in kaart te brengen.

Hoofdstuk 8

Tijdens een circulatiestilstand blijft er een drukverschil bestaan tussen de veneuze bloeddruk (Pmsf) en de arteriële bloeddruk (Pa). Pa daalt tot een niveau, dat arteriële sluitingsdruk (Pcc) wordt genoemd. In dit onderzoek onderzochten wij de mogelijkheid om Pcc te bepalen met de methode van de inademingspauzes. Bij 10 postoperatieve cardiochirurgische patiënten werden tijdens inademings-pauzes met 4 toenemende luchtwegdrukken de CO, Pcv en Pa gemeten. Met de gepaarde waardes van CO en Pa kan een curve worden gemaakt, die we de ventrikel outputcurve noemden. De Pcc werd gedefinieerd als de waarde van Pa bij een extrapolatie van de CO naar nul. De arteriële weerstand (Ra) werd berekend als de deelsom van Pa-Pcc en CO, terwijl Rvr gelijk was aan de deelsom van Pmsf-Pcv en CO. De Pcc was in alle patiënten hoger dan Pmsf, met een gemiddeld drukverschil van 26.8 mmHg. We concluderen dat de drukgradiënten bij cardiochirurgische patiënten wijzen op de aanwezigheid van een vasculaire waterval. Daarnaast tonen we dat de vasculaire weerstand nu gespecificeerd kan worden in een arteriële (Ra) en een veneuze weerstand (Rvr). Ra is nauw gerelateerd aan de totale systemische vasculaire weerstand (Rsys).

Hoofdstuk 9

Met een fysiologisch model, waarin de veneuze terugvloedcurve, Pmsf, Rvr en Rsys zijn opgenomen, onderzochten we de hemodynamische effecten van dobutamine en hypovolemie. Bij 10 biggen werden metingen gedaan voor, tijdens en na dobutamine toediening, en gedurende hypovolemie en na vloeistofresuscitatie. Dobutamine gaf een stijging van CO en hartfrequentie, maar een daling van Pmsf, Rsys en Rvr. De daling in Rvr was groter dan de daling in Rsys. Hypovolemie gaf een afname in CO, Pcv, Pmsf en Rvr en een toename in hartfrequentie. We concluderen dat de stijging in CO tijdens dobutamine toediening veroorzaakt wordt door de combinatie van een verbeterde hartfunctie en een afgenomen Rvr. De daling in CO tijdens hypovolemie wordt toegeschreven aan een daling van Pmsf, maar wordt gedeeltelijk gecompenseerd

door een daling van Rvr, waardoor de veneuze terugvloed en dus de CO gedeeltelijk behouden blijven.

Hoofdstuk 10

In dit onderzoek werden de effecten van noradrenaline op de cardiac output (CO) geanalyseerd met behulp van veneuze terugvloedcurves en hartfunctiecurves. Bij 16 postoperatieve cardiochirurgische patiënten, behandeld met een lage dosis noradrenaline, werden de Pmsf, Pcv, hartfrequentie, slagvolume variatie en CO gemeten voor, tijdens en na het verhogen van de noradrenaline dosering. Tien patiënten reageerden met een daling van de CO op noradrenaline en bij zes patiënten nam de CO toe. Bij alle patiënten werd een stijging gezien van Pmsf, Rsys en Rvr, terwijl de SVV afnam. Bij de patiënten met een afname in CO stegen Rvr en Rsys meer dan bij de patiënten met een CO stijging. De hartfrequentie nam af bij de patiënten met een afname in CO en bleef onveranderd bij de patiënten met een stijging van CO. De basismeting van SVV was hoger in de patiënten met een CO stijging en een basismeting van SVV > 8.7% voorspelde een CO stijging op noradrenaline (oppervlak onder de curve 0.900). We concluderen dat noradrenaline de CO kan verhogen door volume te rekruteren uit het unstressed volume. Een daling in CO op noradrenaline kan worden verklaard door een daling in veneuze terugvloed ten gevolge van een verhoogde Rvr en een mogelijke vermindering van hartfunctie. De verandering in CO in respons op noradrenaline wordt bepaald door de balans tussen rekrutering van volume (stijging Pmsf) en de verandering in Rvr en hartfunctie. De verandering in CO op noradrenaline kan worden voorspeld door de basismeting van SVV.

Hoofdstuk 11

Dit hoofdstuk beschrijft het verschil tussen volumetoestand en vloeistof-responsiviteit. Daarnaast worden de klinische implicaties van veneuze terugvloedcurves, statische vullingsdruk en arteriële sluitingsdruk beschreven.

List of abbreviations

AUC	Area under the curve
AVR	Aortic valve replacement
CABG	Coronary artery bypass graft
CO	Cardiac output
COV	Coefficient of variation
Csys	Total systemic vascular compliance
HR	Heart rate
HUT	Head-up tilt
ICU	Intensive care unit
LOA	Limits of agreement
LV	Left ventricle
NE	Norepinephrine
Pa	Arterial blood pressure
PAC	Pulmonary artery catheter
Pao	Aortic pressure
Parm	Arm equilibrium pressure
Pcc	Critical closing pressure
Pcv	Central venous pressure
PEEP	Positive end-expiratory pressure
Pmsa	Model analogue pressure
Pmsf	Mean systemic filling pressure
Ppa	Pulmonary artery pressure
PPV	Pulse pressure variation
Pra	Right atrial pressure
Pv	Venous pressure
Pvent	Ventilatory plateau pressure
Pvr	Pressure gradient for venous return
Ra	Arterial vascular resistance
ROC	Receiver operating characteristic
Rsys	Total systemic vascular resistance
RV	Right ventricle
Rvr	Resistance to venous return
SD	Standard deviation
SV	Stroke volume
SVV	Stroke volume variation
Temp	Temperature
VR	Venous return
Vs	Stressed volume
Vu	Unstressed volume

Curriculum vitae

Jacinta Maas werd geboren op 20 januari 1966 te Hillegom. Na het behalen van het gymnasium diploma aan het Fioretti College te Lisse in 1984, begon zij met haar studie Geneeskunde aan de Rijksuniversiteit van Leiden. Het doctoraal examen werd behaald in 1988 en het artsexamen in 1991. In 1991 was zij betrokken bij onderzoek naar de diagnose en de behandeling van vorming van aneurysmata spuria en fistels bij aortaprothesen in het Academisch Ziekenhuis Leiden (AZL, Prof. Dr. J.H. van Bockel). Daarna was zij tot 1993 assistent geneeskunde niet in opleiding bij de afdeling Neurochirurgie van het AZL (Prof. Dr. R.W.T.M. Thomeer), waar zij ook betrokken was bij de patiëntenzorg op de neurochirurgische intensive care. Daar raakte zij geinteresseerd in (Neuro-)Intensive Care. In 1999 rondde zij de opleiding Neurologie af in het Leids Universitair Medisch Centrum (LUMC, Prof. Dr. R.A.C. Roos). Hierna deed zij de vervolgopleiding Intensive Care in het Academisch Medisch Centrum te Amsterdam (Prof. Dr. J. Kesicioglu), die zij in 2001 afrondde. Zij behaalde het Europees Diploma Intensive Care (EDIC) in 2001. Vanaf 2001 is zij werkzaam als neuroloog-intensivist in het LUMC. Vanaf 2004 doet zij onderzoek met Dr. Jos Jansen, Dr. Rob de Wilde and Dr. Bart Geerts op de afdeling Intensive Care van het LUMC. De resultaten hiervan staan in dit proefschrift beschreven.

List of publications

1 van Baalen JM, Kluit AB, Maas J, Terpstra JL, van Bockel JH. Diagnosis and therapy of aortic prosthetic fistulas: trends over a 30-year experience. *Br J Surg* 1996; 83**:**1729-1734.

2 Maas JJ, Beersma MF, Haan J, Jonkers GJ, Kroes AC. Bilateral brachial plexus neuritis following parvovirus B19 and cytomegalovirus infection. *Ann Neurol* 1996; 40**:**928-932.

3 Mulder EJ, van Bockel JH, Maas J, van den Akker PJ, Hermans J. Morbidity and mortality of reconstructive surgery of noninfected false aneurysms detected long after aortic prosthetic reconstruction. *Arch Surg* 1998; 133**:**45-49.

4 Leeuwenburgh BP, Versteegh MI, Maas JJ, Dunning J. Should amiodarone or lidocaine be given to patients who arrest after cardiac surgery and fail to cardiovert from ventricular fibrillation? *Interact Cardiovasc Thorac Surg* 2008; 7**:**1148-1151.

5 Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, Jansen JR. Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. *Crit Care Med* 2009; 37**:**912-918.

6 Later AF, Maas JJ, Engbers FH, Versteegh MI, Bruggemans EF, Dion RA, Klautz RJ. Tranexamic acid and aprotinin in low- and intermediate-risk cardiac surgery: a non-sponsored, double-blind, randomised, placebo-controlled trial. *Eur J Cardiothorac Surg* 2009; 36**:**322-329.

7 Geerts BF, Maas JJ, Aarts LP, Pinsky MR, Jansen JR. Partitioning the resistances along the vascular tree: effects of dobutamine and hypovolemia in piglets with an intact circulation. *J Clin Monit Comput* 2010; 24**:**377-384.

8 Jansen JR, Maas JJ, Pinsky MR. Bedside assessment of mean systemic filling pressure. *Curr Opin Crit Care* 2010; 16**:**231-236.

9 Geerts BF, Maas J, de Wilde RB, Aarts LP, Jansen JR. Arm occlusion pressure is a useful predictor of an increase in cardiac output after fluid loading following cardiac surgery. *Eur J Anaesthesiol* 2011; 28**:**802-806.

10 Maas JJ, Geerts BF, Jansen JR. Evaluation of mean systemic filling pressure from pulse contour cardiac output and central venous pressure. *J Clin Monit Comput* 2011; 25**:**193-201.

11 Maas JJ, de Wilde RB, Aarts LP, Pinsky MR, Jansen JR. Determination of vascular waterfall phenomenon by bedside measurement of mean systemic filling pressure

and critical closing pressure in the intensive care unit. *Anesth Analg* 2012; 114**:**803-810.

12 Maas JJ, Pinsky MR, Geerts BF, de Wilde RB, Jansen JR. Estimation of mean systemic filling pressure in postoperative cardiac surgery patients with three methods. *Intensive Care Med* 2012; 38:1452-1460.

13 Maas JJ, Pinsky MR, Aarts LP, Jansen JR. Bedside estimation of total systemic vascular compliance, stressed volume, and cardiac function curves in intensive care unit patients. *Anesth Analg* 2012; 115:880-997.

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