Chapter 1

General introduction and outline of this thesis

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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.

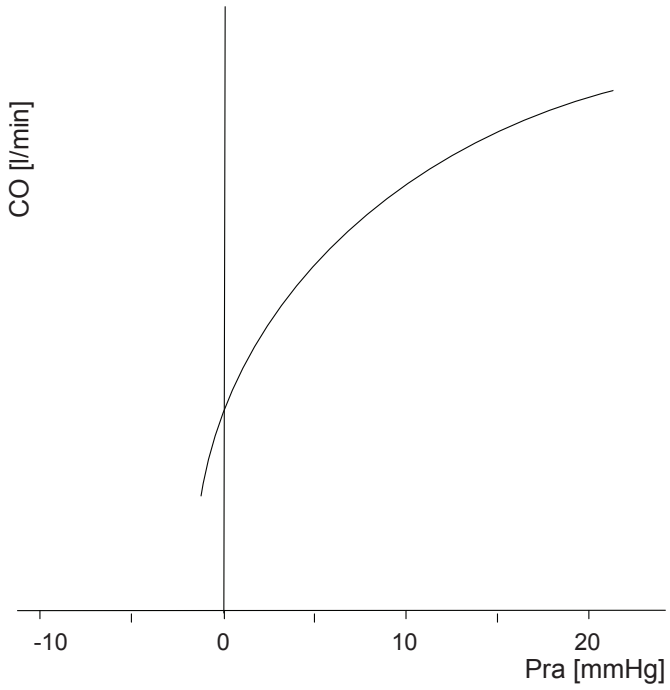

Figure 1.1 Cardiac function curve
Relationship between right atrial pressure (Pra) and cardiac output (CO).

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.

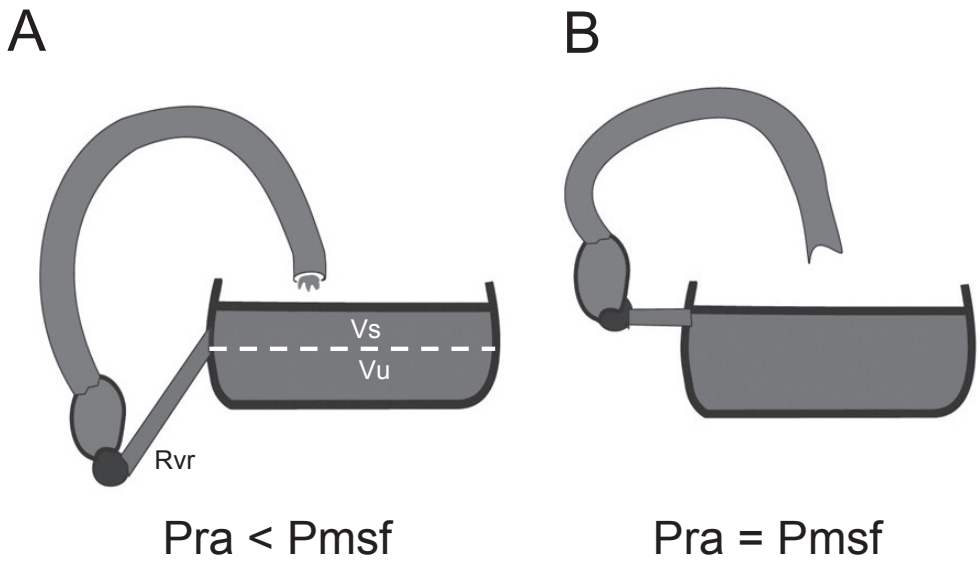

Figure 1.2 Bathtub model of the circulation
The water beneath the drainage pipe, which cannot leave the bathtub, resembles unstressed volume (Vu). The water above the drainage pipe, which can be drained from the bathtub, resembles stressed volume (Vs). The height of the water column above the drainage 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.

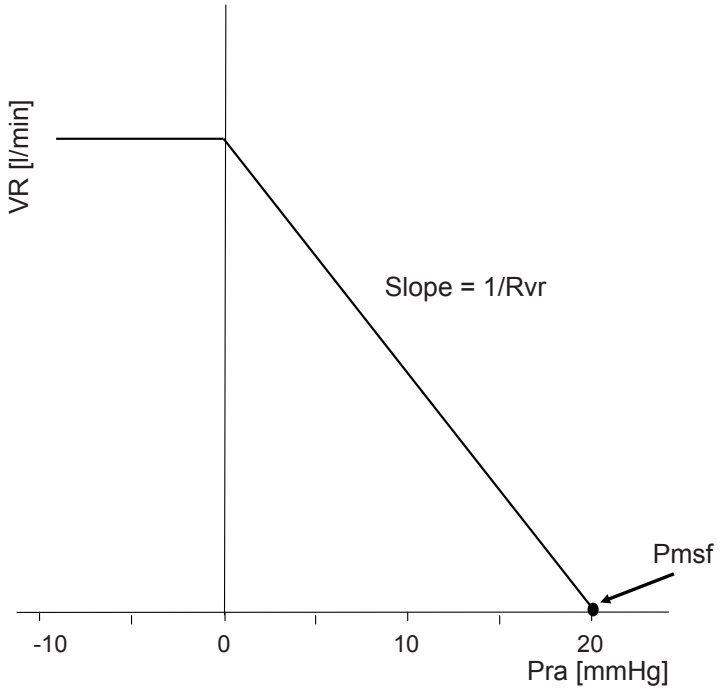

Figure 1.3 Venous return curve
The relationship between right atrial pressure (Pra) and cardiac output (CO), called the venous return (VR) curve, during spontaneous breathing. When VR is zero, Pra is equal to Pmsf. When Pra approaches atmospheric pressure (around 0), VR is maximal. At negative values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

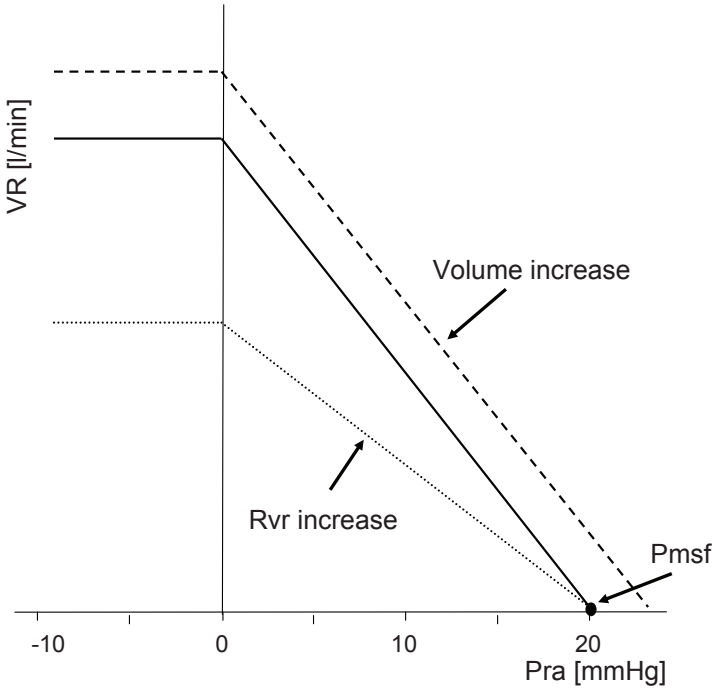

Figure 1.4 Changes in venous return curve
Influences of resistance to venous return (Rvr) and volume increase on the venous return curve. An increase in Rvr will limit venous return (VR), without changing mean systemic filling pressure (Pmsf), flattening the curve. Volume loading will increase Pmsf,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

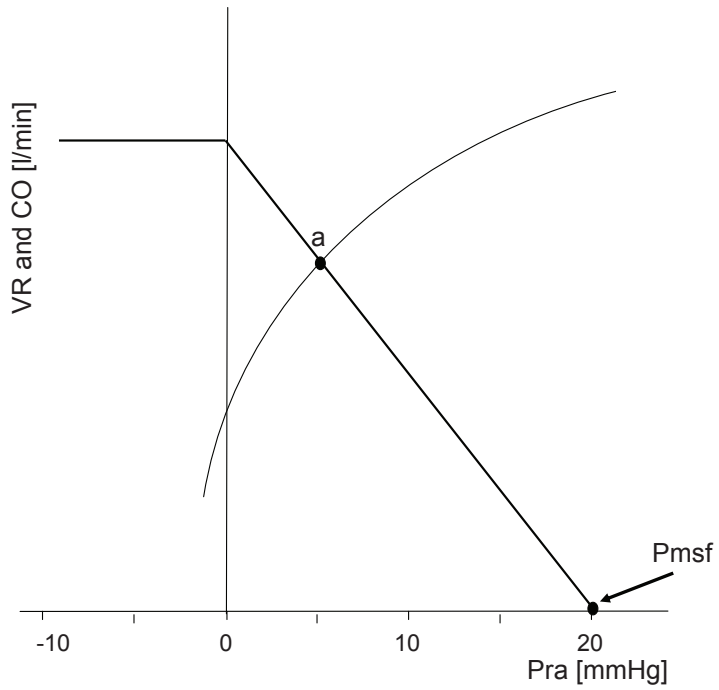

Figure 1.5 Combination of cardiac function curve and venous return curve
The venous return curve and the cardiac output curve are depicted in one graph. The point where venous return (VR) and cardiac output (CO) are equal, is the operating point of the circulation (point a).

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).

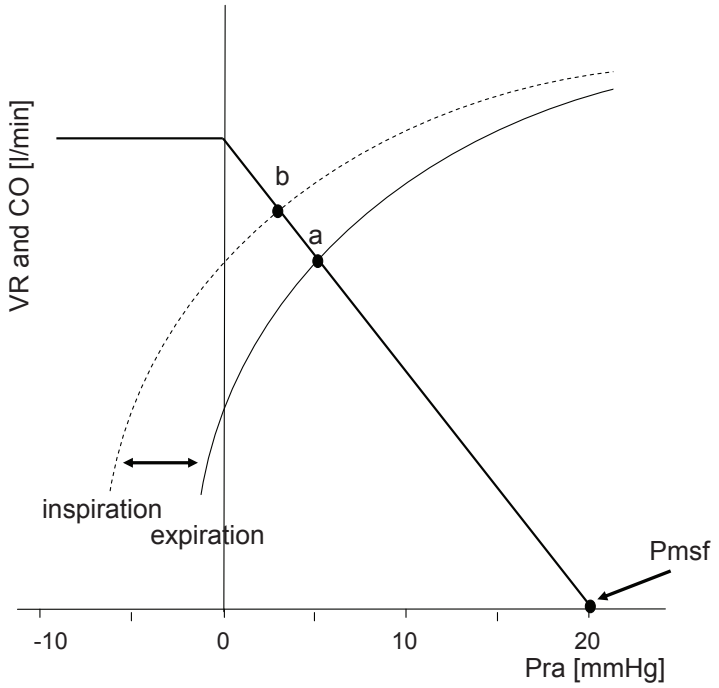

Figure 1.6 Influence of respiration
During spontaneous inspiration intrathoracic pressure and right atrial pressure (Pra) decrease, while venous return (VR) increases. The operating point of the circulation shifts from a to b. Cardiac output (CO) increases, because right atrial transmural pressure increases. 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.

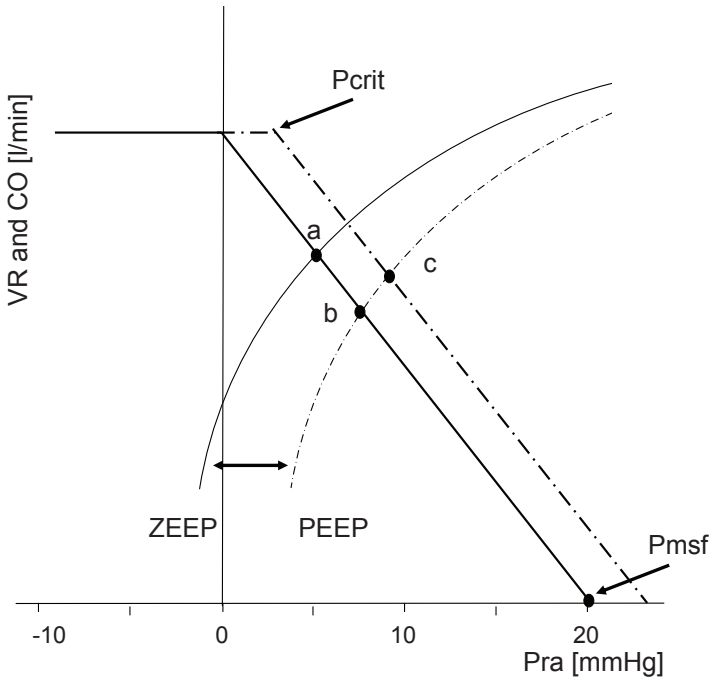

Figure 1.7 Influence of positive end-expiratory pressure
The baseline curve is with zero end-expiratory pressure (ZEEP); point a is the operating point of the circulation. When positive end-expiratory pressure (PEEP) is applied, right atrial pressure (Pra) increases and venous return (VR) decreases; 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.

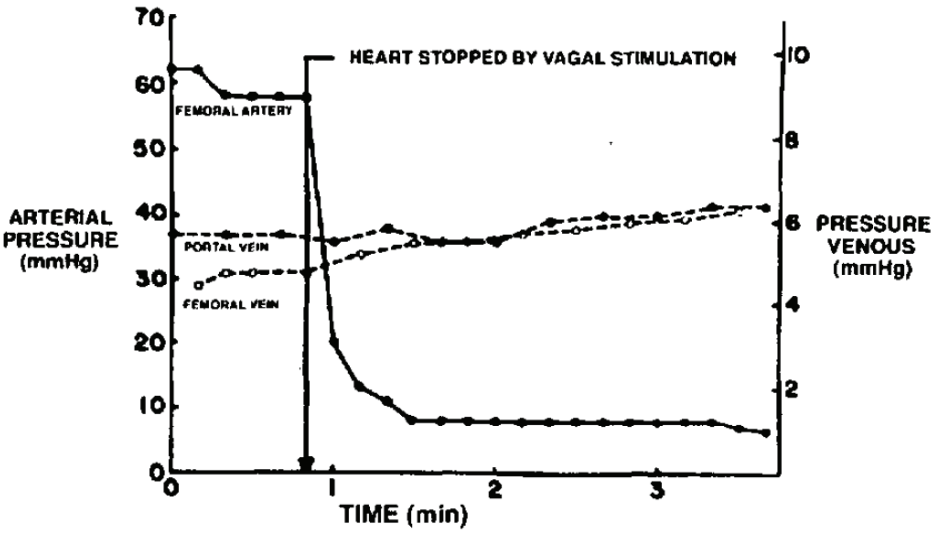

Figure 1.8 Pressure course during cardiac arrest
Bayliss and Starling's[10] experiment to measure mean systemic filling pressure (Pmsf) in a dog. When the circulation is arrested by vagal stimulation, the arterial and venous pressures equilibrate to Pmsf. Figure adopted from Bayliss.[10]

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.

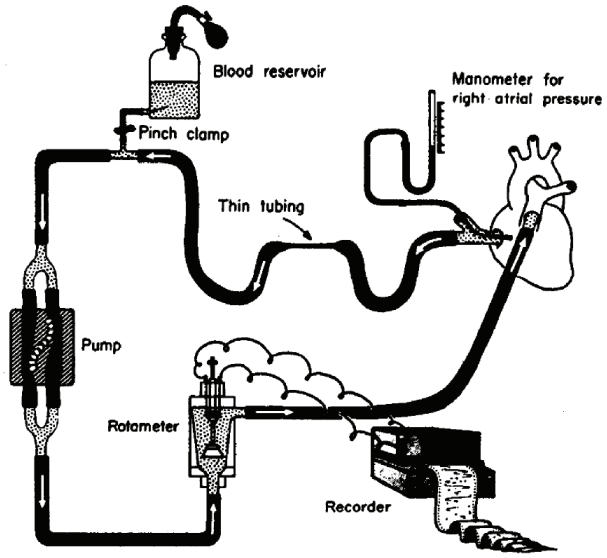

Figure 1.9 Experimental model for controlling right atrial pressure and venous return
The external perfusion system, bypassing the right ventricle, for controlling right atrial pressure and venous return to construct venous return curves. Figure adopted from Guyton.[12]

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.

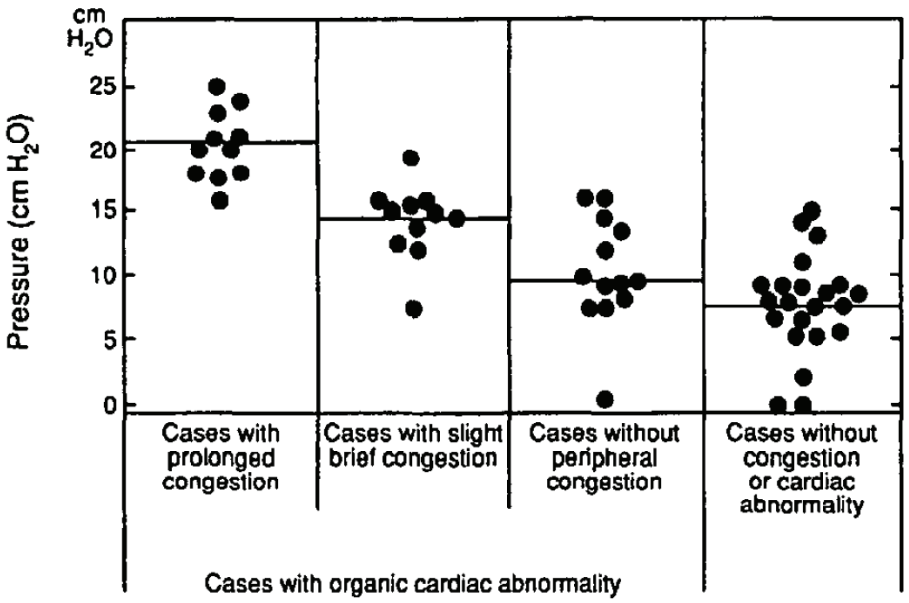

Figure 1.10 Measurement of mean systemic filling pressure (Pmsf)
Starr's measurement of mean systemic filling pressure (Pmsf) in humans soon after death. The crossbars indicate average values. Pmsf in patients with organic heart disease and prolonged congestion is higher than in patients without congestion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

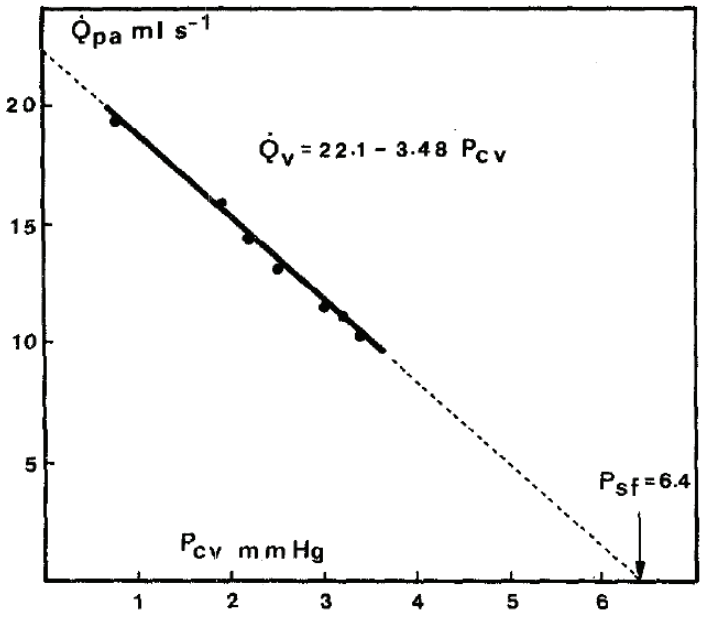

Figure 1.11 Measurement of mean systemic filling pressure with inspiratory holds
Relationship between flow (Qpa, measured in the pulmonary artery, on the y-axis) and central venous pressure (Pcv) during inspiratory hold procedures at 7 different airway pressures. The arrow indicates the value that Pcv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