

REVIEW

Mean systemic filling pressure: its measurement and meaning

J.J. Maas

Department of Intensive Care, Leiden University Medical Center, Leiden, the Netherlands

Correspondence

J.J. Maas – email: j.j.maas@lumc.nl

Keywords - Mean systemic filling pressure, venous return, cardiac output**Abstract**

Mean systemic filling pressure (Pmsf) is the pressure in the vascular system during circulatory arrest. Venous return is determined by the pressure gradient between Pmsf and right atrial pressure. Recent studies now demonstrate that Pmsf can be measured at the bedside in mechanically ventilated intensive care patients. Using continuous monitoring of cardiac output and central venous pressure, venous return curves can be constructed by performing a series of inspiratory holds. From these venous return curves the clinician can obtain Pmsf, but also other derived parameters as resistance to venous return, systemic compliance and stressed volume. Now it is feasible to study the venous side of the circulation. This review describes the importance of venous return, the measurement of Pmsf and the clinical implications of its measurement. In addition the effects of norepinephrine on venous return are described in detail.

Introduction

In the intensive care unit, haemodynamic assessment of patients usually focusses on cardiac output and fluid responsiveness. The evaluation of cardiac output targets preload, contractility, heart rate and afterload. Fluid responsiveness is assessed using dynamic indices as respiratory-induced changes in stroke volume or caval vein diameter.

The venous side of the circulation, although already described by Starling and Bayliss¹ in the 19th century and rediscovered by Guyton and colleagues,² receives less attention in daily practice as well as in the training of critical care physicians. The reason for this is the inability of the practising physician to appropriately assess the venous side of the circulation at the bedside.

Whether it is the heart or the venous return that maintains circulation is still subject to debate.^{3,4} In cardiac failure, the heart obviously is the impeding component in the circulation and will determine the upper limit of cardiac output. However, in persons without heart failure venous return can be seen as

the limiting factor, because the heart can only pump out that which it receives. This review will describe the determinants for venous return and its measurement.

Venous system

Approximately 75% of total blood volume is localised in the venous system, predominantly in small veins and venules, which act as a reservoir. The total intravascular blood volume consists of unstressed volume and stressed volume. The blood volume, which fills up the blood vessels without causing intravascular pressure, is called unstressed volume, while the volume that stretches the blood vessels is called stressed volume. The pressure that exists in the stressed volume compartment is the mean systemic filling pressure (Pmsf).

The distribution of blood between unstressed and stressed volume can be changed. For instance, volume expansion will predominantly increase stressed volume (and thus Pmsf), while in septic patients vasodilation will shift blood from the stressed to the unstressed volume (decreasing Pmsf). Fluid resuscitation will then restore the stressed volume compartment, with an increase in total intravascular volume. Treatment with vasoconstrictive medication could theoretically recruit volume from the unstressed compartment to the stressed compartment, restoring Pmsf and venous return without a change in total intravascular volume.

Venous return

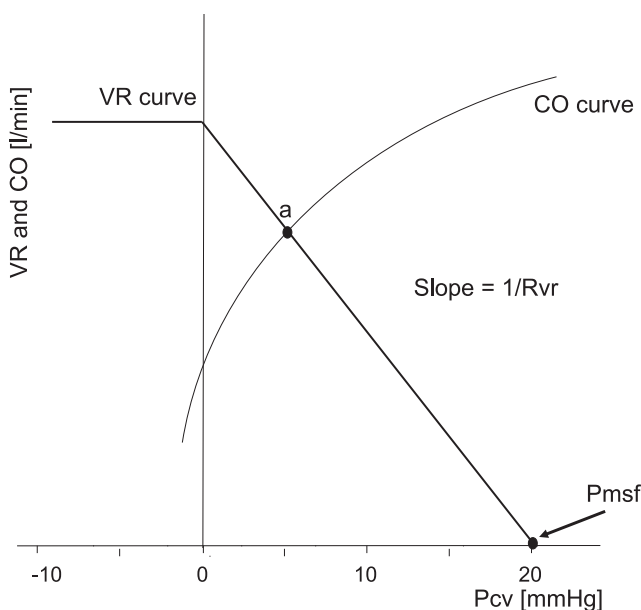
The cardiac output curve is familiar to every intensive care physician, while the venous return curve is less known (*figure 1*). Because transmural intracardiac pressures remain positive,⁵ even during diastole, the heart does not actively suck blood. Thus, there must be a force that drives blood into the heart. Logically, only a peripheral venous pressure which exceeds right atrial pressure or central venous pressure (Pcv) could direct blood into the heart. This peripheral venous pressure is Pmsf and the pressure gradient between Pmsf and Pcv determines

venous return.^{6,7} The greater the difference between Pmsf and Pcv, the greater the venous return will be. Pmsf is the driving pressure for global venous return. It is important to realise that the driving pressure can differ for the various organs and is influenced by body position.

Guyton et al.^{6,8} showed in their experiments in dogs that when Pcv is elevated, cardiac output and venous return are reduced. When Pcv is increased further and further, venous return declines until it ultimately ceases. The value that Pcv reaches at zero flow is Pmsf. On the other hand, with decreasing Pcv, venous return increases. When Pcv becomes close to atmospheric pressure, the transmural pressure of the great veins will become negative, resulting in a collapse of the great veins. This collapse will limit venous return to a maximum value.

The relationship between Pmsf, Pcv and venous return can be plotted in the same figure as the cardiac output curve (figure 1). The intersection of both curves resembles the working point of the circulation. The slope of the curve is determined by resistance, the resistance for venous return (Rvr). Now venous return (VR) and cardiac output (CO) can be formulated as $CO = VR = (Pmsf - Pcv)/Rvr$. The function of the heart is to lower Pcv and return blood into the systemic circulation.

Figure 1. The cardiac output (CO) curve and the venous return (VR) curve are depicted in one graph. The relationship between central venous pressure (Pcv) and CO is called the VR curve. When VR is zero, Pcv is equal to mean systemic filling pressure (Pmsf). When Pcv approaches atmospheric pressure (around 0), VR is maximal. The slope of the VR curve is determined by the resistance to venous return (Rvr). The point where VR and CO are equal is the operating point of the circulation (point a).



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

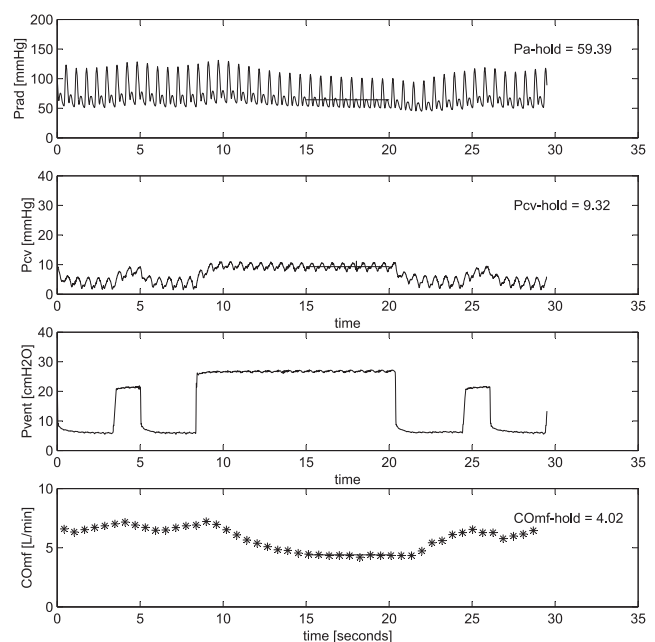
Measurement of mean systemic filling pressure

Measurement of Pcv is part of clinical routine in the intensive care unit (ICU), but until recently Pmsf could not be assessed in the ICU. How could Pmsf be determined? Theoretically, when venous return (or cardiac output) is reduced to zero, then Pcv would become equal to Pmsf. Obviously this is not practically feasible at the bedside.

Pmsf in animals using stop-flow

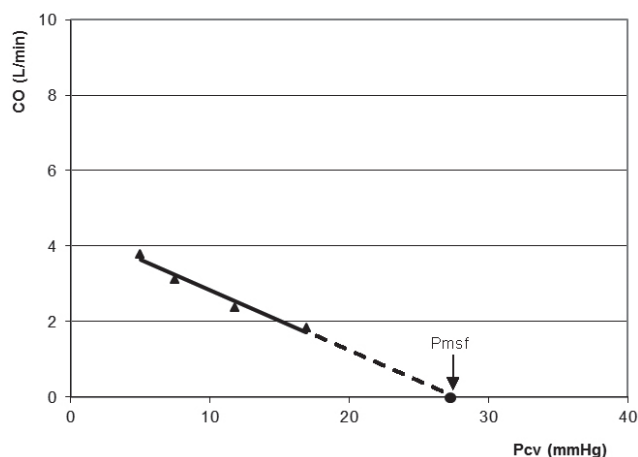
In 1894, Bayliss and Starling were the first to show equilibration of intravascular pressures during cardiac arrest in a dog model.¹ Guyton increased Pcv in a dog model.⁸ When Pcv was increased to a level that cardiac output stopped, Pmsf could be measured. Guyton was the first to construct venous return curves with this method.

Figure 2. Effects of an inspiratory hold manoeuvre of 25 cm H₂O on arterial pressure (Prad), central venous pressure (Pcv), airway pressure (Pvent) and beat-to-beat cardiac output (COMf). Preceding the hold the effects of a normal ventilatory cycle are plotted.



Subsequently, Pmsf was measured in animal studies by inducing a circulatory arrest. Cardiac arrest was achieved by administration of acetylcholine,⁹⁻¹¹ by induction of ventricular fibrillation^{9,12,13} or by applying an obstruction with an inflatable balloon around the pulmonary artery^{14,15} or inside the right atrium¹⁶. Both the cardiac arrest studies and the circulatory obstruction studies found that venous pressure (Pv) remained lower than arterial pressure (Pa). Pmsf was then 1. measured by equilibration of pressures with an arteriovenous pump or 2. calculated with the formula: $Pmsf = Pv + 1/30 \cdot (Pa - Pv)$.¹⁴ The correction factor 1/30 was based on compliance measurements, where venous compliance was 30-fold higher in comparison with arterial compliance.¹⁷

Figure 3. Relationship between venous return (CO) and central venous pressure (Pcv) for an individual patient. The four inspiratory holds (at 5, 15, 25 and 35 cm H₂O) are depicted as triangles. Mean systemic filling pressure (Pmsf) is the value of Pcv, when the curve is extrapolated to zero flow.



Pmsf in animals using inspiratory holds

Pmsf can also be estimated with a method based on the haemodynamic effects of mechanical ventilation in an intact circulation. Mechanical ventilation with positive airway pressures increases intrathoracic pressures, causing an increase in Pcv and a decrease in venous return and cardiac output (an example in a human study is shown in figure 2). With the use of inspiratory holds in pigs, haemodynamic steady-state conditions were met to assure that venous return and cardiac output were equal.¹⁸ Pcv and pulmonary artery flow were measured at the end of each inspiratory hold. Because different airway pressures were used, pairs of Pcv and cardiac output at the different inspiratory holds were obtained. With these pairs of Pcv and cardiac output a venous return curve was plotted, showing an inverse linear relationship between cardiac output

and Pcv. Pmsf was calculated by extrapolation of the curve to a cardiac output value of zero, where Pcv becomes equal to Pmsf (an example in a human study is shown in figure 3). For this method with inspiratory holds a linear relation between Pcv and cardiac output is assumed. This assumption is based on the linearity of the venous return curves presented by Guyton and colleagues.^{2,8} They also showed that Pmsf derived from venous return curves correlated closely with Pmsf measured during cardiac arrest, when pressure was levelled out in the systemic circulation.⁸ Pinsky confirmed this validation in dogs, measuring Pmsf during ventricular fibrillation and estimating Pmsf by extrapolation of the relationship between stroke volume and Pcv.¹⁹

Pmsf in humans during cardiac arrest

The first measurements of Pmsf in humans were performed by Starr, who inserted a needle into the heart or a great vein in patients who had died shortly before.²⁰ Pmsf in patients who died after prolonged cardiac congestion was significantly higher than Pmsf in patients who died without congestion or cardiac disease. The higher Pmsf values in heart failure patients were attributed to a compensation mechanism for the increased Pcv in order to maintain a pressure gradient for venous return.

In 2000 and 2003 measurement of Pmsf during induced cardiac arrest in humans was reported.^{21,22} During a defibrillation test, ventricular fibrillation was induced in patients undergoing surgical implantation of an implantable cardioverter-defibrillator. Arterial and venous pressures were measured, but did not equilibrate during ventricular fibrillation. After 7.5 seconds of stop-flow²¹ and even after 20 seconds of cardiac arrest²² there was no equilibration of pressures. The lack of equilibrium was attributed to a waterfall mechanism, but could also be explained by the relatively short duration of the cardiac arrest. However, longer periods of cardiac arrest are both unethical and potentially influenced by vasomotor reflexes. Furthermore, this method of determining Pmsf is not suitable in the ICU.

Pmsf in humans using inspiratory holds

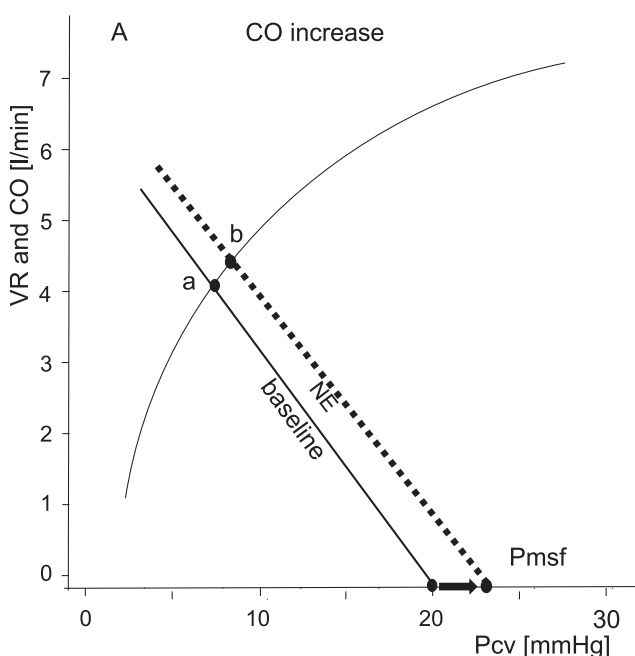
Using the method of inspiratory holds we determined Pmsf in postoperative cardiac surgery patients.²³ We applied four inspiratory holds at 5, 15, 25 and 35 cmH₂O during 12 seconds to create a steady-state situation. Beat-to-beat cardiac output was measured with a pulse contour method (Modelflow), which we have described previously,²⁴⁻²⁶ at the end of the inspiratory hold along with Pcv (figure 2). The four pairs of Pcv and cardiac output were plotted in a venous return curve (figure 3). All curves were linear and extrapolation to zero cardiac output was thus possible. In some patients cardiac output decreased to less than 0.5 l/min during the inspiratory hold with 35 cm H₂O, resulting in a Pcv measurement very near the Pmsf, while the curve was still linear.

Pmsf was calculated as the x-axis intercept of the venous return curve. Measurements were performed at baseline, after placing patients in 30° head-up position (relative hypovolaemia), and after 500 ml volume loading (hypervolaemia). Average baseline Pmsf was 18.8 ± 4.5 mmHg. Pmsf decreased during relative hypovolaemia and increased after 500 ml volume loading, compared with baseline.²³

The inspiratory hold method to estimate Pmsf was slightly modified by two other groups. Keller et al. used another pulse contour method for beat-to-beat cardiac output measurements (PiCCO™), applied shorter inspiratory holds and shorter intervals between inspiratory holds, and he randomised the order of inspiratory holds.²⁷ Median Pmsf during baseline conditions in postoperative cardiac surgery patients was 19.7 mmHg with an interquartile range of 17.0-22.7 mmHg. Pmsf increased during passive leg raising and after volume expansion.²⁷ Persichini et al. used two end-expiratory and two end-inspiratory holds (with airway pressures ranging from 5 to 30 cmH₂O), lasting 15 seconds.²⁸ In septic patients treated with norepinephrine in whom norepinephrine could be tapered, mean baseline Pmsf was 33 ± 12 mmHg. After tapering norepinephrine Pmsf decreased to 26 ± 10 mmHg.

Figure 4. Venous return (VR) curve and cardiac output curve constructed from average values of central venous pressure (Pcv), mean systemic filling pressure (Pmsf) and cardiac output (CO) for patients with increased CO (A) and decreased CO (B) after norepinephrine (NE) dose increase.

A a. working point of the circulation during baseline condition; b. effects of NE: increase in Pmsf due to the volume effect of generalised venoconstriction on CO. Note that the slope of the curve is less steep, implying an increase in Rvr.



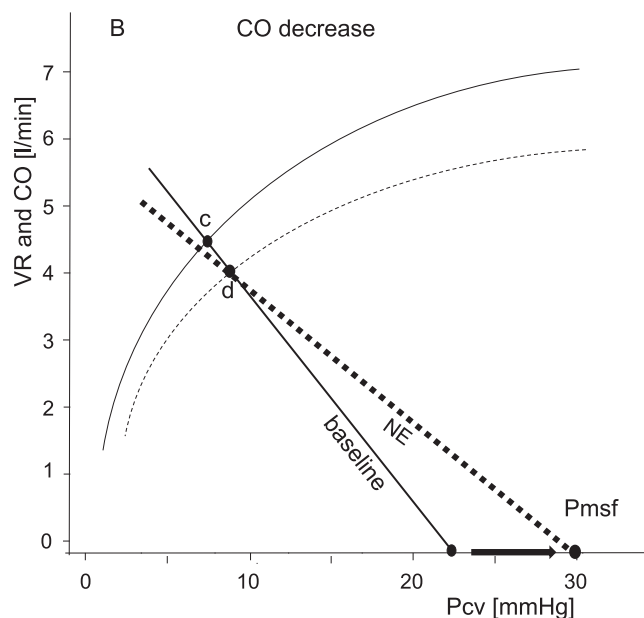
Alternatives to estimate Pmsf in humans

An analogue of Pmsf (Pmsa) can be estimated with a device (Navigator™, Applied Physiology, Pty Ltd, Sydney, Australia) using a mathematical algorithm in which cardiac output, mean arterial blood pressure and right atrial pressure are entered.²⁹ We recently compared Pmsf measured with the inspiratory hold method with Pmsa, determined by the mathematical algorithm.³⁰ Pmsa displayed a systematic bias (underestimation of Pmsf), which could be corrected for. Volume-induced changes in Pmsf were faithfully tracked by changes in Pmsa.

Using the Navigator™ device Cecconi et al. estimated Pmsa in postsurgical patients before and after a fluid challenge.³¹ Pmsa increased in all patients. There was a difference between fluid-responsive patients and patients who were nonresponsive to fluids. In the fluid-responsive patients the pressure gradient for venous return increased, while in the fluid-nonresponsive patients Pcv increased along with Pmsa, resulting in an unchanged pressure gradient for venous return.

As Pmsf is the pressure during circulatory stop flow, it can be measured anywhere in the circulation, e.g. in the arm. In ICU patients we created a stop flow in the arm with a rapid cuff inflator (Hokanson E20, Bellevue, Washington) during 35-60

B c. working point of the circulation during baseline condition; d. effects of NE: increase in Pmsf due to the volume effect of generalised venoconstriction on CO by NE. The increase in Pcv and decline in CO imply that the CO curve has shifted downwards. Note that the slope of the curve is less steep, implying an increase in Rvr.



seconds and measured arterial blood pressure in the radial artery and venous pressure in the same hand.³⁰ Arterial and venous pressures equilibrated after 25-30 seconds. Arterial blood pressure (arm-occlusion pressure, Parm) after 30 seconds was studied, because this measurement showed a stable value with good repeatability. Bland-Altman analysis showed that Parm and Pmsf were interchangeable and volume-induced changes in Pmsf were faithfully tracked by changes in Parm. In my clinical practice, however, measurement of Parm was not always reliable, because the arterial curve sometimes lacked a stable plateau.

Implications of measuring Pmsf

Measurement of Pmsf at the bedside allows the physician to gain knowledge about other haemodynamic parameters such as resistance for venous return, compliance and stressed volume. Resistance to venous return (Rvr) is the reciprocal of the slope of the venous return curve and can be calculated as $Rvr = (Pmsf - Pcv)/CO$. When resistance for venous return is increased, the slope of the venous return curve becomes less steep, because the difference between Pmsf and Pcv increases. Now it is possible to distinguish the resistance on the venous side of the circulation (resistance for venous return) from the resistance on the arterial side (which is total vascular resistance minus Rvr). This allows to describe whether a specific vasoactive agent affects primarily the arterial or the venous side of the circulation.

Vascular compliance (Csys) refers to the change in intravascular pressure induced by a change in volume and thus describes the characteristics of a pressure-volume curve. In a less compliant venous system a small change in volume will induce a greater increase in pressure. With the measurement of Pmsf before and after a fluid challenge, Csys can be determined ($Csys = \Delta Volume / \Delta Pmsf$).

Stressed volume is the effective circulating volume and is therefore an important measure of volume status. It is not possible to measure stressed volume directly, but it can be estimated by the formula $Vs = Csys * Pmsf$. Recently we estimated stressed volume in postoperative cardiac surgery patients. Mean stressed volume was 1265 ± 541 ml (on average 19.6 ml/kg), which corresponded with $28.5 \pm 15\%$ of predicted total blood volume.³² Keller also found a median stressed volume of 19.4 ml/kg in postoperative cardiac surgery patients.²⁷ Both studies report values of stressed volume similar to that of 20.2 ± 1.0 ml/kg reported in five patients undergoing hypothermic circulatory arrest for major vascular surgery.³³ However, there was a wide variation in stressed volume, which could be attributed to the volume status of the patients as both fluid-responsive patients and fluid-nonresponsive patients were studied.³² Another explanation could be that the venous return curve has to be extrapolated beyond the measured values of cardiac output and Pcv and a slight change in the slope of the curve would have a major impact on Pmsf and Csys.

In a small study in postoperative cardiac surgery patients, Parm (as substitute for Pmsf and with a cut-off value of 21.9 mmHg) predicted fluid responsiveness with a sensitivity of 71% and specificity of 88%, comparable with the predictive value of stroke volume variation and pulse pressure variation.³⁴

All the above-mentioned parameters can now be used to describe the determinants for venous return and control of cardiac output in different patient populations, with different pathophysiological conditions, but also to describe different treatment options (volume expansion, vasoactive medication).

Effects of norepinephrine on cardiac output and venous return

In 16 postoperative cardiac surgery patients who were mechanically ventilated and treated with norepinephrine, we studied the effects of an increase in norepinephrine dosage.³⁵ An increment in mean arterial blood pressure of 20 mmHg was induced by a mean increase in norepinephrine dosage of $0.04 \mu\text{g}/\text{kg}/\text{min}$. Inspiratory holds were performed before and after the norepinephrine increment. Pmsf, systemic vascular resistance and resistance for venous return increased in all patients, while cardiac output increased in six patients and decreased in ten patients. We constructed venous return and cardiac output curves to analyse these different cardiac output responses.

In the patients in whom cardiac output increased, the increase in Pmsf implied a rightward shift of the venous return curve. The working point of the circulation shifted along the cardiac output curve to the flatter part of the curve (*figure 4a*). The increase in resistance for venous return corresponded with a less steep slope of the venous return curve. As total intravascular volume was unchanged, the increase in Pmsf could be explained by volume recruitment from the unstressed to the stressed compartment. This volume recruitment could be achieved by either venoconstriction or redirection of flow away from parts of the circulation with high proportions of unstressed volume (e.g. splanchnic circulation).

In the patients in whom cardiac output decreased, there was also an increase in Pmsf and a more pronounced increase in resistance for venous return (*figure 4b*). Thus the venous return curve also shifted to the right with a less steep slope. In addition, the decrease in cardiac output could only be explained by a different, flatter cardiac output curve, which was attributed to a larger increment in systemic vascular resistance (left ventricular afterload). The patients with an increase in cardiac output had higher stroke volume variation at baseline than the patients who had decreased cardiac output.

In conclusion, the cardiac output response to norepinephrine was determined by the balance between volume recruitment and change in resistance for venous return and systemic vascular resistance, and could be predicted by baseline stroke volume variation.³⁵

Persichini studied the reverse: he measured the effects of a decrease in norepinephrine dosage in a group of septic patients.²⁸

The slope of the venous return curves increased, indicating a decrease in resistance to venous return. Cardiac index and Pmsf decreased, implying that the decrease in venous return was caused by a volume shift from the stressed compartment to the unstressed compartment, which counteracted and exceeded the effects of a decrease in resistance for venous return on venous return. These results are thus concordant with our results.³⁵

Future studies

Future research questions could address the changes in Pmsf in different conditions (e.g. in the operating room during global or epidural anaesthesia, in sepsis, in cardiac failure), measurement of Pmsf during therapeutic interventions (especially vasoactive medication) and the value of Pmsf (or Parm) in prediction of fluid responsiveness.

Conclusion

Study of the venous side of the circulation broadens the clinician's horizon beyond fluid responsiveness and cardiac function. Measurement of Pmsf adds to the understanding of physiology and pathophysiology of haemodynamics and the effects of therapeutic interventions.

References

- Bayliss WM, Starling EH. Observations on Venous Pressures and their Relationship to Capillary Pressures. *J Physiol.* 1894;1716:159-318.
- Guyton AC. Determination of cardiac output by equating venous return curves with cardiac response curves. *Physiol Rev.* 1955;35:123-9.
- 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;101:1523-5.
- 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;101:1525-6.
- Guyton AC, Jones C, Coleman T. Heart muscle, the heart as a pump. *Circulatory Physiology*, 2 Edition. Philadelphia: W.B. Saunders Company, 1973, pp 96-106.
- Guyton AC, Hall JE. Cardiac output, venous return, and their regulation. In: Schmitt W, Gruliow R, eds. *Textbook of medical physiology*, 10 Edition. Philadelphia: W.B. Saunders Company, 2000, pp 210-22.
- 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;44:849-67.
- 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;189:609-15.
- Gaddis ML, Rothe CF, Tunin RS, et al. Mean circulatory filling pressure: potential problems with measurement. *Am J Physiol.* 1986;251:H857-H862.
- Nekoeian 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.
- Lee RW, Lancaster LD, Gay RG, et al. Use of acetylcholine to measure total vascular pressure-volume relationship in dogs. *Am J Physiol.* 1988;254:H115-H119.
- Drees JA, Rothe CF. Reflex venoconstriction and capacity vessel pressure-volume relationships in dogs. *Circ Res.* 1974;34:360-73.
- 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.
- Samar RE, Coleman TG. Measurement of mean circulatory filling pressure and vascular capacitance in the rat. *Am J Physiol.* 1978;234:H94-100.
- Samar RE, Coleman TG. Mean circulatory pressure and vascular compliances in the spontaneously hypertensive rat. *Am J Physiol.* 1979;237:H584-H589.
- Yamamoto J, Trippodo NC, Ishise S, Frohlich ED. Total vascular pressure-volume relationship in the conscious rat. *Am J Physiol.* 1980;238:H823-H828.
- Shoukas AA, Sagawa K. Control of total systemic vascular capacity by the carotid sinus baroreceptor reflex. *Circ Res.* 1973;33:22-33.
- Versprille A, Jansen JR. Mean systemic filling pressure as a characteristic pressure for venous return. *Pflugers Arch.* 1985;405:226-33.
- Pinsky MR. Instantaneous venous return curves in an intact canine preparation. *J Appl Physiol.* 1984;56:765-71.
- Starr I. Role of the static blood pressure in abnormal increments of venous pressure, especially in heart failure. II. Clinical and experimental studies. *Am J Med Sci.* 1940;199:40-55.
- Jellinek H, Krenn H, Oczeni W, et al. Influence of positive airway pressure on the pressure gradient for venous return in humans. *J Appl Physiol.* 2000;88:926-32.
- Schipke JD, Heusch G, Sani AP, et al. Static filling pressure in patients during induced ventricular fibrillation. *Am J Physiol Heart Circ Physiol.* 2003;285:H2510-5.
- Maas JJ, Geerts BF, van den Berg PC, et al. Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. *Crit Care Med.* 2009;37:912-8.
- 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;74:2566-73.
- Jansen JR, Schreuder JJ, Mulier JP, et al. A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. *Br J Anaesth.* 2001;87:212-22.
- 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;62:760-8.
- Keller G, Desebbe O, Benard M, et al. Bedside assessment of passive leg raising effects on venous return. *J Clin Monit Comput.* 2011;25:257-63.
- Persichini R, Silva S, Teboul JL, et al. Effects of norepinephrine on mean systemic pressure and venous return in human septic shock. *Crit Care Med.* 2012;40:3146-53.
- Parkin WG, Leaning MS. Therapeutic control of the circulation. *J Clin Monit Comput.* 2008;22:391-400.
- Maas JJ, Pinsky MR, Geerts BF, et al. Estimation of mean systemic filling pressure in postoperative cardiac surgery patients with three methods. *Intensive Care Med.* 2012.
- Cecconi M, Aya HD, Geisen M, et al. Changes in the mean systemic filling pressure during a fluid challenge in postsurgical intensive care patients. *Intensive Care Med.* 2013;39:1299-305.
- Maas JJ, Pinsky MR, Aarts LP, Jansen JR. Bedside assessment of total systemic vascular compliance, stressed volume, and cardiac function curves in intensive care unit patients. *Anesth Analg.* 2012;115:880-7.
- Magder S, De Varennes B. Clinical death and the measurement of stressed vascular volume. *Crit Care Med.* 1998;26:1061-4.
- Geerts BF, Maas J, de Wilde RB, et al. Arm occlusion pressure is a useful predictor of an increase in cardiac output after fluid loading following cardiac surgery. *Eur J Anaesthesiol.* 2011;28:802-6.
- Maas JJ, Pinsky MR, de Wilde RB, et al. Cardiac output response to norepinephrine in postoperative cardiac surgery patients: interpretation with venous return and cardiac function curves. *Crit Care Med.* 2013;41:143-50.