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Mean systemic filling pressure : from Guyton to the ICU

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Citation
Maas, J. J. (2013, January 17). *Mean systemic filling pressure : from Guyton to the ICU*. Retrieved from https://hdl.handle.net/1887/20407

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

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Date: 2013-01-17

Chapter 11

Final considerations and clinical implications

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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).

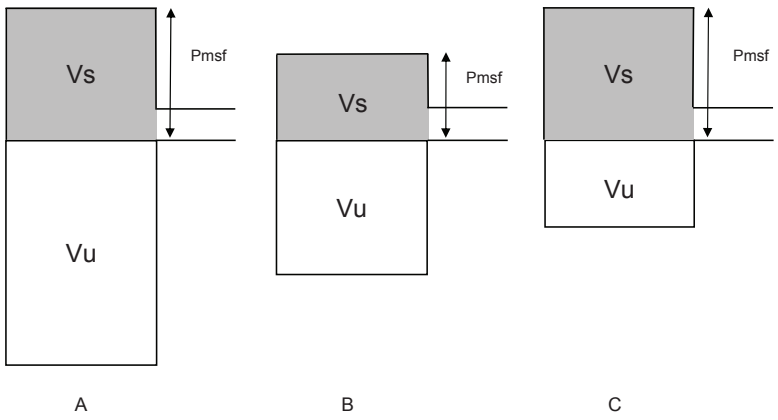

Figure 11.1 Schematic representation of intravascular volumes during normovolemia and hypovolemia

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.

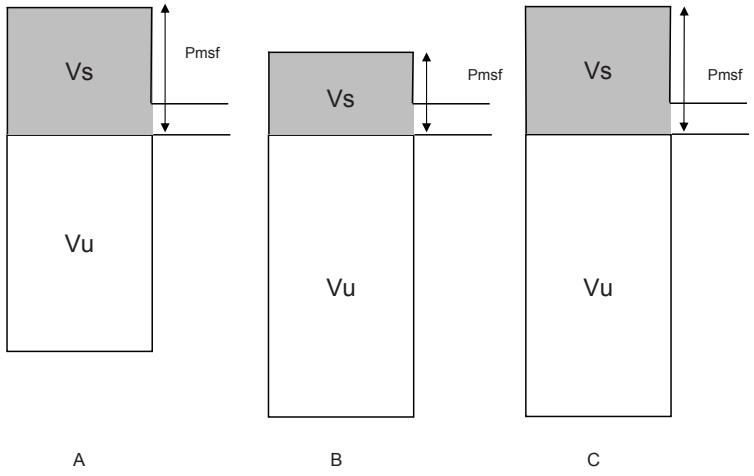

Figure 11.2 Schematic representation of intravascular volumes during sepsis
Panel A: normovolemia, with total blood volume divided into unstressed volume (Vu) and stressed volume (Vs). Mean systemic filling pressure (Pmsf) is the pressure in the compartment of Vs
Panel B: distributive shock, volume has 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.

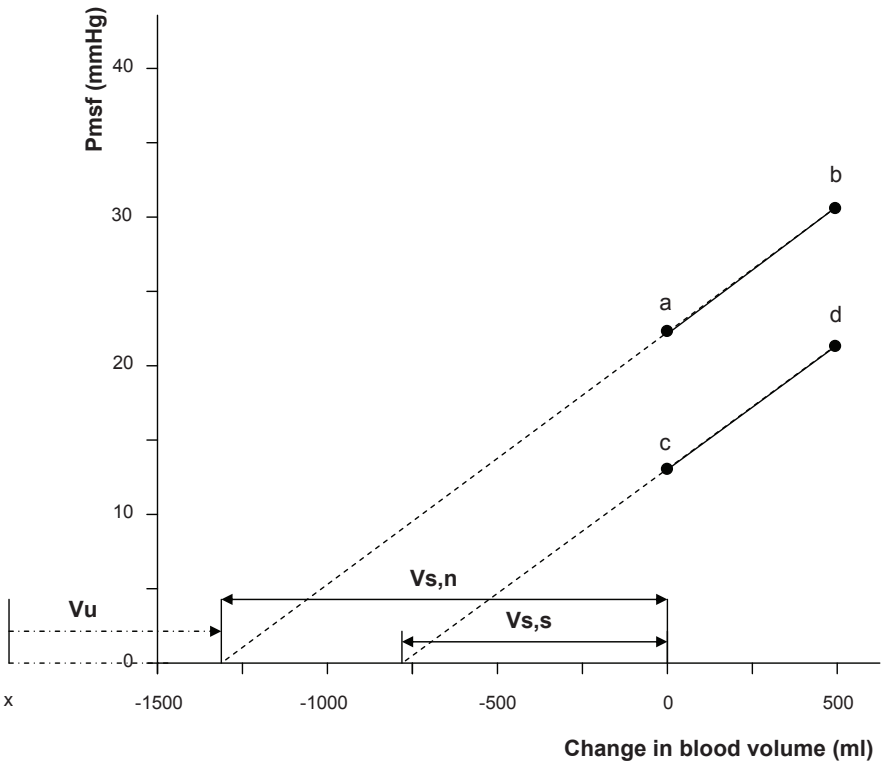

Figure 11.3 Determination of stressed volume
Relationship between change in blood volume and mean systemic filling pressure (Pmsf) for a non-septic patient at normovolemia (a) and after volume loading with 500 ml (b). In the figure stressed volume (Vs,n) is indicated. Removal of 1300 ml blood in this 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.

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