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**Title:** Mean systemic filling pressure : from Guyton to the ICU

**Date:** 2013-01-17

# Chapter 2

## **Bedside assessment of mean systemic filling pressure**

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**Current Opinion in Critical Care 2010;16:231-236**

## **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<sup>1</sup> late in the 19<sup>th</sup> 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.<sup>2-5</sup>

## Short history and basic concepts

When Starling and Bayliss<sup>1</sup> 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<sup>6</sup> 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<sub>2</sub>O) than in patients dying from other causes (average 10.6 cmH<sub>2</sub>O). He concluded that the increase of Pms in heart failure patients was due to

compensatory mechanisms such as fluid retention and vasoconstriction.

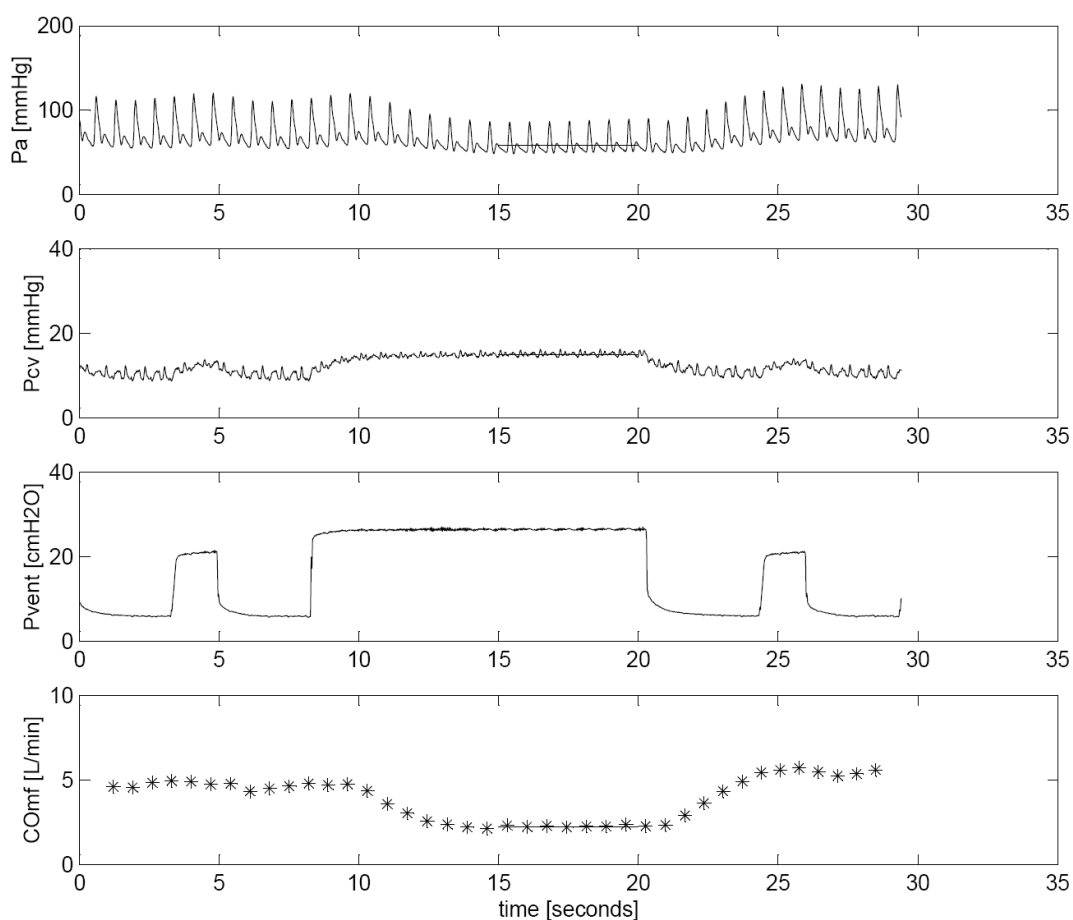
Guyton *et al.*<sup>7,8</sup> showed that the relationship between stepwise changes in right atrial pressure (Pra) and the resulting changes in venous return describes a venous return curve, which itself is a function of the circulating blood volume, vasomotor tone and blood flow distribution. Importantly, 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  $\text{venous return} = (\text{Pmsf} - \text{Pra})/\text{Rvr}$ .<sup>7,8</sup> 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<sup>8,9</sup> and in animals with an intact circulation using invasive hemodynamic monitoring.<sup>10-13</sup> 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<sup>3,11</sup>, congestive heart failure<sup>14</sup>, circulatory effect of mechanical ventilation<sup>15</sup> and the physiological effects of vasoactive drugs.<sup>16-19</sup> 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<sup>20,21</sup>, conditions that occur rarely in clinical critical care settings.

We<sup>22</sup> 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.*<sup>7,8</sup> 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<sub>2</sub>O, 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 ( $P_{cv} - P_{msf}$ ) 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.*<sup>8</sup> 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

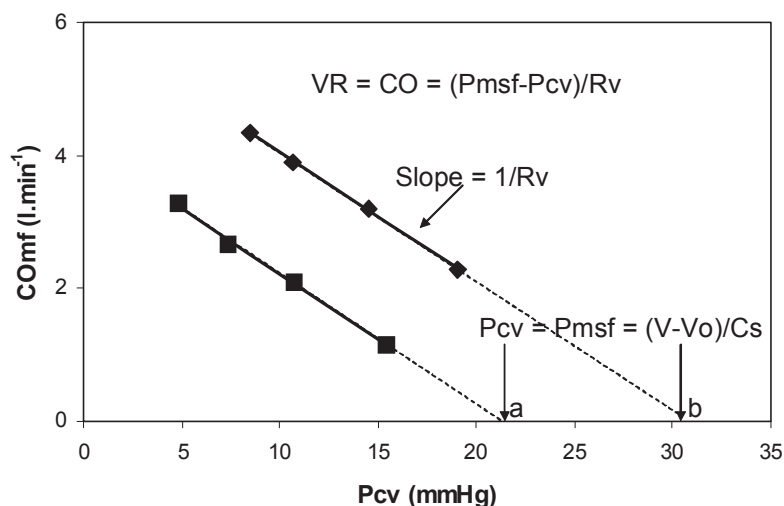
Effects of an inspiratory hold maneuver on arterial pressure (Pa), central venous pressure (Pcv), airway pressure (Pvent) and beat-to-beat cardiac output (COMf). Preceding the hold maneuver the effects of a normal ventilatory cycle are plotted. From<sup>22</sup> with permission.

## 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.<sup>3,23</sup>

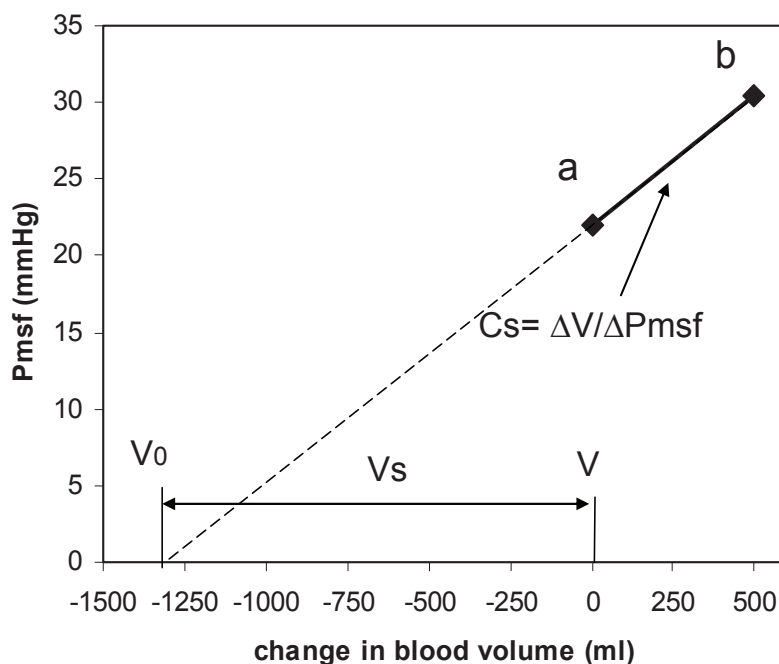


**Figure 2.2 Venous return curves**

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 V<sub>0</sub> is unstressed volume, the difference is stressed volume (V<sub>s</sub>). Cs is systemic compliance (see also figure.2.3). The points a and b indicate Pmsf for normovolemia and hypervolemia respectively.

Our<sup>22</sup> 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.<sup>24</sup> 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.<sup>2,3</sup> 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.<sup>3,25</sup> 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  $\alpha$ - and  $\beta$ 2-adrenergic 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<sup>2</sup>, Rothe<sup>5</sup> and Pang.<sup>17</sup>

### ***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.<sup>26</sup> 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<sup>26</sup> 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.<sup>22</sup>

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  $\alpha$ - and  $\beta$ 1-adrenergic agonist) into anesthetized dogs increased arterial pressure, cardiac output, total peripheral resistance, hepatic vein resistance and Pmsf and reduced heart rate and liver volume.<sup>27</sup> 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.<sup>19</sup> Although it is clear that norepinephrine is capable of increasing Pmsf, there are differences in Pmsf response among different species of animals.<sup>17</sup> 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 administering 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.<sup>4,28</sup> However, inotropic agents, like dobutamine, can cause vasodilation, owing to their peripheral  $\beta$ -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<sup>22</sup> 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.<sup>17</sup>

### **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.<sup>11,13</sup> 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.

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