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The importance of the peripheral circulation in critical illnesses

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Introduction

Because no blood is stored in the heart [1], cardiac output can only increase significantly when venous return increases cardiac filling [2]. The venous system serves as a large low-pressure reservoir through which blood is returned to the heart and may contain as much as 75 % of the total blood volume [3, 4]. Active and passive changes of venous vascular tone alter the quantity of venous blood, which thereby alters cardiac preload. The peripheral circulation, therefore, plays an essential role in the regulation of cardiac output [5]. In critically ill patients circulatory homeostasis may be disrupted by factors that primarily diminish venous return or those that impair compensatory responses which restore cardiac preload.

In this article we examine the forces that govern venous return. We review the relative importance of the peripheral resistance and capacitance vessels for the restoration of cardiac preload and blood pressure during circulatory disturbances. We also analyze the effect on venous return of specific problems inherent to critical illnesses. Based on these considerations, we discuss therapeutic rationales for patients whose cardiovascular homeostasis is in jeopardy.

Vascular control mechanisms

The forces driving venous return

The driving force for venous return is the pressure gradient between the peripheral veins and the right atrium (Fig. 1a, b). The pressure in the periphery is the *mean circulatory filling pressure*, which is conceptualized as the pressure distending the vasculature when the heart is stopped (zero flow) and the pressures in all segments of the circulation have equalized. The mean circulatory filling pressure, which is normally in the range of 8–10 mmHg, is an indicator of the balance between the size of the vascular space and the volume of fluid in the vasculature [6, 7]. Hence, vascular tone or elastic recoil and the blood volume are primary determinants of the mean circulatory filling pressure.

Several terms are required to describe the capacitance, i.e. the overall pressure-volume relationship of the vasculature. The amount of blood that can be accommodated in the vasculature at zero transmural pressure is referred to as the unstressed volume, which may account for 3/4 of the total blood volume in the normal circulation. (Just as the lungs can contain some air when they collapse (zero distending pressure), there can be blood in the vasculature when the transmural pressure is zero.) The additional blood in the circulation, known as the *stressed vascular volume*, causes the

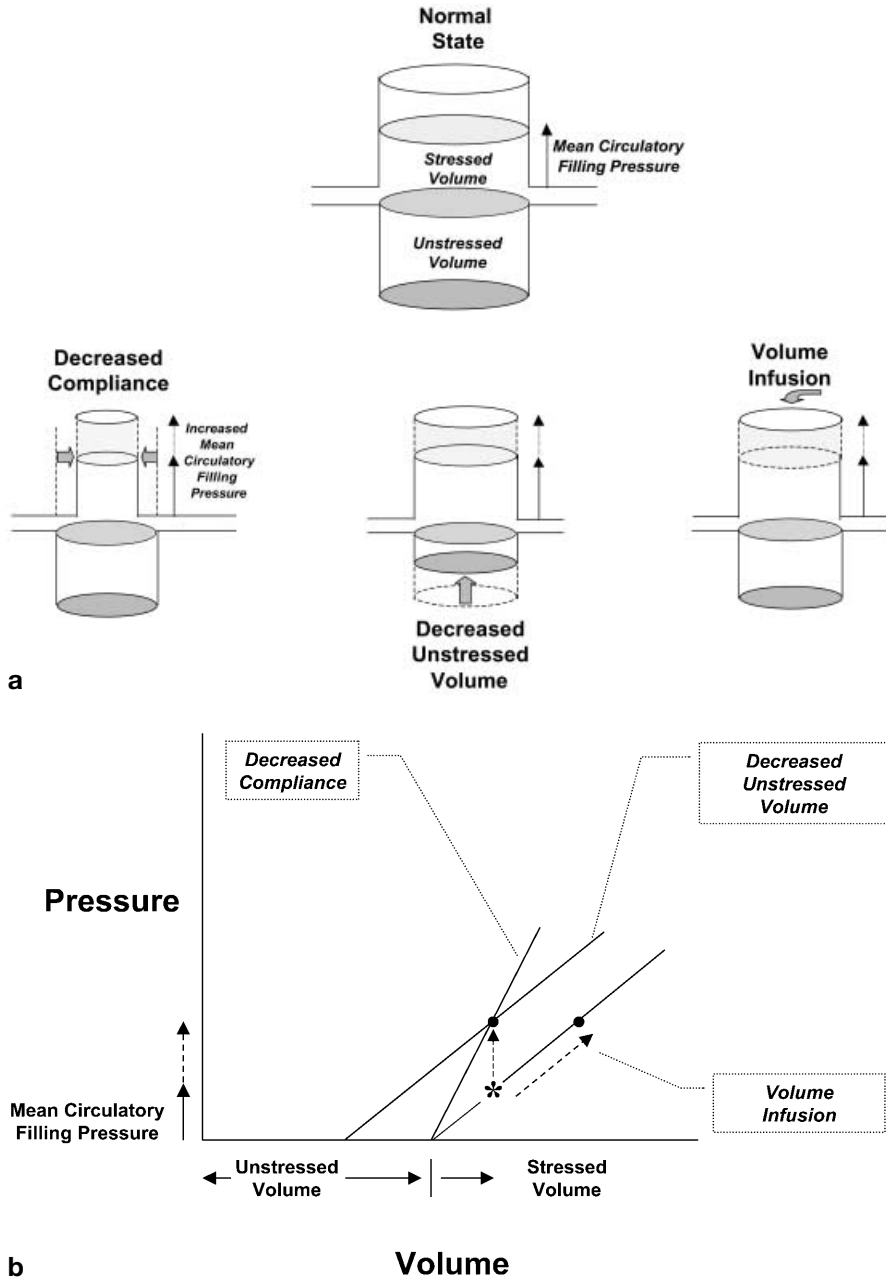


Fig.1 a Diagram showing the relationship between unstressed vascular volume, stressed vascular volume and mean circulatory filling pressure under normal conditions and three states in which mean circulatory filling pressure is increased. The mean circulatory filling pressure (indicated by the height of the arrow) is determined by the capacitance of the vasculature and the intravascular volume (unstressed + stressed volume). Mean circulatory filling pressure increases (dashed arrow): (a) when compliance is decreased, (b) when unstressed volume is decreased (thereby increasing stressed volume) and (c) with volume infusion. **b** Pressure-volume relationship of the vasculature showing the effects of decreased unstressed volume, decreased compliance and volume infusion on mean circulatory filling pressure. The normal state is

shown by the curve to the right. The large volume in the circulation when pressure is 0 represents the unstressed volume. When more volume (stressed volume) fills the circulation, the pressure increases at a rate determined by the vascular compliance. For the normal state (Fig. 1a), an * denotes the initial mean circulatory filling pressure (also shown by the height of the solid arrow along the y-axis). When compliance decreases, the mean circulatory filling pressure increases and follows a steeper than normal pressure-volume relationship. When unstressed volume is decreased, blood is shifted increasing the stressed volume and, thereby, raising mean circulatory filling pressure. When volume is infused, stressed volume rises as does mean circulatory filling pressure

pressure to increase to the mean circulatory filling pressure. The term *compliance* describes the changes in (stressed) volume with respect to changes in pressure and is a measure of vascular distensibility. Accordingly, capacitance depends on both the unstressed volume and the compliance of the vasculature. The unstressed volume resides predominantly in the venous system because veins are 30–50 times more compliant than arteries. Thus, the capacitance of the vascular space is largely determined by the veins.

The anatomic site where vascular pressure is equivalent to the mean circulatory filling pressure under dynamic conditions is generally believed to be in the post-capillary small venules; this segment in the circulation contains the largest fraction of total blood volume. Either an increase in venous capacitance (venodilatation) or a reduction in blood volume can decrease mean circulatory filling pressure. Interestingly, the mean circulatory filling pressure does not change with flow, although the distribution of the blood among the various compartments changes.

For practical purposes *right atrial pressure* is identical to central venous pressure. Right atrial pressure serves both as the back-pressure for venous return and as the filling pressure of the right heart. (It is important to remember that the pleural pressure surrounding the heart is sub-atmospheric in the spontaneously breathing subject, so that the transmural pressure of the right atrium is greater than right atrial pressure, referenced to atmosphere). When right atrial pressure decreases relative to mean circulatory filling pressure, e.g. by an increase in cardiac contractility that decreases end-diastolic volume and pressure, venous return increases to restore the filling pressure [6].

Venous return is not only influenced by the pressure gradient, it is also affected by the resistance to venous blood flow. A change in the dimension of vessels can change capacitance and resistance simultaneously and disproportionately because the volume (V) contained in a blood vessel is related to the second power of its radius (r) ($V \propto r^2$), whereas resistance (R) is related to the fourth power of radius ($R \propto 1/r^4$). For this reason, the consequences of venoconstriction are not easy to predict. Both the resultant decrease in capacitance and the associated increase in mean circulatory filling pressure could augment venous return. However, increased venous resistance may oppose this effect. Alterations on the arterial side of the circulation may then be needed to sustain blood flow when the venous tone is increased [3, 4, 6, 7].

Baroreflex control

Cardiac filling pressures are sensed by low-pressure stretch- or mechanoreceptors across the wall of the right atrium and the pulmonary artery. A reduction in cardiac

blood volume decreases the firing rate of afferent vagal fibers to the central nervous system where they sustain a tonic inhibition of sympathetic outflow to the vasculature [8, 9]. Thus, when venous return decreases, reduced atrial stretch and lower transmural pressures disinhibit sympathetic activity and this increases arterial vasomotor and venomotor tone [10, 11, 12]. When cardiac preload is decreased further, the hemodynamic adaptation mediated by the low-pressure baroreceptors will not suffice to prevent a drop in pulse pressure and eventually mean arterial pressure will also decrease. This stimulates arterial “high-pressure” baroreceptors located in the carotid sinus and the aortic arch. In response, sympathetic outflow to the heart and the peripheral circulation is increased causing tachycardia, increased myocardial contractility and additional vasoconstriction, particularly in the splanchnic circulation. These reflex responses serve to restore mean arterial pressure and to decrease venous capacitance by mechanisms described below.

Active and passive control of venous capacitance

Active venoconstriction occurs in response to adrenergic stimulation of venous smooth muscle via neural or humoral pathways [11]. The most richly innervated veins are those in the splanchnic and cutaneous circulation whereas muscle veins appear to respond less to adrenergic stimuli [3, 12]. Since the cutaneous veins are primarily subservient to thermoregulatory reflexes, the splanchnic circulation may well be the only site where significant active venoconstriction occurs for restoration of cardiac preload [3, 10]. There is no evidence that venoconstriction ever occurs independently of arterial vasoconstriction [13]. In fact, sustained isolated venoconstriction might be detrimental to venous return because it would cause an increased resistance to venous blood flow, thereby reducing venous return, and a rise in upstream pressure, thereby facilitating fluid extravasation from the capillaries [3, 14]. These adverse consequences could be minimized by simultaneous constriction of small venules and arterial resistance vessels, which will prevent the engorgement of the capacious postcapillary vessels and promote the transfer of blood toward the heart [10]. In this manner, active changes in capacitance, through vaso- and venoconstriction, can increase mean circulatory filling pressure (Fig. 1a, b). The net result is a rise in venous return despite the increase in venous resistance.

Because the vasculature is not composed of rigid pipe but has elastic properties, changes in flow or vascular resistance have an important impact on the distribution of blood volume. The volume contained in a vessel is dependent on the balance between the intravascular or distending pressure and the elastic recoil forces.

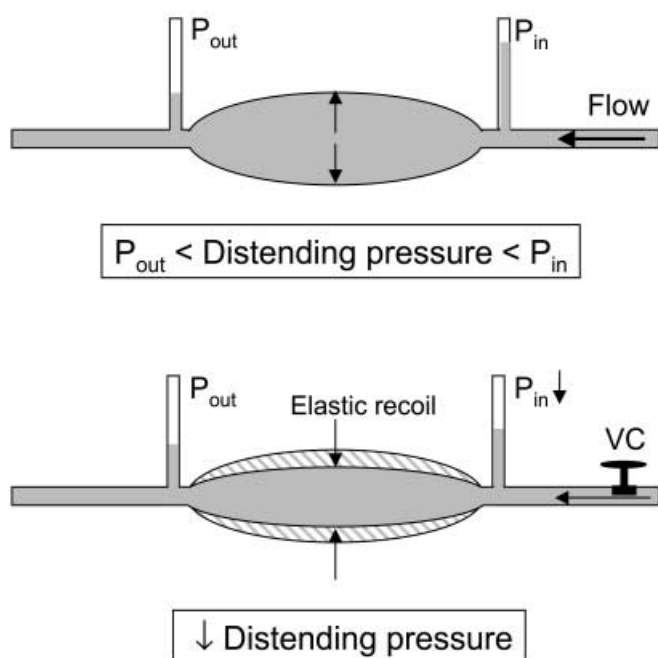


Fig. 2 The effect of a change of flow on distending pressure. The elastic properties of the venous system result in flow-dependent changes of the contained volume. **Upper panel:** The inflow and outflow pressure determine the distending pressure acting on the inside of the blood vessel. The distending pressure is counteracted by the interstitial pressure and elastic recoil forces. **Lower panel:** When blood flow decreases subsequent to arteriolar vasoconstriction (*VC*), inflow pressure to a particular vein is decreased. Consequently, outflow transiently exceeds inflow until a new equilibrium between the reduced distending pressure and elastic recoil is reached. By this mechanism, blood volume is transferred centrally

Thus, changes in intravascular pressure may induce passive changes in capacitance that do not influence mean circulatory filling pressure [10, 15, 16]. For example, the distending pressure of a particular venule declines when blood flow is reduced, i.e. subsequent to arteriolar vasoconstriction. Elastic recoil forces may then act to reduce the intravascular volume and to transfer blood volume towards the heart until a new equilibrium between the distending pressure and recoil forces is reached (Fig. 2). Thus, blood volume mobilization may occur in the absence of active venoconstriction. In addition to the changes in blood flow, the distending pressure of a blood vessel is also determined by the inflow and outflow resistance.

As originally noted by De Jager [17] as well as Krogh [15], the distribution of blood flow between organs has important consequences for the volume of blood available to fill the heart because some organs are much more compliant than others. For example, a reduction of blood flow to the highly compliant vasculature of the splanchnic region or the skin will passively displace blood volume into the central circulation. Conversely,

an increase in flow to these regions will sequester blood volume in the periphery and decrease central blood volume. Figure 3 illustrates in a hydraulic model by Rowell [12] how blood flow through circuits with different compliances could affect the distribution of blood volume.

Animal studies often measure the volume changes in an external reservoir between the central veins and the right atrium to assess changes in systemic vascular capacitance. In such studies both α - and β -adrenergic mechanisms were effective in transferring blood volume toward the heart [18, 19, 20, 21, 22, 23, 24, 25]. α -Adrenergic receptor stimulation induces active vaso- and venoconstriction, which are associated with an increased mean circulatory filling pressure [19, 20, 21]. In contrast, β -adrenergic receptor stimulation with isoproterenol increased external reservoir volumes in the absence of alterations of mean circulatory filling pressure [24, 25]. These observations suggest that the β -adrenergic system causes blood volume mobilization through passive capacitance changes, most likely secondary to a decrease in hepatic outflow resistance [18, 26, 27].

One major limitation of studies using an external reservoir is that venous return drains into the reservoir at a constant pressure whereas, in the intact circulation, central venous pressure would be expected to change in similar conditions and this may attenuate the increase in central blood volume observed in open loop experiments. The importance of passive volume shifts may therefore be smaller than suggested by these studies.

Factors that can disrupt circulatory homeostasis

Mechanical ventilation

Positive pressure ventilation or PEEP often reduces cardiac output [28, 29, 30]. Changes in lung volume can increase pulmonary vascular resistance and cause mechanical compression of the heart (Fig. 4). Also, some studies have observed reflex ventricular depression [31, 32, 33], although cardiac function is generally found to be normal with PEEP [34, 35]. The primary cause of reduced cardiac output, however, appears to be impedance to venous return [29, 36, 37]. The underlying mechanisms are complex.

Positive end-expiratory pressure elevates the transpulmonary pressure, which compresses the large intrathoracic veins and right atrium. As a result, central venous pressure rises, even though the transmural pressure of the right atrium decreases [29, 38, 39]. These changes potentially reduce the driving pressure for venous return, but PEEP also increases mean circulatory filling pressure by a similar amount as the change in right atrial pressure [14, 38, 40, 41] (Table 1). The associated rise in mean circulatory filling pressure results from a parallel shift of the systemic pressure-volume curve to

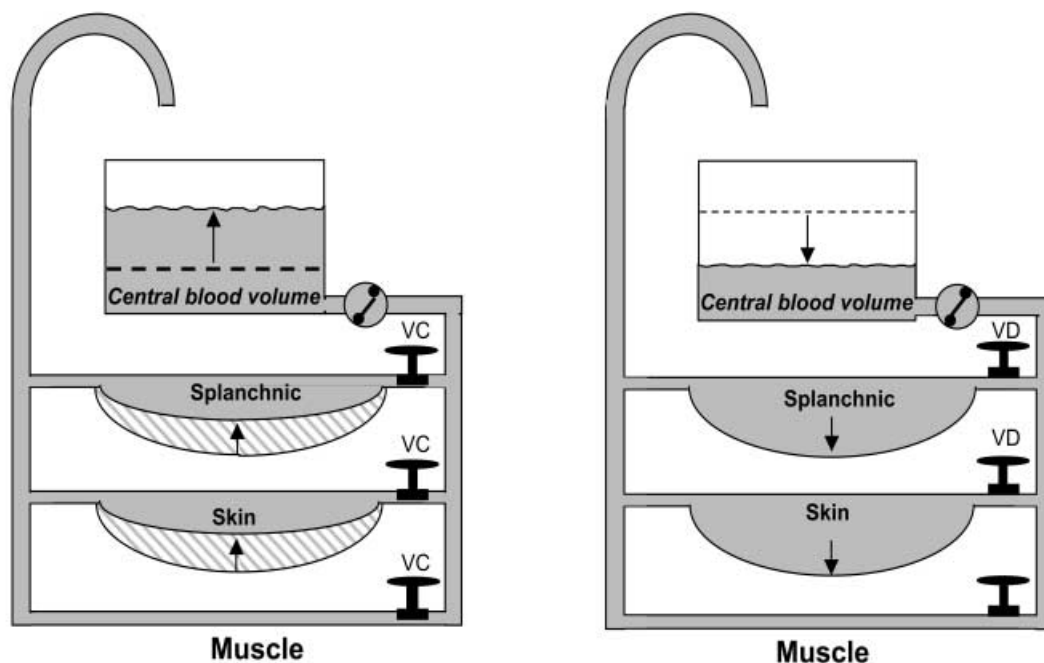


Fig. 3 The effect of vasoconstriction and vasodilatation on the distribution of blood volume. Changes in blood flow through compliant and non-compliant vascular beds have important effects on the distribution of blood volume between the peripheral and the central circulation. Vasoconstriction (VC) and reduction of blood flow to the compliant splanchnic and cutaneous veins decrease peripheral and increases central blood volume (**left panel**), whereas vasodilatation (VD) has the opposite effects (**right panel**). In contrast, changes of blood flow through the non-compliant muscle circulation has minimal effects on the blood volume distribution. From Rowell LB (1993) *Human Cardiovascular Control*, Oxford University Press, with permission

Table 1 Effect of circulatory disturbances on vascular volumes and pressures (CVP central venous pressure)

Condition	CVP	Central blood volume	Mean circulatory filling pressure	Unstressed volume
Mechanical ventilation	↑	↓	↑	↓
Hemorrhage	↓	↓	↓	↓
Depressed myocardial function	↑	↑	↑	↓
Sepsis	↓	↓	↓	↑
High peripheral blood flow	↓	↓	=	↑

the left, which indicates a volume shift from the unstressed to the stressed compartment with no change in compliance [14] (Fig. 5). Two questions arise from these observations: (1) Which factors contribute to the rise in mean circulatory filling pressure? and (2) Why is venous return reduced by PEEP when the pressure gradient for venous return is sustained?

(1) The rise in intrathoracic pressure may transfer blood volume from the thorax to the systemic veins [42]. When PEEP is increased enough to lower cardiac output by 65%, this amounts to a shift of 7.2 ml/kg of blood into the peripheral compartment [43]. Particularly in the splanchnic region, a rise in blood volume is commonly observed during PEEP [44, 45]. Thus, passive volume shifts may increase the upstream venous pressure and buffer the decrease in cardiac output [46], but how much the pressure rises depends on the distensibility of the upstream veins. For example, sympathetic blockade attenuates the increase in mean circulatory filling pressure during PEEP and the decline in cardiac

output is exaggerated [39, 40]. Therefore, during PEEP, active responses must contribute to a reduction in vascular capacitance. The afferent sensory signal for this reflex is probably the reduction of right atrial stretch or transmural pressure [47].

(2) If venous return decreases during PEEP, despite a constant pressure gradient, there is either an increased resistance to venous flow or a collapse owing to critical closing pressure of the veins. Fessler and co-workers studied the effects of PEEP on the shape of the venous return curve [41]. They showed that PEEP not only increases mean circulatory pressure (i.e. the right atrial pressure at which venous flow would be zero) but also the point of flow limitation (P_{crit}), below which venous return is maximal (see Fig. 6). In addition, the change in the slope of the pressure-flow curve indicates an increased vascular resistance. These factors, which are ev-

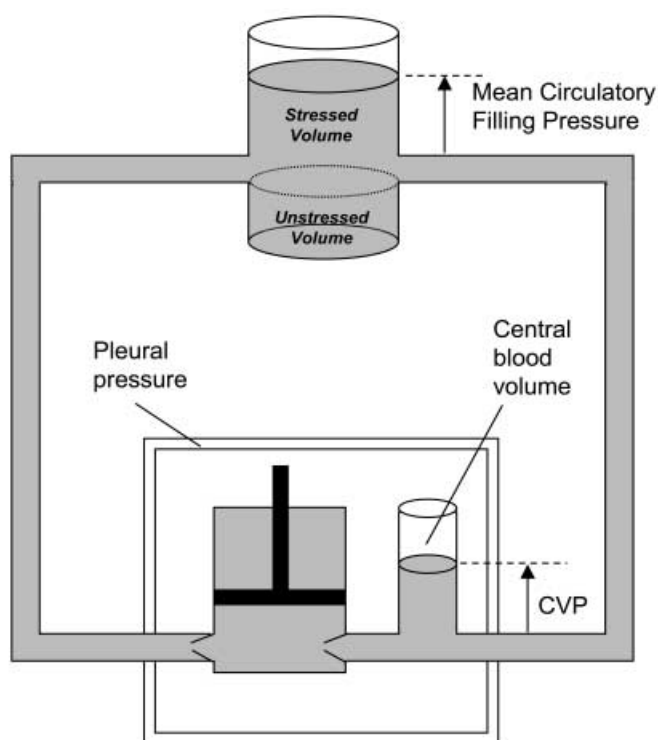


Fig. 4 Simplified model of the circulation demonstrating the relationship between peripheral and central blood volume. The difference between the mean circulatory filling pressure and the central venous pressure (CVP) is the force driving venous return. Table 1 indicates the changes in CVP, central blood volume, mean circulatory filling pressure and unstressed volume caused by various conditions

ident in the inferior vena cava, limit maximal venous flow. In a subsequent study Fessler and co-workers demonstrated that PEEP may increase P_{crit} more than right atrial pressure by direct compression of the inferior vena cava at the level of the diaphragm [48]. This condition has been referred to as a “vascular waterfall”, because the venous pressure gradient is no longer determined by the right atrial pressure as the effective back-pressure. Thus, PEEP may produce venous flow limitation despite the elevation of pleural and venous pressures when these are exceeded by high extravascular pressures that are generated by hyperexpanded lungs.

The PEEP-induced changes in the splanchnic circulation are of particular interest because this compartment contributes the largest single fraction of venous return. PEEP reduces venous return from the splanchnic region and increases splanchnic blood volume [44, 45, 49]. Similar to the systemic circulation, the increase in right atrial pressure causes an increase in portal venous back pressure [49]. Contrary to what would be expected with the resulting venous distension, there is an increase, not a decrease, in portal and hepatic venous outflow resistance [49, 50]. It has been proposed that this

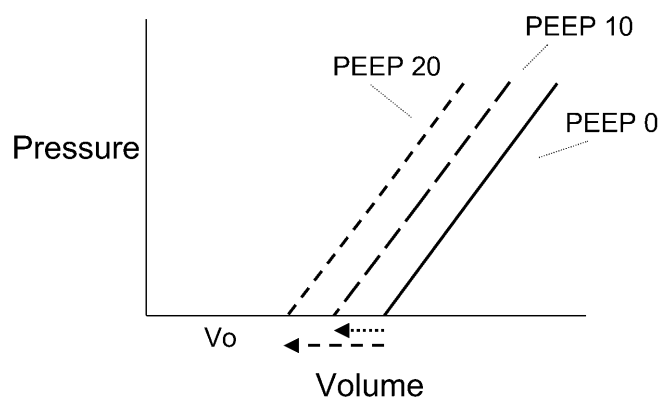


Fig. 5 The response of the vasculature to PEEP. PEEP decreases unstressed volume and thereby increases stressed volume with no change in compliance (i.e. the slope of the pressure-volume relationship). These adaptations help to increase the mean circulatory filling pressure needed to sustain the pressure gradient for venous return. From [14] with permission

increase in splanchnic resistance is caused by the diaphragmatic descent and mechanical compression of the liver [49, 51].

On the arterial side, splanchnic blood flow decreases during PEEP proportionately with cardiac output and may be restored with volume loading [50]. Independent of the changes in blood flow, measurements of indocyanine green extraction indicate that both blood volume and hepatic outflow resistance may modulate hepatic function during PEEP [50].

In summary, PEEP alters venous return by mechanisms affecting back-pressures and resistance to venous flow, both in the systemic and the splanchnic circulation. These consequences may be reversed by volume expansion, which not only increases mean systemic pressure but also overcomes the elevated venous resistances (by raising the distending pressures across the portal and intrathoracic great veins) [5, 14, 49, 50]. Although beta-agonists are effective in reducing splanchnic resistance they may be ineffective when there is mechanical compression of the liver [26, 49].

These data may help us to understand why critically ill patients tolerate positive pressure ventilation poorly when their blood volume is diminished even though there may be significant endogenous sympathetic stimulation. In contrast, patients with blood volume expansion, e.g. in cardiac failure, are relatively resistant to these effects of PEEP.

Shock

Changes of vascular capacitance and resistance play a central role in the pathogenesis of shock. Peripheral vaso- and venodilation, for example in sepsis or anaphy-

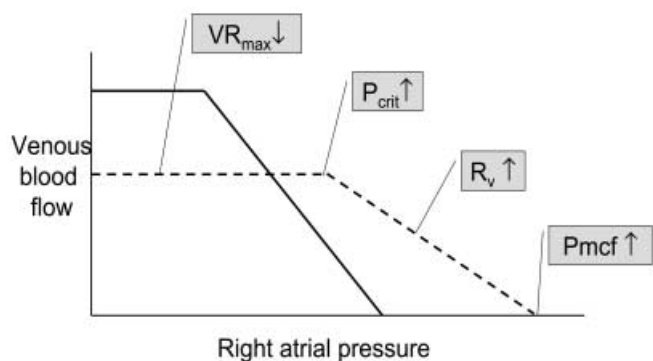


Fig. 6 The effects of PEEP on the venous return curve. PEEP (dashed line) increases mean circulatory filling pressure (P_{mcf}) and P_{crit} , i.e. that right atrial pressure below which venous return is maximal. The altered slope indicates increased venous resistance (R_v) limiting the maximally possible venous return (VR_{max}) From [41] with permission

laxis, may be the primary cause for the development of shock. On the other hand, constriction of the capacitance vessels serves to increase cardiac filling pressure and compensate for blood loss or poor ventricular function.

Hemorrhage

Severe hemorrhage decreases the mean circulatory filling pressure and, subsequently, right atrial pressure (Table 1). Because stressed volume is only 25% of the total blood volume (which is approximately 80 ml/kg), a rapid blood loss of 20 ml/kg would reduce the mean circulatory filling pressure close to zero and stop venous return in the absence of active compensation [1, 52]. The stressed volume can be transferred to the heart by elastic recoil, but additional responses are needed to mobilize more fluid to restore venous return. Baroreflexes and capillary fluid reabsorption from the extravascular space can compensate for an additional fluid loss of as much as 30 ml/kg over 1 h.

With the activation of baroreflexes, peripheral blood volume is transferred into the central circulation by reducing venous capacitance. The largest contribution is from the splanchnic circulation [3, 12], which differs in its drainage characteristics from the non-splanchnic vasculature, as reflected by a longer time constant [15, 53, 54]. One mechanism to reduce splanchnic capacitance is redistribution of blood flow towards regions with faster time constants. A second mechanism is the reduction of portal venous and hepatic outflow resistance during hypotension, which enhances the drainage of the splanchnic capacitance vessels [55]. Thus, at least some splanchnic veins can dilate to decrease venous resistance at the same time as the arterial resistance increas-

es. There is also evidence that small intestinal venules decrease their diameter at constant pressure when blood pressure decreases during hemorrhage [56]. Therefore, alpha adrenergic venoconstriction is a third important mechanism in the control of splanchnic capacitance. Taken together, carotid sinus hypotension reduces splanchnic blood flow, unstressed volume and venous outflow resistance. These responses are partly, but not fully, reversed by alpha-adrenergic blockade [55]. As discussed before, other vascular beds, in particular skin and muscle, also participate in baroreflexes.

Fluid absorption from the tissue to blood is a rapid and powerful mechanism to increase plasma volume during states of hypovolemia [57]. In humans as much as 500 ml can be mobilized over about 10 min largely from skeletal muscle, which serves as the body's largest fluid reservoir [58]. This volume transfer may not only result from a passive decrease in capillary pressure but more likely from sympathetically mediated adjustments of the pre- and postcapillary resistances [59, 60, 61]. Just as adjustments in afferent and efferent arterioles can alter filtration of fluid out of the glomerulus of the kidney, changes in pre- and postcapillary resistances can change the quantity of fluid reabsorbed from the interstitium. Accordingly, an increase in precapillary and decrease in postcapillary resistance would promote fluid reabsorption.

Positive pressure ventilation may counteract fluid absorption from the interstitium in hypovolemic states because the elevated venous pressures may be transmitted to the capillaries [3], which can result in fluid losses into the tissues. Thus, positive pressure breathing can aggravate volume-depleted states and intravenous fluids may be required to restore cardiac filling.

Depressed myocardial function

When myocardial function is acutely depressed and systemic blood flow decreases, cardiovascular reflexes induce active vaso- and venoconstriction to decrease vascular capacitance, thereby increasing cardiac filling pressures (Table 1). In addition, blood volume is passively redistributed by elastic recoil. The relative contribution of active vasomotor responses and elastic recoil forces for the restoration of preload has been examined in dogs using a reservoir to accommodate all of the venous return at constant venous outflow pressure [62]. The cardiac output was set at various levels by pumping blood from the reservoir into the right atrium. The additional amount of fluid collected in the reservoir was a measure of the movement of blood from the periphery to the central circulation. The mechanism for the redistribution was assessed by repeating measurements after blocking cardiovascular reflexes with hexamethonium. When cardiac output was lowered from 110 to

80 ml·kg⁻¹·min the amount of blood transferred into the reservoir was 9.2 ml/kg with reflexes intact, and 6.8 ml/kg with reflexes blocked. Thus, elastic recoil forces provided about 80% and baroreceptor-mediated reflexes 20% of blood volume redistribution.

Reflex blockade did not affect the fraction of venous return from the superior vena cava, indicating that the splanchnic circulation may be the predominant source of reflex blood volume mobilization. This and several other studies using external reservoirs have emphasized the importance of passive redistribution of blood volume by the elastic characteristics of the vasculature [3, 10, 19, 62, 63]. However, in the intact circulation central venous pressure increases during cardiac failure, because systolic ejection is impaired, which increases end-diastolic volume and pressure. Under these conditions, the blood volume redistribution may differ from those studies using the external reservoir, which is specifically designed to keep central venous pressure constant. Such disparities in interpretation of data are illustrated by a study using radionuclide imaging in pigs to assess the changes in splanchnic volume during pacing-induced acute heart failure [64]. The pigs were studied after carotid sinus denervation and cervical vagotomy to eliminate all neurovascular reflexes. Under these conditions the volume decrement of the spleen was matched by a volume increment of the liver, leaving the net splanchnic intravascular volume unchanged. Thus, the potentially large effects of passive volume shifts under conditions of low systemic blood flow seem to depend on the related changes in right atrial pressure, i.e. they may be greater with hemorrhage than with heart failure or PEEP.

There is also evidence for active changes in the vasculature when cardiac function is depressed. This is exemplified by a study in which chronic heart failure was induced in dogs by rapid right ventricular pacing for 6 weeks with subsequent recovery [65]. Heart failure was associated with a reduction in unstressed volume while central blood volume increased. The relative contribution of active and passive capacitance changes could not be determined in that study, but the associated increase in mean circulatory filling pressure indicates that active constriction of the vasculature must have occurred. After 2 weeks of recovery all variables had returned to baseline values.

Sepsis

Severe endotoxemia is commonly associated with a diminished systemic vascular resistance and hypotension (Table 1). Although the circulation is often hyperdynamic, cardiac function may be depressed in severe septic shock. Cytokines, such as interleukin-1 β and tumor necrosis factor- α , which are induced by endotoxin,

seem to impair myocardial contractility directly via a nitric oxide synthase-dependent mechanism [66, 67, 68, 69, 70]. On the arterial side, increased production of nitric oxide is responsible for massive peripheral vasodilatation, depressed vascular reactivity in response to endogenous and exogenous vasoconstrictors, and impaired tissue perfusion [71, 72, 73, 74, 75]. In contrast, during sepsis and endotoxemia there is increased resistance and hypertension in vascular beds with venous characteristics, including the pulmonary circulation [76].

Endotoxemia increases portal venous pressure and the venous pressure-flow relationship of the splanchnic circulation is shifted upwards, i.e. there is decreased venous blood flow for a given portal venous pressure [77, 78]. This impairment of portal blood flow appears to be caused by active portal-sinusoidal constriction and by vascular obstruction secondary to cell swelling, hemorrhage and congestion within the liver [76, 78]. These alterations contribute to the increased venous resistance and generate a back-pressure to portal venous flow. In addition, sepsis and endotoxemia may disrupt the so-called veno-arterial response in the splanchnic vascular bed, a physiological mechanism that increases mesenteric arterial resistance and limits splanchnic arterial blood flow when portal venous pressure increases [79, 80]. Thus, at the same time as venous outflow from the splanchnic vascular bed is impeded mesenteric arterial vasodilatation may augment blood flow to this region. In association with increased vascular permeability, this causes splanchnic blood pooling and edema formation [81]. These factors contribute to the loss of circulating blood volume and decreased cardiac preload culminating in septic shock.

High peripheral blood flow demands

In adult humans the maximal cardiac output is about 25 l/min. This flow is insufficient to sustain maximal blood flow simultaneously to all regions of the body, so blood flow redistribution mandates that when flow to one region is increased flow to another must be curtailed. Such circumstances require complex interactions between competing reflexes to sustain circulatory homeostasis [82, 83]. For example, exercise in a hot environment creates an inherent competition between baroreflexes that maintain arterial blood pressure when flow to the working muscle is increased and thermoregulatory reflexes that induce cutaneous vasodilatation for heat dissipation [84]. The increase in skin blood flow during thermal stress may approach 8 l/min in resting humans [85, 86] and is associated with an increase in cutaneous blood volume because venous drainage from the skin occurs with a very long time constant [87]. Thus, in heat stress, but not in thermoneutral condi-

tions, the skin may be an important blood reservoir and the redistribution of blood volume away from the central circulation may jeopardize blood pressure regulation. Accordingly, the cardio-circulatory reserve appears to be greater in a cool environment because less skin blood flow is required for heat dissipation [88].

Maintenance of body core and skin temperature is the predominant thermoregulatory drive in the control of skin blood flow. When an internal temperature threshold is exceeded, skin blood flow increases briskly both by withdrawal of sympathetic vasoconstrictor activity and by active vasodilatation. At the same time sweating begins. The threshold for cutaneous vasodilatation and sweating is increased to a higher temperature when baroreflexes are activated with exercise or lower body negative pressure [82, 89, 90, 91]. Hence, thermoregulation is attenuated in favor of blood pressure control. In heat stressed subjects, the contribution of the cutaneous circulation to baroreflexes is greatly enhanced. For example, forearm vascular conductance may increase more than threefold with skin or body core heating [92, 93]. The application of lower body negative pressure in these conditions induces much greater reductions in forearm vascular conductance than in that of normothermic controls. While lower body negative pressure is effective in sustaining cardiac filling pressures at similar levels as in normothermic subjects, this may occur at the expense of heat dissipation [92, 93].

Mobilization of blood from the splanchnic circulation is an important compensation during heat stress and exercise. In response to sympathetic vasoconstriction, vascular capacitance and unstressed volume decrease [10, 83]. Notice, however, that the impact of regional vasoconstriction on arterial blood pressure is dependent on the cardiac output and total vascular resistance. It has been estimated that an 80% reduction in splanchnic blood flow, e.g. from 1,500 to 300 ml/min, would increase arterial blood pressure by 32 mmHg when cardiac output is 5 l/min, but only by 6 mmHg when cardiac output is 25 l/min [82]. Thus, the translocated volume has a greater effect on the pressure in the systemic circuit when there is high resistance to flow.

Critically ill patients who are hemodynamically compromised may suffer significant additional circulatory strain when there is high peripheral blood flow demand. The mechanisms that divert blood volume to the periphery include fever, high environmental temperatures, thyrotoxicosis, catecholamine infusion and increased muscle work, e.g. with dyspnea or seizures. It is easy to envisage that, in an unstable circulatory state with high metabolic demands, the reduction in central blood volume may be further aggravated when the hydration of a patient is decreased [82]. For example, the high work of breathing increases cardiac output and thermoregulatory demands and may be associated with significant

evaporative fluid losses. Such disturbances compromise the efficacy of baroreceptor reflexes directed to restore cardiac preload in patients with low systemic blood flow. In the patient with significant cardiovascular dysfunction, therefore, close attention must be paid to the volume status and strategies to lower blood flow demands.

Therapeutic implications

In the previous sections we have described how venous return may be compromised in critical illness. There are three principal therapeutic strategies to restore a sufficient cardiac preload: (1) administration of intravenous fluids, (2) pharmacological modulation of vascular tone and (3) reduction of peripheral blood flow demands.

Intravenous fluids increase the stressed volume. When the circulatory stress is mild and compensatory mechanisms suffice to maintain cardiac output and blood pressure, this fluid may only restore the normal ratio of unstressed and stressed venous volume. An increase in urine output may be one of the earliest clinically apparent responses. With more severe hemodynamic compromise, i.e. in septic shock, more volume may be required to restore venous return because of the increased size of the unstressed volume compartment, splanchnic pooling and third space losses [75]. In raising the vascular distending pressure, the most important effect of fluid resuscitation may be to overcome or attenuate the increased portal and systemic venous resistances, which appear to be a major limitation of cardiac output in septic shock [94]. In experimental endotoxemia both the restoration of depressed cardiac output by volume resuscitation and the presence of a hyperdynamic circulation were associated with supranormal levels of mean circulatory filling pressure [94, 95]. In sepsis, therefore, large quantities of fluid may be required to increase the driving pressure for venous return above normal values even though this may cause further blood pooling and third space losses in the peripheral compartments. There is also evidence that volume expansion is effective in reversing the effects of PEEP on venous return by increasing mean circulatory filling pressure and by lowering systemic and splanchnic venous outflow resistance [49].

Epinephrine and norepinephrine (β_1 only) are both α - and β -adrenergic agonists that increase total vascular resistance and mean circulatory filling pressure [6, 96]. It is well known that resistance vessels constrict with α -receptor stimulation (e.g. phenylephrine) and dilate with β -receptor stimulation (e.g. isoproterenol). In contrast, the mechanism by which venous capacitance is reduced is less certain. Since veins have predominantly α -receptors, a direct vasoconstrictor effect that reduces

unstressed volume and increases stressed volume seems likely [97, 98]. However, substantial evidence suggests that β -adrenergic receptors may also be involved in the control of venous capacitance. For example, epinephrine increases cardiac filling pressures in dogs when cardiac output is held constant by ventricular pacing; this response is markedly attenuated during β -receptor blockade with propranolol [19]. Since β -agonists, e.g. isoproterenol, have minimal effects on the mean circulatory filling pressure [25, 96], the change in vascular capacitance must be accomplished by other mechanisms. These include lowering of splanchnic venous outflow resistance [17] and an increase of fractional blood flow to regions with fast time constants [53, 54, 99].

In summary, through their effects on the peripheral circulation, catecholamines may be effective in increasing venous return. However, before exogenous sympathetic stimulation is provided to a critically ill patient whose endogenous vasoconstrictor tone may already be extreme, the intravascular volume status should be optimized. Also bear in mind that intense arterial vasoconstriction, while restoring resistance and blood pressure, may be associated with a significant reduction in blood flow. For example, in sepsis, norepinephrine may reduce splanchnic blood pooling by increasing mesenteric resistance, but the concomitant reduction in splanchnic flow may aggravate some pre-existing ischemia in the gut and liver [100].

Inhibition of nitric oxide synthase (NOS) has been investigated as a further approach in modifying vascular tone. In conditions of clinical and experimental sepsis, NOS inhibitors are effective in reversing systemic hypotension [95, 101, 102, 103]. However, this is commonly associated with a reduction in cardiac output [43, 95, 104, 105]. These adverse effects of NOS inhibition appear to be related to an increased resistance to systemic

venous return and the generation of increased resistance and back-pressure to portal venous flow [80, 95]. Thus, there is evidence to suggest that, in vascular beds with venous characteristics, i.e. the splanchnic and the pulmonary circulation, endothelial nitric oxide production may be important in counteracting the effects of vasoconstricting mediators activated by endotoxemia [76]. Therefore the margin between potentially beneficial and harmful effects of NOS inhibition in sepsis and septic shock may be very narrow.

Finally, measures that reduce peripheral blood flow demands are effective in raising central blood volume. For example, the sudden decrease in skin temperature of a heat stressed subject may immediately increase central venous pressure and cardiac stroke volume by diverting flow from the skin and shifting a large volume of blood from the cutaneous capacitance vessels to the central circulation [12]. Similarly, the initiation of assisted ventilation when the work of breathing is increased or the suppression of seizure activity can cause a dramatic improvement in circulatory function.

Summary

The purpose of this review was to highlight the importance of the peripheral circulation in the regulation of cardiac output and to identify some mechanisms by which this regulation may be disrupted in critical illness. Unfortunately, no easily performed tests are available to measure the mean circulatory filling pressure, venous resistance or the fractions of unstressed and stressed venous volume. However, understanding of the relationship among these factors provides useful insight into the nature of circulatory disturbances and untoward responses to interventions in critically ill patients.

References

- Guyton AC, Jones CE, Coleman TG (1955) Determination of cardiac output by equating venous return curves with cardiac output curves. *Physiol Rev* 35: 123–129
- Starling EH (1918) The Linacre lecture on the law of the heart. Longmans, London (held in Cambridge, 1915)
- Hainsworth R (1986) Vascular capacitance: its control and importance. *Rev Physiol Biochem Pharmacol* 105: 101–173
- Rothe CF (1983) Reflex control of veins and venous capacitance. *Physiol Rev* 63: 1281–1342
- Sylvester JT, Goldberg HS, Permutt S (1983) The role of the vasculature in the regulation of cardiac output. *Clin Chest Med* 4: 111–126
- Rothe CF (1993) Mean circulatory filling pressure: its meaning and measurement. *J Appl Physiol* 74: 499–509
- Tyberg JV (1992) Venous modulation of ventricular preload. *Am Heart J* 123: 1098–1104
- Thames MD, Donald DE, Shepherd JT (1977) Behavior of cardiac receptors with nonmyelinated vagal afferents during spontaneous respiration in cats. *Circ Res* 41: 694–701
- Mark AL, Mancia G (1983) Cardiopulmonary baroreflexes in humans. In: *Handbook of Physiology. The cardiovascular system: circulation*. Am Physiol Soc, Bethesda, Md. Sect 2, Vol III:795–813
- Johnson JM, Rowell LB, Niederberger M, Eisman MM (1974) Human splanchnic and forearm vasoconstrictor responses to reductions in right atrial and aortic pressure. *Circ Res* 34: 515–524
- Rothe CF (1986) Physiology of venous return. An unappreciated boost to the heart. *Arch Intern Med* 146: 977–982
- Rowell LB (1986) *Human circulation: regulation during physical stress*. Oxford University Press, New York
- Gow BS (1980) Circulatory correlates: vascular impedance, resistance, and capacity. In: *Handbook of Physiology. The cardiovascular system: vascular smooth muscle*. Am Physiol Soc, Bethesda, Md. Sect 2, Vol II:353–408

14. Nanas S, Magder S (1992) Adaptations of the peripheral circulation to PEEP. *Am Rev Respir Dis* 146: 688–693
15. Krogh A (1912) Regulation of the supply of blood to the right heart (with a description of a new circulation model). *Scand Arch Physiol* 27: 227–248
16. Skokland O (1983) Factors contributing to acute blood pressure elevation. *J Oslo City Hosp* 33: 81–95
17. De Jager S (1886) Experiments and considerations on haemodynamics. *J Physiol* 7: 130–215
18. Shigemi K, Brunner MJ, Shoukas AA (1994) Alpha- and beta-adrenergic mechanisms in the control of vascular capacitance by the carotid sinus baroreflex system. *Am J Physiol* 267:H201–210
19. Imai Y, Satoh K, Taira N (1978) Role of the peripheral vasculature in changes in venous return caused by isoproterenol, norepinephrine and methoxamine in anesthetized dogs. *Circ Res* 43: 553–561
20. Kaiser GA, Ross J, Braunwald E (1964) Alpha and beta adrenergic receptor mechanisms in the systemic venous bed. *Pharmacol Exp Ther* 144: 154–162
21. Müller-Ruchholtz ER, Löscher HM, Grund E, Lochner W (1977) Effect of alpha-adrenergic receptor stimulation on integrated systemic venous bed. *Pfluegers Arch* 370: 241–246
22. Müller-Ruchholtz ER, Löscher HM, Grund E, Lochner W (1977) Effect of beta-adrenergic receptor stimulation on integrated systemic venous bed. *Pfluegers Arch* 370: 247–251
23. Bennett TD, Wyss CR, Scher AM (1984) Changes in vascular capacity in awake dogs in response to carotid sinus occlusion and administration of catecholamines. *Circ Res* 55: 440–453
24. Hirakawa S, Itoh H, Kotoo Y, Abe C, Endo T, Takada N, Fuseno H (1984) The role of alpha and beta adrenergic receptors in constriction and dilation of the systemic capacitance vessels: a study with measurement of the mean circulatory filling pressure in dogs. *Jpn Circ J* 48: 620–632
25. Rothe CF, Flanagan AD, Maass-Moreno R (1990) Role of beta-adrenergic agonists in the control of vascular capacitance. *Can J Physiol Pharmacol* 68: 575–585
26. Green JF (1977) Mechanism of action of isoproterenol on venous return. *Am J Physiol* 232:H151–H156
27. Rutlen DL, Supple EN, Powell WJ (1981) β -Adrenergic regulation of total systemic intravascular volume in the dog. *Circ Res* 48: 112–120
28. Cournaud A, Motley HL, Werko L, Richards DW Jr (1948) Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. *Am J Physiol* 152: 162–174
29. Braunwald E, Binion JT, Morgan WL Jr, Sarnoff SJ (1982) Alterations in central blood volume and cardiac output induced by positive pressure breathing and counteracted by metaraminol (Aramine). *Circ Res* 5: 670–675
30. Cassidy SS, Robertson CH, Pierce AK, Johnson RL (1948) Cardiovascular effects of positive end-expiratory pressure in dogs. *J Appl Physiol* 44: 743–750
31. Ashton JH, Cassidy SS (1985) Reflex depression of cardiovascular function during lung inflation. *J Appl Physiol* 58: 137–145
32. Cassidy SS, Eschenbacher WL, Johnson RL (1979) Reflex cardiovascular depression during unilateral lung hyperinflation in the dog. *J Clin Invest* 64: 620–624
33. Robotham JL, Lixfeld W, Holland L, MacGregor D, Bromberger-Barnea B, Permutt S, Rabson JL (1980) The effects of positive end-expiratory pressure on right and left ventricular performance. *Am Rev Respir Dis* 121: 677–683
34. Scharf SM (1992) Cardiovascular effects of positive pressure ventilation. *J Crit Care* 7: 268–279
35. Pinsky MR (1997) The hemodynamic consequences of mechanical ventilation: an evolving story. *Intensive Care Med* 23: 493–503
36. Wise RA, Robotham JL, Bromberger-Barnea B (1981) Effect of PEEP on left ventricular function in right-heart-bypassed dogs. *J Appl Physiol* 51: 541–546
37. Culver BH, Marini JJ, Butler J (1981) Lung volume and pleural pressure effects of ventricular function. *J Appl Physiol* 50: 630–635
38. Scharf SM, Caldini P, Ingram RH (1977) Cardiovascular effects of increasing airway pressure in the dog. *Am J Physiol* 232:H35–43
39. Scharf SM, Ingram RH (1977) Influence of abdominal pressure and sympathetic vasoconstriction on the cardiovascular response to positive end-expiratory pressure. *Am Rev Respir Dis* 116: 661–670
40. Fessler HE, Brower RG, Wise RA, Permutt S (1991) Effects of positive end-expiratory pressure on the gradient for venous return. *Am Rev Respir Dis* 143: 19–24
41. Fessler HE, Brower RG, Wise RA, Permutt S (1992) Effects of positive end-expiratory pressure on the canine venous return curve. *Am Rev Respir Dis* 146: 4–10
42. Versprille A, Jansen JR, Frietmann RC, Hulsmann AR, Van-den-Klaauw MM (1990) Negative effect of insufflation on cardiac output and pulmonary blood volume. *Acta Anaesthesiol Scand* 34: 607–615
43. Scharf SM (1998) Mechanical cardiopulmonary interactions in critical care. In: Dantzker DR, Scharf SM (eds) *Cardiopulmonary critical care*, 3rd edn. Saunders, Philadelphia
44. Risoe C, Hall C, Smiseth OA (1991) Splanchnic capacitance and positive end-expiratory pressure in dogs. *J Appl Physiol* 70: 818–824
45. Manyari DE, Wang Z, Cohen J, Tyberg JV (1993) Assessment of the human splanchnic venous volume-pressure relation using radionuclide plethysmography. *Circulation* 87: 1142–1151
46. Mitzner W, Goldberg H, Lichtenstein S (1976) Effect of thoracic blood volume changes on steady state cardiac output. *Circ Res* 38: 255–261
47. Peters J, Lister G, Nadel ER, Mack GW (1997) Venous and arterial reflex responses to positive pressure breathing and lower body negative pressure. *J Appl Physiol* 82: 1889–1896
48. Fessler HE, Brower RG, Wise RA, Permutt S (1993) Effects of positive end-expiratory pressure and body position on pressure in the thoracic great veins. *Am Rev Respir Dis* 148: 1657–1664
49. Brienza N, Reelly JP, Ayuse T, Robotham JL (1995) Effects of PEEP on liver arterial and venous blood flow. *Am J Respir Crit Care Med* 152: 504–510
50. Matuschak GM, Pinsky MR, Rogers RM (1987) Effects of positive end-expiratory pressure on hepatic blood flow and performance. *J Appl Physiol* 62: 1377–1383
51. Moreno A, Burchell A, Van Der Woude R, Burke JH (1967) Respiratory regulation of splanchnic and systemic venous return. *Am J Physiol* 213: 455–465
52. Rothe CF (1983) Venous system: physiology of the capacitance vessels. In: *Handbook of Physiology. The cardiovascular system: peripheral circulation and organ blood flow*. Am Physiol Soc, Bethesda, Md. Vol III:397–451
53. Caldini P, Permutt S, Waddell JA, Riley RL (1974) Effect of epinephrine on pressure, flow and volume relationships in the systemic circulation of dogs. *Circ Res* 34: 606–623

54. Mitzner W, Goldberg H (1975) Effects of epinephrine on resistive and compliant properties of the canine vasculature. *J Appl Physiol* 39: 272–280
55. Deschamps A, Magder S (1992) Baroreflex control of regional capacitance and blood flow distribution with or without alpha-adrenergic blockade. *Am J Physiol* 263:H1755–1763
56. Shoukas AA, Bohlen HG (1990) Rat venular pressure-diameter relationships are regulated by sympathetic activity. *Am J Physiol* 259:H674–680
57. Rothe CF, Drees JA (1976) Vascular capacitance and fluid shifts in dogs during prolonged hemorrhagic hypotension. *Circ Res* 38: 347–356
58. Lundvall J, Länne T (1989) Large capacity in man for effective plasma volume control in hypovolemia via fluid transfer from tissue to blood. *Acta Physiol Scand* 137: 513–520
59. Lundvall J, Hillman J (1978) Fluid transfer from skeletal muscle to blood during hemorrhage. Importance of beta-adrenergic vascular mechanisms. *Acta Physiol Scand* 102: 450–458
60. Öberg B (1964) Effects of cardiovascular reflexes on net transcapillary fluid transfer. *Acta Physiol Scand* 62 (Suppl):229–235
61. Lundvall J, Länne T (1989) Much larger transcapillary conductivity in skeletal muscle and skin in man than previously believed. *Acta Physiol Scand* 136: 7–16
62. Rothe CF, Gaddis ML (1990) Autoregulation of cardiac output by passive elastic characteristics of the vascular capacitance system. *Circulation* 81: 360–368
63. Greenway CV (1983) Role of splanchnic venous system in overall cardiovascular homeostasis. *Fed Proc* 42: 1678–1684
64. Rutlen DL, Welt FGP, Iiebekk A (1992) Passive effect of reduced cardiac function on splanchnic intravascular volume. *Am J Physiol* 262:H1361–H1364
65. Ogilvie RI, Zborowska-Sluis D (1992) Effect of chronic rapid ventricular pacing on total vascular capacitance. *Circulation* 85: 1524–1530
66. Parrillo JE, Parker MM, Natanson C, Suffredini AF, Danner RL, Cunnion RE, Ognibene FP (1990) Septic shock in humans. Advances in understanding the pathogenesis, cardiovascular dysfunction and therapy. *Ann Intern Med* 113: 227–242
67. Abel FL (1989) Myocardial function in sepsis and endotoxin shock. *Am J Physiol* 257:R1265–1281
68. Hung J, Lew WY (1993) Cellular mechanisms of endotoxin-induced myocardial depression in rabbits. *Circ Res* 73: 125–134
69. Schulz R, Panas DL, Catena R, Moncada S, Olley PM, Lopashuk GD (1995) The role of nitric oxide in cardiac depression induced by interleukin-1 beta and tumor necrosis factor-alpha. *Br J Pharmacol* 114: 27–34
70. McKenna TM, Li S, Tao S (1995) PKC mediates LBS- and phorbol-induced cardiac cell nitric oxide synthase activity and hypocontractility. *Am J Physiol* 269:H1891–1898
71. Pinsky MR, Matuschak GM (1986) Cardiovascular determinants of the hemodynamic response to acute endotoxemia in the dog. *J Crit Care* 1: 18–31
72. Wright C, Rees D, Moncada S (1992) Protective and pathological roles of nitric oxide in endotoxin shock. *Cardiovasc Res* 26: 48–57
73. Szabo C, Mitchell JA, Thiemermann C, Vane JR (1993) Nitric oxide-mediated hyporeactivity to noradrenaline precedes the induction of nitric oxide synthase in endotoxin shock. *Br J Pharmacol* 108: 786–792
74. Filep J, Foldes-Filep E, Rousseau A, Sirois P, Fournier A (1993) Vascular responses to endothelin-1 following inhibition of nitric oxide synthesis in the conscious rat. *Br J Pharmacol* 110: 1213–1221
75. Breslow MJ, Miller CF, Parker SD, Walman AT, Traystman RJ (1987) Effect of vasopressors on organ blood flow during endotoxin shock in pigs. *Am J Physiol* 252:H291–H300
76. Brienza N, Ayuse T, Revelly JP, Robotham JL (1998) Peripheral control of venous return in critical illness. Role of the splanchnic vascular compartment. In: Dantzker DR, Scharf SM (eds) *Cardiopulmonary critical care*, 3rd edn. Saunders, Philadelphia
77. Brienza N, Ayuse T, Revelly JP, O'Donnell CP, Robotham JL (1995) Effects of endotoxin on isolated porcine liver. Pressure-flow analysis. *J Appl Physiol* 78: 784–792
78. Ayuse T, Brienza N, Revelly JP, O'Donnell CP, Boitnott JK, Robotham JL (1995) Alternations in liver hemodynamics in an intact porcine model of endotoxin shock. *Am J Physiol* 268:H1106–1114
79. Mitzner W (1974) Effect of portal venous pressure on portal venous inflow and splanchnic resistance. *J Appl Physiol* 37: 706–711
80. Revelly JP, Ayuse T, Brienza N, Robotham JL (1995) Dysregulation of the veno-arterial response in the superior mesenteric artery during endotoxic shock. *Crit Care Med* 23: 1519–1527
81. Parrillo J (1993) Pathogenetic mechanisms of septic shock. *N Engl J Med* 328: 1471–1477
82. Rowell LB (1974) Human cardiovascular adjustments to exercise and thermal stress. *Physiol Rev* 54: 75–159
83. Deschamps A, Magder S (1994) Effects of heat stress on vascular capacitance. *Am J Physiol* 266:H2122–2129
84. Johnson JM (1986) Nonthermoregulatory control of human skin blood flow. *J Appl Physiol* 61: 1613–1622
85. Rowell LB, Brengelmann GL, Murray JA (1969) Cardiovascular response to sustained high skin temperature in resting man. *J Appl Physiol* 27: 673–680
86. Johnson JM, Proppe DW (1996) Cardiovascular adjustments to heat stress. In: *Handbook of Physiology. Environmental physiology*. Am Physiol Soc, Bethesda Md. Vol. I:215–243
87. Deschamps A, Magder S (1990) Skin vascular bed is a potential blood reservoir during heat stress. *Am J Physiol* 259:H1796–H1802
88. Pérgola PE, Johnson JM, Kellog DL, Kosiba WA (1996) Control of skin blood flow by whole body and local skin cooling in exercising humans. *Am J Physiol* 270:H208–215
89. Tripathi A, Mack GW, Nadel ER (1990) Cutaneous vascular reflexes during exercise in the heat. *Med Sci Sports Exerc* 22: 796–803
90. Kellog DL, Johnson JM, Kosiba WA (1991) Control of internal temperature threshold for active cutaneous vasodilation by dynamic exercise. *J Appl Physiol* 71: 2476–2483
91. Nadel ER, Cafarelli E, Roberts MF, Wenger CB (1979) Circulatory regulation during exercise in different ambient temperatures. *J Appl Physiol* 46: 430–437
92. Heistad DD, Abboud FM, Mark AL, Schmid PG (1973) Interaction of thermal and baroreceptor reflexes in man. *J Appl Physiol* 35: 581–586
93. Peters J, Nishiyasu T, Mack GW (2000) Reflex control of the cutaneous circulation during passive body core heating in humans. *J Appl Physiol* 88: 1756–1764
94. Bressack MA, Morton NS, Hortop J (1987) Group B streptococcal sepsis in the piglet: effects of fluid therapy on venous return, organ edema and organ blood flow. *Circ Res* 61: 659–669

-
95. Magder S, Vanelli G (1996) Circuit factors in the high cardiac output of sepsis. *J Crit Care* 11: 155–166
 96. Tabrizchi R, Pang CCY (1992) Effects of drugs on body venous tone, as reflected by mean circulatory filling pressure. *Cardiovasc Res* 26: 443–448
 97. Appelton CP, Lee RW, Martin GV, Olajos M, Goldman S (1986) Alpha₁- and alpha₂-adrenoreceptor stimulation: changes in venous capacitance in intact dogs. *Am J Physiol* 250:H1071–1078
 98. Ruffolo RR (1985) Distribution and function of peripheral alpha-adrenoreceptors in the cardiovascular system. *Pharmacol Biochem Behav* 22: 827–833
 99. Brunner MJ, Shoukas AA, MacAnespie CL (1981) The effect of the carotis sinus baroreceptor reflex on blood flow and blood volume distribution in the systemic vascular bed of the dog. *Circ Res* 48: 274–285
 100. Dahn MS, Lange P, Lobdell K, Hans B, Jacobs LA, Mitchell RA (1987) Splanchnic and total body oxygen consumption differences in septic and injured patients. *Surgery* 101: 69–80
 101. Petros A, Bennett D, Vallance P (1991) Effect of nitric oxide synthase inhibitors on hypotension in patients with septic shock. *Lancet* 338: 1557–1558
 102. Landin L, Lorente JA, Renes E, Canas P, Jorge P, Liste D (1994) Inhibition of nitric oxide synthesis improves the vasoconstrictive effect of noradrenaline in sepsis. *Chest* 106: 250–256
 103. Avontuur JA, Boomsma F, Van den Meiracker AH, De Jong FH, Bruining HA (1999) Endothelin-1 and blood pressure after inhibition of nitric oxide synthesis in humans, *Circulation* 99: 271–275
 104. Petros A, Lamb G, Leone A, Moncada S, Bennett D, Vallance P (1994) Effects of nitric oxide synthase inhibitor in humans with septic shock. *Cardiovasc Res* 28: 34–39
 105. Lorente JA, Landin L, De Pablo R, Renes E, Liste D (1993) L-Arginine pathway in the sepsis syndrome. *Crit Care Med* 21: 1287–1295