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REVIEW ARTICLE/BRIEF REVIEW

The physiologic basis for goal-directed hemodynamic and fluid therapy: the pivotal role of the venous circulation

Les fondements physiologiques de la thérapie hémodynamique et liquidienne ciblée: le rôle fondamental de la circulation veineuse

Simon Gelman, MD, PhD · Luca Bigatello, MD

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Abstract

Purpose *Understanding cardiovascular physiology should help clinicians to understand the purpose of fluid and drug management during the perioperative period. The purpose of this narrative review is to describe the pivotal role of the venous circulation in goal-directed hemodynamic and fluid therapy.*

Source *We selected relevant literature that examines the appropriateness of fluid therapy and pharmacologic interventions during the perioperative period.*

Principal findings *The interaction between the stressed and unstressed intravascular volume (Vs and Vu, respectively) regulates the venous return, which is the main determinant of cardiac output. The lack of hemodynamic response to an intravascular fluid challenge likely results from an unpredictable distribution of infused fluid between the Vs and Vu. Other factors affecting hemodynamic responses include the pharmacodynamics of common vasoactive drugs, which further highlight the complexity of the regulation of venous return during infusion of exogenous catecholamines. The response to even a highly selective agent can result in different hemodynamic effects. Low doses of α-adrenergic agonists constrict veins and may often shift blood from the Vu to the Vs, subsequently increasing the venous return and cardiac output, whereas higher drug doses constrict arteries and usually decrease cardiac output.*

Conclusions *The physiologic basis of goal-directed hemodynamic therapy is complex and not necessarily reflected in the information received from hemodynamic monitors. Understanding the physiologic basis of such therapy is a logical step towards its optimal use.*

Résumé

Objectif *Une bonne compréhension de la physiologie cardiovasculaire aidera les cliniciens à comprendre les objectifs d'une prise en charge liquidienne et médicamenteuse en période périopératoire. L'objectif de ce compte rendu narratif est de décrire le rôle de la circulation veineuse dans la thérapie hémodynamique et liquidienne ciblée.*

Source *Nous avons sélectionné des articles qui examinent la pertinence d'une thérapie liquidienne et des interventions pharmacologiques en période périopératoire.*

Constatations principales *L'interaction entre le volume intravasculaire contraint et le volume non contraint régule le retour veineux, le principal déterminant du débit cardiaque. L'absence de réponse hémodynamique à un bolus liquidien intravasculaire est probablement le résultat d'une distribution imprévisible du liquide perfusé entre le volume contraint et le volume non contraint. Parmi les autres facteurs affectant la réponse hémodynamique, citons la pharmacodynamie des médicaments vasoactifs courants, ce qui met encore plus en évidence la complexité de la régulation du retour veineux pendant une perfusion de catécholamines exogènes. La réponse à un agent même très*

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S. Gelman, MD, PhD (✉)
Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA
e-mail: sgelman@bwh.harvard.edu

L. Bigatello, MD
Department of Anesthesiology, Critical Care, and Pain Medicine, St. Elizabeth Medical Center, Brighton, MA, USA

sélectif peut entraîner différents effets hémodynamiques. De faibles doses d'agonistes alpha-adrénergiques compriment les veines et peuvent souvent faire migrer le sang du volume non contraint au volume contraint, ce qui augmente par la suite le retour veineux et le débit cardiaque, tandis que des doses plus importantes de médicaments compriment les artères et réduisent en général le débit cardiaque.

Conclusion *Les fondements physiologiques de la thérapie hémodynamique ciblée sont complexes et ne se reflètent pas nécessairement dans les informations transmises par les moniteurs hémodynamiques. La connaissance des fondements physiologiques d'une telle thérapie constitue une étape logique vers son utilisation optimale.*

The concept of adjusting hemodynamics to reach certain physiologic endpoints to improve outcome in high-risk surgical patients developed in the 1980s with the work of Shoemaker and collaborators.[1] They aimed to reach "supra-normal" hemodynamic values via the liberal use of fluids, blood products, and inotropic agents.[1,2] Subsequent work revisited and rejected the physiologic and clinical validity of "supranormal" values,[3] but the concept of using a measurable endpoint to guide perioperative fluid and drug therapy (so-called "goal-directed therapy") persisted.[4] Tested parameters in the perioperative setting have included cardiac output (CO) and oxygen delivery,[5] mixed venous PO_2,[2,6] and fluid responsiveness.[7] Current protocols of enhanced recovery after surgery (ERAS) often aim to support organ function through some adaptation of goal-directed fluid and drug therapy (i.e., goal-directed hemodynamic therapy [GDHT]).[8,9] A number of trials have tested the effect of various forms of GDHT in the perioperative setting, with variable degrees of success. A recent large randomized trial[7] and a Cochrane Review[10] came to the same conclusion that GDHT that aims at increasing tissue blood flow may have marginal advantages but not on a composite outcome of major complications and death.

Although many factors may be responsible for the lack of consistent results with GDHT (including study size, unclear controls, and monitor performance), there are key physiologic questions that deserve further thought, such as: Why does "optimizing" a hemodynamic parameter not regularly translate into improved outcomes? Why is it considered better to reach a full response to fluid challenge? What is the advantage of optimizing CO other than in extreme situations such as severe hypovolemia or acute congestive heart failure, which occur in only a small minority of the patients for whom GDHT is intended? How do we explain the large number of non-responders to fluid therapy who are not in cardiac failure?

We have read with great interest many recent publications reviewing hemodynamic principles under a variety of perspectives[11-13] that can be applied to GDHT. This present article complements and extends their observations in several respects. The logic behind the use of GDHT during the perioperative period is convincing but the results have been inconsistent at best. The main purpose of this article is to uncover the possible physiologic mechanisms that may be responsible for the lack of consistent effectiveness of GDHT in its present form. Specifically, we suggest a model that assumes a constantly changing relationship between the venous stressed and unstressed volumes (Vs and Vu, respectively). Such a model assumes that the fluid administered perioperatively is distributed between Vs (affecting hemodynamics and tissue perfusion) and Vu (not having an immediate hemodynamic functional response). The model further assumes that an increase in the Vs:Vu ratio—which is not necessarily a specific increase in the total volume—may improve tissue perfusion with decreased probability of circulatory overload. This model also may explain the high number of non-responders to a fluid challenge. Although such a model does not offer easy ways to measure Vs and Vu, it brings us closer to physiologic reality. In addition, by reviewing the pharmacodynamics of vasoactive drugs widely used perioperatively, the model justifies the suggestion that small doses of vasopressors included in GDHT may elicit benefits by decreasing the Vu and directing the infused fluid to the Vs to a greater extent than to the Vu.

The endpoint of GDHT is to provide adequate blood flow to maintain normal organ function, prevent complications from hypovolemia or volume overload, and reduce further interventions and hospital stay. Organ blood flow is determined by the concerted function of the heart and the vasculature. In the following sections, we describe the factors that affect cardiovascular performance as it relates to GDHT including the regulation of venous return and CO, the diagnostic and physiologic significance of fluid responsiveness, and the pharmacodynamic effects of commonly used vasoactive drugs.

Control of venous return

To facilitate an understanding of the role of the venous system in the control of CO, several physiologic concepts and models used in this section are defined in Table 1. Venous return (VR) is blood flowing from the periphery back to the heart; the same volume of blood that reaches

Table 1 Terms and definitions of vascular variables in the venous circulation

Variable	Units	Definition	Measurement	Comment
Intramural or intraluminal pressure	mmHg	Hydrostatic pressure inside a blood vessel	Pressure inside	Same as "intravascular" pressure
Transmural pressure (Ptm)	mmHg	Pressure across the wall of the vessel	Pressure inside – pressure outside	Pressure that directly affects VR
Venous capacity	mL or L	Volume of blood within a vein at a certain Ptm	V/Ptm	A volume of blood exerting a pressure
Venous compliance	mL/mmHg	Change in volume of blood in a vein over change in Ptm	$\Delta V/\Delta Ptm$	The slope of the $\Delta V/\Delta Ptm$ line
Venous capacitance*	mL or L	Volume of blood accommodated in a vein without appreciable increase in Ptm > 0		Not well defined, has also been used interchangeably with capacity and compliance
Venous resistance (Rv)	mmHg/mL/min	Drop in pressure due to the friction of blood flowing along a vessel wall	$\Delta Ptm/flow$	An increase of Rv in different veins affects VR in different ways
Unstressed volume (Vu)	mL or L	Volume of blood under Ptm ≈ 0		It is a reservoir of blood that does not directly affect VR
Stressed volume (Vs)	mL or L	Volume of blood over Vu that exerts Ptm $>$ 0	Volume of blood to to be removed to reach Ptm ≈ 0	It affects VR by its Ptm; it constantly exchanges with Vu
Mean circulatory filling pressure (MCFP)†	mmHg	Ptm within the cardiovascular system when the circulation is stopped	Measured by circulatory arrest. Surrogates include Ptm during inspiratory hold maneuvers	Head pressure for VR, determined mainly by Vs
Fast compartment	mL or L	Blood leaving the aorta to multiple organs other than the splanchnic circulation, returning to the heart directly *via* the venae cavae		From skeletal muscle, skin, and others and returns to the heart *via* the venae cavae
Slow compartment	mL or L	Blood leaving the aorta to the splanchnic organs and returning via hepatic veins and inferior cava		From splanchnic organs; consists of compliant veins, functions as reservoir. Main part of Vu is located here

*Venous capacitance is a vague term. In this text we use the term as the ability of a vein or venous system to accommodate a volume of blood without a drastic increase in pressure (Fig. 1). Capacitance of a venous bed can be changed by contraction or relaxation of vascular smooth muscles. A decrease in capacitance occurs when vascular smooth muscles of veins and venules shorten. This recruits Vu into Vs and may increase VR. †MCFP is the main determinant of VR and in turn is mainly determined by Vs. There are a few clinically acceptable methods to estimate MCFP; one is to plot the values of CVP against CO at different airway pressures, draw a line through the dots, and extrapolate it to the CO line; the intersection with the pressure line is the MCFP (see text). VR = venous return

the heart will be ejected out of the heart—i.e., at steady state, VR and CO are equal.

Blood flow back to the heart occurs because of a pressure gradient between the upstream veins and the right atrium (RA). The transmural pressure (Ptm) in the veins and the RA is determined by their blood volume and the compliance of their walls (Table 1). However, not all the blood leaving the periphery reaches the heart at the same time; the venous system is not just a conduit for blood flow but also a reservoir of blood that remains within the veins to regulate VR.

Approximately 30% of the total blood volume represents Vs, while the remaining 70% is Vu.[14,15] At a low blood volume in a vein (or in a venous system), an increase in volume is initially not associated with an increase in Ptm because of high venous compliance; this volume is the Vu. Once a certain volume has been reached (capacitance, Table 1), a further increase in volume starts to increase the Ptm; this volume is the Vs (Fig. 1).

Partitioning of the stressed and unstressed venous volumes

To illustrate the relationship between Vu and Vs, the model of a tub with a spigot has often been used.[15,16] The volume of blood above the spigot (Vs) exits the tub at a rate depending upon its own pressure, which is the mean

circulatory filling pressure (MCFP). The volume of blood below the spigot (Vu) does not affect the MCFP and does not exit the tub. Values of Vs and Vu can be estimated from induced changes in the Ptm (Fig. 2). A technique based on the principle illustrated in Fig. 2 is called the "inspiratory hold" and has been used in the clinical arena.[17,18]

This and other models seem to strictly separate venous vessels without flow from those with flow, which is an unlikely scenario. It is more likely that two volumes coexist at any one point in time, at least in some vessels. Figure 1 shows that Vu (to the left of the capacitance point) is a volume of blood that does not exert a Ptm and hence does not produce flow; any volume to the right of the capacitance point exerts a certain Ptm and generates flow. Let us imagine what is happening within a single vein with flow. There is a certain blood volume under a Ptm above zero. This by definition is Vs. Is there Vu in this vein? Yes, and part of the blood in this vein moves fast (Vs) while another part is not moving, or moving slowly (Vu). This model may help clarify how Vs and Vu may exist within the same vein. Splanchnic veins can accommodate a large blood volume that flows slowly without drastically increased Ptm. Therefore, the large amount of this blood is Vu while blood that flows faster (and under a bit higher pressure) is Vs. So, it is possible, even likely, that in complaint veins, the two volumes coexist and there is always a mixture of Vu and Vs. Moreover, the Vu and Vs components are constantly mixing with each other, changing the relationships between Vu and Vs within every vessel with every breath and every heartbeat. Thus, when we say Vs or Vu, in reality we mean predominantly Vs or predominantly Vu. The vessel in Fig. 1 may represent a vein or the whole venous vasculature. At any particular moment, the flow through a single vessel is the same at any point above the capacitance point (Fig. 1) but becomes higher at more distal parts of the venous vasculature because of the drainage from other veins joining this one. All such veins will drain blood into the larger veins eventually forming the VR. The higher the Ptm is, the higher the Vs:Vu ratio and the higher the flow through this vessel at that moment. Such a hypothetical model does not provide us with easy measurements of the Vs, but visualizing the physiologic system may help us better understand the relationship among Ptm, flow, and Vs. The most compliant veins are within the splanchnic venous system, although any vein may contain a certain amount of Vu depending on its compliance. When compliant veins are constricting, they decrease their capacity and squeeze blood out into the systemic circulation. This is how the body mobilizes the blood from the splanchnic and other compliant veins when needed.

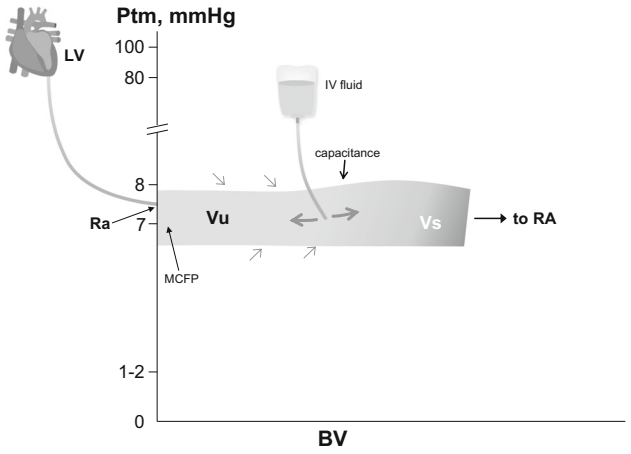

Fig. 1 Model of the venous circulation as a single vein. BV = venous blood volume; LV = left ventricle: MCFP = mean circulatory filling pressure; Ptm = transmural pressure; Ra = arterial resistance; RA = right atrium; Vs and Vu = stressed and unstressed venous volumes, respectively. Multiple small arrows outside of venous wall refer to the veins entering the large single vein/entire venous system. Volume from intravenous fluids as well as from upstream portions of the vein moves downstream without stretching of the vessel walls, hence without generating a Ptm or flow. This is Vu (light shade), about 70% of BV under normal circumstances. As inflow progresses, stretch of the vessel walls generates Ptm and flow; this is Vs (dark shade), about 30% of the venous BV. The point of volume at which Ptm starts to increase can be called capacitance (Table 1). Vs provides the blood flow for venous return (VR). The rate of VR is determined by Ptm in a vein, and MCFP for venous system. Note that the fluctuations in MCFP are minimal and venous blood flow is enhanced by increased stretching of the venous wall. Thus, the venous smooth muscle partially fulfills the function of a "heart for the venous system"

Mean circulatory filling pressure

The main determinant of VR is the MCFP,[19] which is the pressure within the circulatory system when the heart and therefore circulation are stopped (Table 1). This is one way to measure the MCFP, but it is not practical in the clinical setting. The acceptable methods to estimate the the MCFP include plotting the central venous pressure (CVP) against CO at different airway pressures, drawing a line through the dots and extrapolating it to the CO line; the intersection with the pressure line is the MCFP.[20] When the heart starts pumping, the arterial pressure increases above the MCFP and pushes the blood through the whole circulatory system—i.e., through the arteries, then capillaries, and then through the venous system. The largest pressure drop in the circulatory system is at the level of arterioles and capillaries. This leads to a very large pressure gradient between arteries and veins, resulting in hydraulic isolation of the venous system from the arterial system. Therefore, the blood flow through the venous system is driven by arterial pressure only to a limited extent; it is mainly driven by the pressure at the very beginning of the venous system. When Rothe measured the pressure at that level, it turned

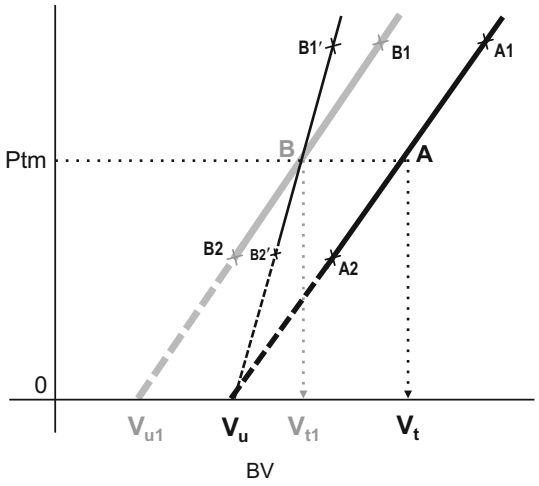

Fig. 2 Determination of venous compliance, capacity, stressed and unstressed volumes. BV = blood volume; C = compliance; Ptm = transmural pressure; Vu and Vs = unstressed and stressed volumes, respectively. The plot depicts the relationship between BV and Ptm. Point A represents BV in the vein (Vt) at a certain Ptm. Points A1 and A2 represent values of Vt observed during temporary partial occlusion of the vein at different points and different degrees of occlusion. The line drawn through points A1 and A2 is a compliance line; when extrapolated to zero Ptm, the point on the X-axis is the unstressed volume (Vu). The difference between Vt and Vu is the stressed volume (Vs). If some volume of blood is withdrawn from the vein, point A moves to the left to point B. Then, points B1 and B2 are obtained using the same technique as for points A1 and A2, and a new compliance line (thick gray line) is drawn. When the new compliance line is extrapolated to zero Ptm, the point on the X-axis is a new value of Vu, the Vu1. The slopes of the two lines (thick black and thick gray) are identical, indicating that venous compliance did not change, and the decrease in Vu and Vt was associated with a decrease in venous capacity. The withdrawal of blood during different conditions may move point A to the same point B. Partial occlusions of the vein are repeated, points B1' and B2' are identified, and the new compliance line (thin black line) is built. The volume within the vein is at the same point B, but the new compliance line has a steeper slope, indicating that venous compliance has decreased. Thus, the blood volume can be mobilized from a vein or a venous reservoir by two different mechanisms, namely by a decrease in capacity (first mechanism) or a decrease in compliance (second mechanism). These two mechanisms may work in concert

out to be equal to the MCFP; this pressure was named the pivotal venous pressure as this is the pressure that really drives VR.[14,21] The most effective way to increase CO (assuming normal cardiac function) is to increase the MCFP.[14]

The main determinant of VR is the MCFP, though the second important pressure that determines VR is the right atrial pressure, which is clinically measured as the CVP. An increase in the CVP would impede VR, while a decrease would facilitate it, according to this formula:

$$VR = (MCFP - CVP)/Rv$$

Where:
VR = venous return
MCFP = mean circulatory filling pressure
CVP = central venous pressure
Rv = resistance to blood flow in the venous circulation

Thus, the upstream (MCFP) and downstream (CVP) gradient determines VR. Fluid infusion may be associated with simultaneous increases in the CVP and CO. This may seem counterintuitive as the equation above suggests that an increase in CVP should impede the flow and decrease VR. The opposite occurs under normal heart pumping conditions and in the absence of hypervolemia—i.e., although the fluid infusion usually increases the CVP for a short time, it increases the MCFP to a greater extent and for a longer period.

The main determinant of the MCFP is the Vs (Fig. 1). The venous system uses several mechanisms to control the Vu:Vs ratio. For example, an increase in the tone of the compliant veins decreases the venous capacitance and Vu, transferring blood from the Vu to Vs; this is associated with an increase in the MCFP and VR. Another way to increase the MCFP and VR is to infuse fluid, which may increase both the Vu and Vs. The degree to which each increase depends on the difference between pressures within the Vu and Vs as well as on the mixing process between these two volumes (Fig. 3, also see below under "Fluid responsiveness").

The last component of the VR equation is the Rv, which is low compared with the arterial tone and should not have a significant effect on VR. The reason for this might be that the pressures in the veins are low and the gradient between up- and downstream pressures is small (although it may change by 100% or more), while the differences in flow may be huge. Therefore, the calculated values of resistance would mainly depend on flow, not on pressure. High compliance of the veins also suggests that any change in the diameter of a vein does not drastically affect the flow. Changes in the Rv in different parts of the venous circulation may affect the MCFP and thus VR. The function of the Rv is more complex than the equation above depicts.

The two-compartment model of the venous system

The complexity of the Rv may be explained by a *two compartment model of the venous system* as suggested by the Dutch physiologist August Krogh more than 100 years ago.[22] In the *fast compartment*, the blood leaves the heart, flows through the aorta and arterial vasculature, capillaries, and veins, and continues to flow back through the caval veins to return to the heart. The other compartment is the *slow compartment*, which is anatomically represented mostly by the splanchnic circulation, where the blood leaves the aorta through the celiac and mesenteric arteries, flows through the splanchnic system, through the portal

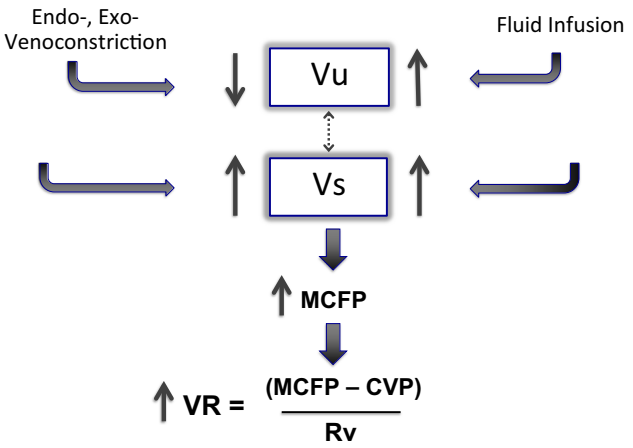

Fig. 3 Effects of veno-constriction and of fluid load on venous return. CVP = central venous pressure; MCFP = mean circulatory filling pressure; Rv = venous resistance; VR = venous return; Vs = stressed volume; Vu = unstressed volume; ↑ = increase; ↓ = decrease. Fluid infusion may increase both Vu and Vs. Constriction of veins decreases Vu and increases Vs. At the bottom of the schema is a venous return equation. Resistance to flow is low

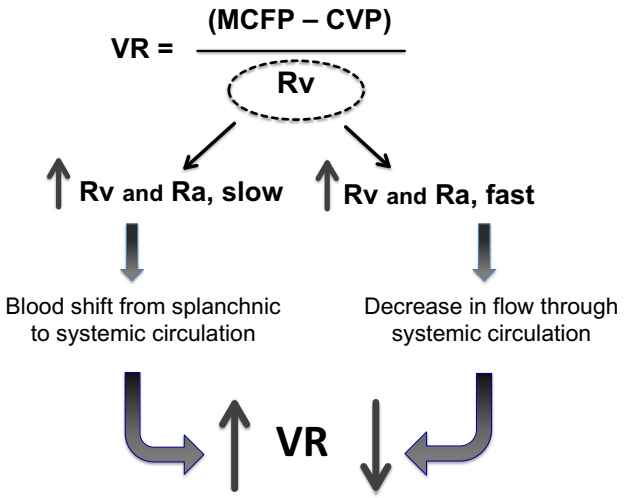

Fig. 4 Vascular tone and venous return. CVP = central venous pressure; MCFP = mean circulatory filling pressure; Ra = arterial resistance; Rv = venous resistance; Rv and Ra fast = venous and arterial resistance, respectively, of the fast compartment; slow = Rv and Ra slow = venous and arterial resistance, respectively, of the slow compartment; VR = venous return; ↑ = increase; ↓ = decrease. Change in venous tone often coincides with change in arterial tone in the same direction. Both are associated with drastic changes in flow and volume shifts

vein, liver, and hepatic veins, and then enters the inferior caval vein as it flows back to the heart.[15] The veins in the slow compartment are very compliant and can accommodate (or release) large amounts of blood into the fast compartment. When flow into the slow compartment is decreased secondary to constriction of arteries feeding the slow compartment, the amount of blood entering splanchnic organs decreases, and compliant veins recoil in response to the decreased volume and pressure, squeezing blood from the splanchnic venous vasculature through the liver and hepatic veins into the systemic circulation (fast compartment). This means that the constriction of arteries within the slow compartment (Fig. 4) leads to an increase in VR because some blood volume leaves the splanchnic venous system and enters the systemic circulation/fast compartment. On the other hand, constriction of arteries in the fast compartment leads to a decrease in flow through the systemic circulation and in VR. Arterial dilation in the fast compartment, if not associated with a serious decrease in blood pressure (BP), would lead to a decrease in the pressure gradient between the arterial and venous systems. A decrease in this gradient would lead to a transfer of pressure from the arterial system to the MCFP, as well as an increase in VR and CO, without serious changes in blood volume in the whole compartment. The complexity of the interaction between the arterial and venous circulations in the fast (systemic) and slow (mostly splanchnic) compartments is illustrated in Fig. 4.

Control of CO

The previous section describes how the venous circulation supplies blood flow to the heart through VR; as the VR and CO are equal at steady state, what controls VR also controls CO. Nevertheless, analysis of cardiovascular performance in the perioperative setting focuses preferentially on the left ventricle (LV). Assessment of LV function by echocardiography is accurate, easily obtainable, and often determines the choice of monitoring, fluid, and drug management. However, under normal circumstances, the LV merely accommodates and ejects the aliquot of blood received from the venous circulation via the right heart and pulmonary circulation.[11] This permissive role of the LV persists across wide variations in CO during exercise and non-cardiogenic types of shock[23,24] but it changes during conditions such as acute coronary syndromes and congestive heart failure. The existence of pathologic states of LV dysfunction in the perioperative period prompts the need to monitor the contribution of the LV to CO. We will approach the regulation of CO following the common teaching of "preload", "contractility", and "afterload", although it will become apparent that this paradigm is somewhat restrictive.

Preload, also referred to as "filling" or "load", is the tension of a cardiac chamber before it begins to contract,[25] probably best characterized physiologically as the volume

of the RV at end diastole (RVEDV). The same is true for the LV and its volume at end diastole, but in the regulation of CO, the right side of the heart is the primary structure of interest since the preload to each heart beat originates from the venous side of the circulation. Because the RVEDV is not easily measured, a number of surrogates of preload have been used, the CVP remaining the most common. Unfortunately, the CVP is affected by multiple and at times opposite hemodynamic events, and its clinical interpretation is complex.[26,27] The CVP as a surrogate for RA pressure is the downstream pressure for VR (MCFP − CVP; see the VR equation), and a low CVP increases the VR and consequently the RVEDV. On the other hand, a fluid bolus also increases the RVEDV, generally with a concomitant *increase* of the CVP, which in this case is just a consequence of higher MCFP. A low CVP can also be a consequence of higher RV ejection (the same is true for the LV and the LA pressure) and consequent decrease in the RVEDV; the lower CVP in this case does not indicate a primary decrease in preload and may not require intervention. In summary, preload is a term that refers to a number of physiologic measurements including VR, MCFP, and Vs. Clinically, preload can be estimated using a variety of parameters; what is most important is not which parameter is chosen, but whether or not the function of that parameter (e.g., CVP, RVEDV) is understood in the context of the cardiovascular system in its entirety.

Contractility is the functional ability of the myocardium to pump blood; with normal function, the ventricle ejects the amount of blood that it receives with each heartbeat, leaving a constant volume at end diastole. Filling of the RV with venous blood (and of the LV with arterial blood) stretches the myocytes to an optimal degree for force generation. With increasing filling, the force of contraction increases and so does the systolic output of the ventricle. This relationship between filling pressure (e.g., CVP) and ventricular output (e.g., stroke work, stroke volume [SV], or CO) is initially steep and then plateaus when increasing volume continues to be administered. This relationship illustrates the *Starling principle* of the heart, developed in the early 20th century by the eminent British physiologist Ernest Starling and his collaborators.[28] Each Starling curve represents a functional state of the myocardium at which ventricular output increases with increased preload independently from central nervous system stimuli. Hence, a decrease in output occurring at a constant preload (and afterload, see below) indicates an acute change of functional state and a move onto a new Starling curve, lower and to the right of the original. Clinically, this may be a manifestation of acute myocardial dysfunction. Changes in the functional state of the myocardium during surgery are unusual in the absence of acute myocardial events; on the other hand, changes in CO are frequent. The latter are related primarily to VR (and less often to afterload, see below) rather than to contractility, as demonstrated by an abundance of physiologic data.[13,19,29]

Role of heart rate (HR). Generally speaking, within the limits of regular sinus rhythm the contribution of the HR to CO is less significant than the Starling mechanism. Clinically, it may be difficult to separate from the simultaneous occurrence of different phenomena; for example, sympathetic stimulation (e.g., by ephedrine or epinephrine) may increase CO through simultaneous chrono- and inotropic effects. Normally, modest increases in HR tend to leave the CO unchanged because of decreased diastolic filling time.[30] Heart rate-dependent CO is rare and generally associated with pathologic states such congestive heart failure, severe LV hypertrophy (with concomitant diastolic dysfunction), low LV compliance and soon after cardiac transplantation.[31] Hence, pharmacologically increasing a normal HR to increase blood flow and tissue perfusion is unlikely to successfully augment CO.

Afterload is the force developed by the myocardium to overcome factors opposing ventricular outflow[32] (Table 2). A simple concept for the contraction of isolated myocardial fibres[33] becomes remarkably complex in the context of a cardiac chamber ejecting pulsatile blood flow into an elastic network of conduits (i.e., the aorta and its branches). Part of the afterload develops within the contracting ventricle ("wall stress", Table 2) from its shape, size, and rate of contraction,[34] but for practical purposes, afterload tends to be identified with extra-cardiac factors (Table 2).[32,35,36] Impedance is a measure of pressure/flow (P/V) relationships within the arterial tree as determined by the physical properties of blood and blood vessels and by the sinusoidal oscillations of the vascular walls generated by pulsatile flow. Hence, afterload is not properly described with a single number such as systemic and pulmonary vascular resistance (SVR and PVR). Although appealing because they combine easily available P and V parameters, e.g., SVR = (mean arterial pressure [MAP] − CVP)/CO, their clinical relevance is overstated. The SVR simply describes a static point in the overall relationship of MAP and CO that does not take into account the mechanics of pulsatile flow in a complex network of vessels. The clinical pitfall of using SVR as a measure of afterload is exemplified in the situation of low CO, which is inevitably associated with high SVR, indicating a state of high resistance without describing the underlying physiology. If this low CO were caused by hypovolemia, the high SVR would not be the result of active vasoconstriction and treating it with a vasodilator could be disastrous. In fact, MAP alone may have comparable usefulness to SVR and has been used in physiologic studies as an index of afterload.[37]

Table 2 Terms and definitions of vascular variables in the arterial circulation

Variable	Definition	Measurement	Comment
Afterload	Force developed by the myocardium to overcome the factors opposing ventricular outflow	Arterial resistance: SVR/PVR and MAP Arterial impedance Myocardial wall stress	SVR/PVR is static P/V ratio along a single, non-pulsatile conduit Impedance is dynamic P/V ratio along a network of pulsatile vessels
Myocardial wall stress	Energy generated by the myocardium at end systole	Modified Laplace law: wall stress is proportional to P and radius, inversely to wall thickness Dynamic image reconstruction by ECHO, MRI	Generally referred to as myocardial component of afterload, is also affected by aortic impedance
Arterial/ aortic Impedance	External factors from aorta and its branches opposing ventricular outflow	Aortic impedance relates R to pulsatile flow. R measured at various oscillatory frequencies in the aorta measures impedance	SVR/PVR do not include the complex effects of pulsatile flow, which can be obtained noninvasively (below)
Arterial stiffness	Loss of compliance due to aging, cyclical stress on arterial walls; augments systolic BP, wave reflection, afterload	Systolic BP; pulse-wave velocity by pulse-wave Doppler	Reciprocal value to compliance Alters arterial BP trace Fosters hypertension
Wave reflection	Pulsatile flow generates pressure waves along arterial walls that also reflect backwards	P and V relationship obtained from carotid artery (surrogate of aortic) tonometry and ECHO imaging and flow Doppler at various oscillatory frequencies	Backward pressure waves distort BP waveform, increase systolic BP and afterload
Myocardial-arterial coupling	Myocardial contraction and pulsatile arterial flow are coupled to generate best flow with least resistance	Arterial tonometry, phase-contrast MRI, pulse-wave Doppler	Noninvasive methods can analyze central pressures and flow and separate various components of afterload

BP = blood pressure; ECHO = echocardiogram; MAP = mean arterial pressure; MRI = magnetic resonance imaging; P = pressure; R = resistance; SVR/PVR = systemic/pulmonary vascular resistance; V = flow

In the context of pulsatile flow in a complex network of vessels, each SV generates rhythmic pressure waves forward and backward ("wave reflection", Table 2) along the arterial tree, which contribute afterload to aortic flow and are highly implicated in the pathogenesis of hypertension and peripheral vascular disease.[35,36] Modern hemodynamic monitoring provides the tools to assess afterload within the full context of its myocardial and vascular components using non-invasive (albeit highly specialized) methods such as high-fidelity tonometry, echocardiography, and pulse-wave Doppler ultrasound.[36,38] Optimal coupling of the heart and vascular functions (myocardial-arterial coupling, Table 2)[39] generates the highest ventricular outflow with the lowest force exerted (i.e., a low afterload). Alterations of myocardial-arterial coupling due to hypertension, diastolic dysfunction, or acute myocardial ischemia increase the afterload and may move the Starling curve rightward and downward.

In summary, afterload is a complex concept that clinically is mostly related to arterial impedance. In the absence of continuous specialized monitoring, afterload may at best be inferred from non-specific parameters such as the MAP, SVR, and echocardiographic examination combined with a thorough knowledge of the hemodynamic context.

Fluid responsiveness

The fluid challenge

Hypotension during surgery and anesthesia may occur through three main physiologic mechanisms: low VR (preload), low myocardial contractility, and low vascular tone (afterload). The CVP alone (as a single measurement or trend) has little discriminating power because many factors other than blood volume can affect it, as discussed earlier.[15,26] In the presence of hypotension, perturbing the existing steady state with a known intervention such as a fluid bolus will create a new steady state along an imaginary Starling curve that will be steep under conditions of hypovolemia and then flatten with further fluid boluses as preload is optimized.[13]

The increase in CO or arterial pressure that follows a fluid challenge has been termed "fluid responsiveness",[40,41] Importantly, fluid responsiveness is not synonymous with hypovolemia; for example,

hypotension that occurs with the application of positive end-expiratory pressure (PEEP) is related to a low Vs *relative* to that level of PEEP and is not necessarily related to hypovolemia *per se*. Hence, identifying fluid responsiveness does not answer the frequent conundrum of whether a patient is "wet" or "dry"; it simply reveals a situation where fluid administration corrects hypotension. From a functional standpoint, the volume that counts in this context is the Vs.

About 40-50% of perioperative and intensive care unit patients do not respond to a fluid load with an increase in CO or BP.[42] This would imply that in approximately half of perioperative patients, hypotension is due to factors other than absolute or relative hypovolemia and that a number of other possible reasons need to be considered. These include: normo- or hypervolemia, and severe hypovolemia requiring further additional volume infusion than expected. A hypovolemic patient may not immediately show fluid responsiveness when in the nearly vertical segment of the Starling curve, because the infused fluid may be shared between Vs and Vu, delaying or even preventing the rise in MCFP and increase in VR. Under a high neuraxial block or deep general anesthesia, sympathetic reflexes are blunted, thereby increasing Vu and decreasing Vs. A larger amount of fluid may be needed to achieve the same increase in Ptm, Vs, CO, and BP. This same fluid may turn out to be in excess of the hemodynamic needs and cause volume overload when the effects of the anesthetic dissipate. An additional reason why patients may not respond to a fluid load could be that the infused fluid is distributed between the Vs and Vu based on respective pressures in those two spaces. By definition, the Vu is under zero Ptm while the Vs is under positive pressure. Therefore, the first portion of infused fluid ends up in the Vu and does not affect the hemodynamics until it reaches the capacitance point (Fig. 1). Only when the Ptm in Vu increases (i.e., when a part of the Vu becomes Vs) does the infused fluid end up in both the "former" and the "newly formed" Vs; increases in both constitute an increase in total Vs, MCFP, VR, and CO. In other words, the fluid that accumulates within Vu increases the Ptm, converting blood that is in Vu into Vs. Thus, Vs is being increased by direct infusion of fluid there, as well as by addition of fluid to Vu, leading to an increase in Ptm and "converting" the Vu blood into Vs.

Measuring fluid responsiveness

A fluid challenge is the most immediate way to test fluid responsiveness, but its use is limited by the potential for volume overload and the need for measuring CO. Passive leg raising has been validated as a useful alternative to external fluid challenges to temporarily increase VR.[43] Alternatively, specialized monitors quantify the variation of arterial BP associated with respiration using parameters such as variations in the systolic pressure, SV, and pulse pressure.[41,44,45] A number of physiologic events occurring during spontaneous and mechanical breathing subtly interact with the function of the heart and intra-thoracic blood vessels.[46,47] With considerable simplification, the increase in intra-thoracic pressure that occurs with a mechanical inspiration results in two sequential hemodynamic effects (Fig. 5). First, it reduces the pressure necessary to eject SV into the extra-thoracic aorta, resulting in an increase in CO and arterial BP. Second, it decreases the gradient for VR through an increase of CVP, resulting in less filling of the right ventricle (RV) and less output from the RV to LV. On the first heartbeat of a mechanical inspiration, the LV ejects more blood than during the preceding few beats and the arterial BP rises; shortly thereafter, decreased RV output reaches the LV and the SV decreases. With the onset of expiration, BP settles to its baseline until the next cycle. Additional phenomena that may affect CO and BP include effects on the pulmonary circulation (where the positive

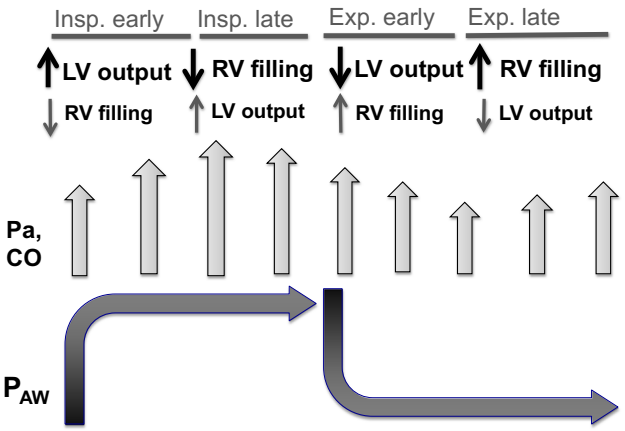

Fig. 5 Effect of positive pressure ventilation on arterial blood pressure/cardiac output. CO = cardiac output; LV = left ventricle; Pa = arterial blood pressure; P_{AW} = airway pressure; RV = right ventricle; ↑ = increase; ↓ = decrease. The first line identifies the steps during one respiratory cycle; the second and third lines describe the events occurring in the LV and RV over one respiratory cycle, the top event being the most relevant at that phase of the breath. As a mechanical breath starts, positive intrathoracic pressure augments the output of the LV into the extrathoracic aorta and decreases the filling of the RV from the venous circulation; the immediate effect is an increase of Pa and CO, until decreased RV output reaches the LV and Pa and CO start to decline. With the onset of expiration, the LV output decreases and RV filling increases; Pa and CO continue to decline until late expiration when the effect of RV filling predominates and Pa and CO are back to baseline

pressure may squeeze blood out and into the LV) and the mechanical interaction between the RV and LV (where the decreased volume of the RV increases the compliance of the LV and helps its filling). This cycle of events has little physiologic consequence during quiet breathing and normovolemia, but can become very useful diagnostically. The degree of arterial BP change is determined primarily by hypovolemia, the magnitude of intrathoracic pressure changes.

With respect to hypovolemia: the negative effect of an increase in intrathoracic pressure on VR will be more pronounced than a simultaneous decrease in afterload. This will result in an accentuated step-down of the systolic BP—often measured as the "delta-down"—which is the gradient between the systolic BP at exactly the last heart beat at inspiration and the first heart beat at the subsequent expiration.[48]

With respect to intrathoracic pressure changes, both a high inspiratory pressure and tidal volume will result in larger arterial BP changes. It is important that measurement of respiratory-induced BP variations be conducted during full mechanical ventilation, because spontaneous ventilatory activity adds negative intra-thoracic pressure, which contributes to the changes in BP but is not measured. Furthermore, there are other effects of altered respiratory mechanics. The extent of hemodynamic changes during tidal breathing is in large part determined by how much of the ventilating pressure reaches the heart and thoracic blood vessels. This depends on the compliance of the lung (C_L) and chest wall (C_{CW}), the two structures that encase the thoracic organs. With stiff lungs (low C_L) such as seen with acute respiratory distress syndrome (ARDS), very little of the pressure applied at the airway reaches the thoracic cavity, thus minimizing hemodynamic changes. With a rigid chest wall (low C_{CW}), as with abdominal distention, a substantial portion of the applied pressure reaches the thoracic cavity, thus accentuating hemodynamic changes. It has been stated that low tidal volume and low C_L, as seen in ARDS, invalidate the diagnostic value of arterial BP variations.[49] Patients who have ARDS may appear *relatively* euvolemic because they are isolated from the hemodynamic effects of the ventilating pressure. It has also been stated that the wide BP swings observed with low C_{CW} in patients with abdominal compartment syndrome[45] overestimate the diagnostic value of arterial BP variations. The patient with abdominal compartment syndrome may appear hypovolemic because the high intra-abdominal pressure may impede flow through the interior vena cava and decrease the VR and CO. Infusing fluid at that moment would increase the MCFP and Vs and temporarily increase the VR and CO. Resolution of the cause of the high intra-abdominal pressure would be the more permanent solution and would possibly avoid any subsequent volume overload.

Effects of vasoactive drugs used during GDHT

This section addresses only issues relevant to the global hemodynamics during the perioperative period. It does not describe the specific indications for treatment of shock (either hemorrhagic or septic) and mainly describes the effect of drugs on global hemodynamics and interactions among those drug effects.

The effects of vasoactive drugs during the perioperative period depend on many factors including the plasma concentrations of the drugs themselves, relative density of receptors (α-1, α-2, β-1, and β-2 adrenoceptors), and affinity of different catecholamines for the receptor subtype. The effect of any drug also depends on the cardiovascular function at the time of administration, including the vascular tone, myocardial contractility, and intravascular volume status.

Adrenoreceptors are much more abundant in the veins than arteries.[50,51] This difference may lead to different degrees of constriction in response to catecholamines—i.e., small doses affect vascular tone in the veins to a greater extent than in the arteries, while larger doses significantly affect both arterial and venous tone.[52] The constriction of arteries is usually associated with a decrease in flow, while the constriction of veins is usually associated with a shift of the blood volume downstream to such veins. Hence, one drug with even a narrow spectrum of action and affecting only one type of receptors can induce difficult to predict hemodynamic changes, as illustrated in Fig. 6.

Alpha-1 adrenoreceptor agonists constrict the arteries in the fast compartment (systemic circulation), leading to a decrease in flow through the arterial and pre-capillary vasculature and impeding the transfer of high arterial pressure to the venous site, thereby decreasing the MCFP and VR. On the other hand, constricting the arteries of the splanchnic vasculature (slow compartment) leads to a decrease in pressure and volume within the splanchnic veins (a decrease in capacity) secondary to initiation of elastic recoil, a shift of blood volume from these veins into the systemic circulation, and an increase in VR. This mechanism is quite important, and experiments using preparations that allow measurements of VR in different parts of the circulation have demonstrated that approximately two-thirds of the increase in BP during norepinephrine or phenylephrine (PE) administration resulted from an increase in VR with only one-third resulting from an increase in arterial tone.[53] Adding to the complexity of factors to consider when administering

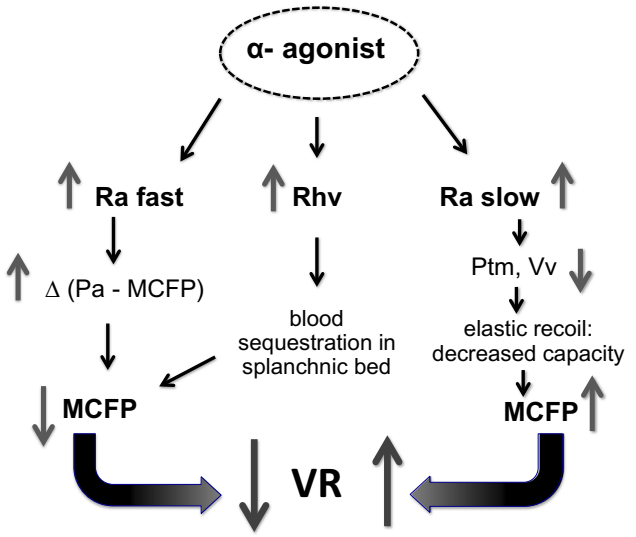

Fig. 6 Alpha-adrenergic agonists and venous return. CO = cardiac output; MCFP = mean circulatory filling pressure; Pa = arterial blood pressure; Ptm = transmural venous pressure; Ra fast = arterial resistance in the fast vascular compartment (systemic circulation); Rhv = resistance in hepatic veins; Ra slow = arterial resistance in the slow vascular compartment (splanchnic venous system); VR = venous return; Vv = blood volume within veins in the slow compartment (splanchnic veins). ↑ = increase; ↓ = decrease. α-Adrenergic agonists may change VR and CO in opposite directions. The final result depends on which influence is stronger: constriction of compliant veins and shift of blood volume from the slow to the fast compartment and subsequent increase in stressed volume, MCFP, and VR or a constriction of arteries and decrease in flow through the vasculature of the fast compartment and decrease in CO and VR

alpha-1 adrenoreceptor agonists is that constriction of hepatic veins and vasculature within the liver, which has a high density of α-1 adrenergic receptors, may lead to blood sequestration within the splanchnic vascular bed, resulting in a decrease in VR[54] (Fig. 6).

Such physiologic complexity explains why α-1 agonists may increase or decrease the VR and CO, making the prediction of their effect in a specific clinical situation quite difficult. It is not surprising that many studies describe contradictory observations—i.e., with the administration of α-adrenergic agonists having been associated with a decrease[55-59] or an increase[60-64] in VR and CO. Analysis of the differences in clinical situations or experimental details might reveal the factors responsible for such differences. For example, relatively large doses of an α-adrenergic agonist were associated with a decrease in CO, while small doses increased CO.[63,64] Infusion of gradually increasing doses of an α-adrenergic agonist was associated with an increase in CO at smaller doses and drastic decrease in CO with increasing doses.[52,65] The small doses probably led mainly to a constriction of veins, a shift of blood volume from the splanchnic to the systemic circulation, and an increase in Vs, MCFP, VR, and CO. The constriction of splanchnic veins *per se* did not meaningfully increase the Rv, but squeezed the remaining blood from those veins downstream, increasing VR. Larger doses only led to minimal additional veno-constriction (because small doses already elicited nearly maximal veno-constriction), but their main effect was to gradually increase the arterial constriction and the gradient between arterial pressure and MCFP, subsequently decreasing the MCFP, VR, and CO.

The volume status may also affect the response to α-adrenergic agonists. Phenylephrine increased CO in conditions of volume (preload) dependency (i.e., somewhat hypovolemic state) and decreased CO at volume/preload independency in pigs[58] and human patients.[66] Volume- dependent patients and animals had decreased Vu and Vs, and, as such, PE constricted veins to a greater extent than arteries, leading to shift of blood volume from Vu to Vs with subsequent increases in MCFP, VR, and CO. In volume-/preload-independent states, the CO decreased during PE administration possibly because these hearts were on the horizontal portion of the Starling curve[58]; additional volume shifted from Vu to Vs and moved the hearts further to the right to the descending part of the curve.[67] Another and likely the main reason for a decrease in CO during PE administration is an increase in arterial resistance (Ra) and decrease in flow through the constricted arteries. An increase in arterial pressure cannot overcome an increased impedance to arterial flow because the arterial constriction prevents the transfer of pressure from the arterial to venous side of the circulation and the consequent increase in VR. Besides, in these circumstances, PE administration may be associated with tissue hypoperfusion and a decrease in Vs, MCFP, VR, and CO. Stimulation of α-1 adrenoceptors[68] in the pulmonary vasculature as well as α-2C adrenoceptors[69] in the pulmonary veins is associated with vasoconstriction. Consequently, one cannot rule out that the administration of PE may constrict the pulmonary vasculature, decreasing the pulmonary blood flow and CO. There is a "competition" between the effects of PE on CO—on the one hand, PE constricts arteries and decreases the arterial flow and CO; on the other, PE constricts the veins, decreases the Vu, and increases the Vs, MCFP, VR, and CO. In different situations, different "outcome effects" of such a competition may be observed. For example, in hypovolemic patients and/or when large doses of PE are used, a decrease in arterial flow probably plays a particularly important role in the hemodynamic response.

β-2 Adrenoreceptor agonists partially counteract some of the effects of α-1 agonists and result in a decrease in Ra, a decrease in the gradient between arterial BP and

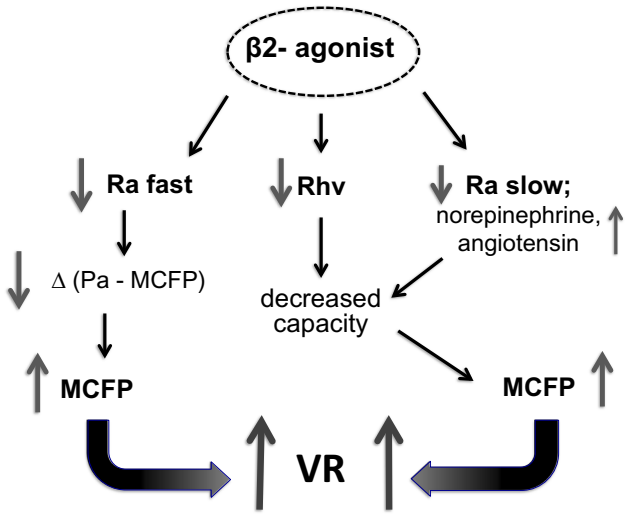

Fig. 7 Beta-2 Adrenergic agonists and venous return. MCFP = mean circulatory filling pressure; Pa = arterial pressure; Ra fast = arterial resistance in fast vascular compartment (systemic circulation); Ra slow = arterial resistance in slow vascular compartment (splanchnic venous system); Rhv = resistance in hepatic veins; VR = venous return; Δ = difference; ↑ = increase; ↓ = decrease. Beta 2-adrenergic agonists increase the VR by 1) decreasing arterial tone and increasing in flow through the fast compartment secondary to a decrease in pressure gradient between the arterial and venous site of circulation and 2) decreasing the Rhv thereby facilitating flow from splanchnic veins into the systemic circulation (from unstressed to stressed venous volumes). A concomitant increase in release norepinephrine and angiotensin facilitates the process

MCFP, an increase in MCFP, and an increase in VR (Fig. 7).[70]

An increase in CO during administration of combined α and β adrenoceptor agonists is mainly due to vascular effects (via α-1 and β-2 receptors) of the drugs, while the effect on myocardial contractility has minimal consequences if baseline contractility is preserved. Isoproterenol, a β-1 and β-2 agonist, dramatically decreased the blood volume within the splanchnic system and increased CO in both animals[71] and humans.[55] Under conditions of β-1 receptor blockade with metoprolol (a pure β-1 antagonist), the hemodynamic effect of isoproterenol did not change dramatically. However, in conditions of β-1 and β-2 adrenoceptor blockade with propranolol, the observed blood volume shifts were practically abolished.[55] This demonstrates that the increase in VR and CO during activation of β-2 adrenoceptors results from vascular effects rather than from an increase in myocardial contractility. Activation of β-2 adrenoceptors also led to relaxation within hepatic veins,[56,72] which facilitated emptying of the splanchnic venous vasculature (mainly Vu) into the systemic circulation. A concomitant increase in the production of norepinephrine[71,73,74] and angiotensin[75] acts in concert with the relaxation of the hepatic veins. Thus, stimulation of β-2 adrenoreceptors, directly and indirectly, leads to a transfer of blood from Vu to Vs, increasing MCFP, VR, and CO. Stimulation of β-1 adrenoceptors might be important in the condition of cardiac failure, but is often irrelevant in the condition of a normally functioning heart.

The vascular effects of recruiting α and β adrenoreceptors may prove to be beneficial in conditions of shock where excessive volume resuscitation may eventually lead to volume overload and increased morbidity.[76,77] Recent studies on mice demonstrated improved recovery from hemorrhagic shock when norepinephrine infusion was included in the treatment regimen[78] as it decreased the amount of fluid needed to maintain adequate hemodynamics. Moreover, that study demonstrated that the intestinal villi microcirculation was much better preserved when norepinephrine was included in the treatment. This and some similar observations in other settings[79,80] can be explained, at least partially, by the optimization of the Vs:Vu ratio. It is quite possible that norepinephrine in this experimental setting decreased the Vu and that more of the fluid infused at that time ended up in the Vs—which is exactly what one would like to see—than in the Vu.

Vasodilators may elicit a variety of responses because of different effects on one or another (fast or slow) vascular compartment. For example, captopril, an angiotensin-converting enzyme inhibitor, is effective in treating congestive heart failure, apparently by decreasing the afterload.[81] Experiments in dogs in which the preparation allowed researchers to distinguish the parts of VR coming separately from fast and slow compartments[82] demonstrated that captopril as well as prazosin (an α-adrenoceptor antagonist) increased the flow through slow compartment vessels, explaining the observed decrease in VR. On the other hand, the calcium channel antagonist nifedipine, as well as the direct vasodilator hydralazine, increased the part of the VR coming from the fast compartment and total VR. This may explain, at least partially, an increase in CO despite a decrease in arterial BP during nifedipine therapy. Verapamil, another calcium channel antagonist, produced similar effects.[83] Increasing doses of nifedipine or verapamil progressively reduced the arterial BP and increased CO.[84] The combination of these observations is in agreement with the notion that the VR and CO increase when flow through the fast compartment increases and/or flow through the slow compartment decreases.

Conclusions, future directions, and the "take-home" messages

Though the principles behind GDHT make good sense, evidence of benefit remains inconsistent. Titrating the fluid

load to target adequate values of CO during GDHT may not reflect the ultimate fluid distribution once steady state has been reached. The fluid needed to increase the Vs and MCFP may redistribute to the Vu, thereby requiring further volume to maintain CO. Administration of excess volume may cause loss of plasma proteins into the interstitium and promote edema, local inflammation, and organ dysfunction.[85] The effects of anesthetic agents and vasoactive drugs on preload, contractility, and afterload add complexity to the dynamic equilibrium between Vs and Vu.

Additionally, aggressive volume resuscitation is often ineffective in patients with sepsis.[86-88] Because such patients have significant impairment in vascular tone, their Vu remains large and Vs inadequate and the infused fluid ends up more in the Vu than Vs, and CO does not increase. Some data[56,64,77-80] we presented and analyzed in the section on vasoactive drugs may justify the hypotheses that fluid therapy combined with small doses of veno-constricting drugs achieves a more beneficial distribution of infused fluid between the Vu and Vs and prevents fluid overload in the perioperative setting.

If it were possible to directly assess and affect changes in Vu and Vs separately, it would allow for the determination of the appropriate degree of volume administration to avoid overload. Developing ways to determine Vu, Vs, and their proportion in real time could be integrated into research in the field of contemporary perioperative applied physiology, paving the way to improving the results of perioperative GDHT.

Clinically useful take-home points for GDHT

- Infused fluids are distributed between the Vs and Vu. The portion of infused fluid that ends up in the Vu does not result in an immediate change in the hemodynamics at that moment. This may be one of the reasons for the large number of non-responders to fluid challenges.
- The higher the venous capacity and/or venous compliance, the larger the portion of the infused fluid that will end up in the Vu, without an expected increase in CO.
- In patients that do not have myocardial insufficiency and where there is a high likelihood of hypovolemia, using small doses of vasopressors may be beneficial. The latter may decrease Vu, redistribute infused fluid from Vu to Vs, and thus increase the MCFP and CO. If it does not happen, the volume status and cardiac function should be reassessed including the analyses of blood gases, measurement of lactate concentration, or other physiologic parameters.

Conflicts of interest None declared.

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References

1. *Shoemaker WC*, *Appel PL*, *Kram HB*, *Waxman K*, *Lee TS*. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 1988; 94: 1176-86.
2. *Tuchschmidt J*, *Fried J*, *Astiz M*, *Rackow E*. Elevation of cardiac output and oxygen delivery improves outcome in septic shock. Chest 1992; 102: 216-20.
3. *Russell JA*, *Phang PT*. The oxygen delivery/consumption controversy. Approaches to management of the critically ill. Am J Respir Crit Care Med 1994; 149: 533-7.
4. *Rivers E*, *Nguyen B*, *Havstad S*, *et al*. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345: 1368-77.
5. *Sandham JD*, *Hull RD*, *Brant R*, *et al*. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. N Engl J Med 2003; 348: 5-14.
6. *Gattinoni L*, *Brazzi L*, *Pelosi P*, *et al*. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. N Engl J Med 1995; 333: 1025-32.
7. *Pearse RM*, *Harrison DA*, *MacDonald N*, *et al*. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. JAMA 2014; 311: 2181-90.
8. *Miller TE*, *Roche AM*, *Mythen M*. Fluid management and goal-directed therapy as an adjunct to Enhanced Recovery After Surgery (ERAS). Can J Anesth 2014; 62: 158-68.
9. *Corcoran T*, *Rhodes JE*, *Clarke S*, *Myles PS*, *Ho KM*. Perioperative fluid management strategies in major surgery: a stratified meta-analysis. Anesth Analg 2012; 114: 640-51.
10. *Grocott MP*, *Dushianthan A*, *Hamilton MA*, *et al*. Perioperative increase in global blood flow to explicit defined goals and outcomes after surgery : a Cochrane systematic review. Br J Anaesth 2013; 111: 535-48.
11. *Magder S*. Volume and its relationship to cardiac output and venous return. Crit Care 2016; 20: 271.
12. *Meng L, Heerdt PM*. Perioperative goal-directed haemodynamic therapy based on flow parameters: a concept in evolution. Br J Anaesth 2016; 117(suppl 3): iii3-7.
13. *Funk DJ*, *Jacobsohn E*, *Kumar A*. The role of venous return in critical illness and shock-part I: physiology. Crit Care Med 2013; 41: 255-62.
14. *Rothe CF*. Mean circulatory filling pressure: its meaning and measurement. J Appl Physiol 1985; 1993(74): 499-509.
15. *Gelman S*. Venous function and central venous pressure: a physiologic story. Anesthesiology 2008; 108: 735-48.

16. *Magder S*, *De Varennes B*. Clinical death and the measurement of stressed vascular volume. Crit Care Med 1998; 26: 1061-4.
17. *Maas JJ*, *Pinsky MR*, *Aarts LP*, *Jansen JR*. Bedside assessment of total systemic vascular compliance, stressed volume, and cardiac function curves in intensive care unit patients. Anesth Analg 2012; 115: 880-7.
18. *Berger D*, *Moller PW*, *Weber A*, *et al*. Effect of PEEP, blood volume, and inspiratory hold maneuvers on venous return. Am J Physiol Heart Circ Physiol 2016; 311: H794-806.
19. *Guyton AC*. Determination of cardiac output by equating venous return curves with cardiac response curves. Physiol Rev 1955; 35: 123-9.
20. *Maas JJ*, *Geerts BF*, *van den Berg PC*, *Pinsky MR*, *Jansen JR*. Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. Crit Care Med 2009; 37: 912-8.
21. *Rothe CF*. Reflex control of veins and vascular capacitance. Physiol Rev 1983; 63: 1281-342.
22. *Krogh A*. The regulation of the supply of blood to the right heart. Scand Arch Physiol 1912; 27: 227-48.
23. *Volianitis S*, *Secher NH*. Cardiovascular control during whole body exercise. J Appl Physiol 1985; 2016(121): 376-90.
24. *Funk DJ*, *Jacobshon E*, *Kumar A*. Role of the venous return in critical illness and shock: part II - shock and mechanical ventilation. Crit Care Med 2013; 41: 573-9.
25. *Hall JE*. Guyton and Hall Textbook of Medical Physiology. Thirteenth ed. PA: Elsevier; 2016 .
26. *Magder S*. Central venous pressure: a useful but not so simple measurement. Crit Care Med 2006; 34: 2224-7.
27. *Teplick RS*. Measuring central vascular pressures: a surprisingly complex problem. Anesthesiology 1987; 67: 289-91.
28. *Starling EH*, *Visscher MB*. The regulation of the energy output of the heart. J Physiol 1927; 63: 243-61.
29. *Patterson SW*, *Starling EH*. On the mechanical factors which determine the output of the ventricles. J Physiol 1914; 48: 357-79.
30. *Sala-Mercado JA*, *Ichinose M*, *Hammond RL*, *et al*. Spontaneous baroreflex control of heart rate versus cardiac output : altered coupling in heart failure. Am J Physiol Heart Circ Physiol 2008; 294: H1304-9.
31. *Ingels NB Jr, Ricci DR, Daughters GT 2nd, Alderman EL, Stinson EB*. Effects of heart rate augmentation on left ventricular volumes and cardiac output of the transplanted human heart. Circulation 1977; 56(3 Suppl): II32-7.
32. *Milnor WR*. Arterial impedance as ventricular afterload. Circ Res 1975; 36: 565-71.
33. *Sonnenblick EH*, *Downing SE*. Afterload as a primary determinant of ventricular performance. Am J Physiol 1963; 204: 604-10.
34. *Genet M*, *Lee LC*, *Nguyen R*, *et al*. Distribution of normal human left ventricular myofiber stress at end diastole and end systole: a target for in silico design of heart failure treatments. J Appl Physiol 1985; 2014(117): 142-52.
35. *O'Rourke M*. Arterial stiffness, systolic blood pressure, and logical treatment of arterial hypertension. Hypertension 1990; 15: 339-47.
36. *Mitchell GF*. Clinical achievements of impedance analysis. Med Biol Eng Comput 2009; 47: 153-63.
37. *Levy MN*. The cardiac and vascular factors that determine systemic blood flow. Circ Res 1979; 44: 739-47.
38. *Segers P*, *Rietzschel ER*, *De Buyzere ML*, *et al*. Noninvasive (input) impedance, pulse wave velocity, and wave reflection in healthy middle-aged men and women. Hypertension 2007; 49: 1248-55.
39. *Bell V*, *Mitchell GF*. Influence of vascular function and pulsatile hemodynamics on cardiac function. Curr Hypertens Rep 2015. https://doi.org/10.1007/s11906-015-0580-y17.
40. *Weil MH*, *Henning RJ*. New concepts in the diagnosis and fluid treatment in circultory shock. Thirteenth annual Becton, Dickinson and Company Oscar Schwidetsky Memorial Lecture. Anesth Analg 1979; 58: 124-32.
41. *Michard F*, *Teboul JL*. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest 2002; 121: 2000-8.
42. *Bentzer P*, *Driesdale DE*, *Boyd J*, *Maclean K*, *Sirounis D*, *Avas NT*. Will this hemodynamically unstable patient respond to a bolus of intravenous fluids? JAMA 2016; 316: 1298-309.
43. *Cavallaro F*, *Sandroni C*, *Marano C*, *et al*. Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies. Intensive Care Med 2010; 36: 1475-83.
44. *Perel A*, *Pizov R*, *Cotev S*. Systolic blood pressure variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. Anesthesiology 1987; 67: 498-502.
45. *Magder S*. Clinical usefulness of respiratory variations in arterial pressure. Am J Respir Crit Care Med 2004; 169: 151-5.
46. *Buda AJ*, *Pinsky MR*, *Ingels NB Jr*, *Daughters GT 2nd*, *Stinson EB*, *Alderman EL*. Effect of intrathoracic pressure on left ventricular performance. N Eng J Med 1979; 301: 453-9.
47. *Robotham JL*, *Cherrry D*, *Mitzner W*, *Rabson JL*, *Lixfeld W*, *Bromberger-Barnea B*. A re-evaluation of the hemodynamic consequences of intermittent positive pressure ventilation. Crit Care Med 1983; 11: 783-93.
48. *Pizov R*, *Eden A*, *Bystritski D*, *Kalina E*, *Tamir A*, *Gelman S*. Hypotension during gradual blood loss: waveform variables response and absence of tachycardia. Br J Anaesth 2012; 109: 911-8.
49. *Lakhal K*, *Ehrmann S*, *Benzekri-lefèvre D*, *et al*. Respiratory pulse pressure variation fails to predict fluid responsiveness in acute respiratory distress syndrome. Crit Care 2011; 15: R85.
50. *Hottenstein OD*, *Kreulen DL*. Comparison of the frequency dependence of venous and arterial responses to sympathetic nerve stimulations in guinea-pigs. J Physiol 1987; 384: 153-67.
51. *Birch D*, *Turmaine M*, *Boulos PB*, *Burnstock G*. Sympathetic innervation of human mesenteric artery and vein. J Vasc Res 2008; 45: 323-32.
52. *Thiele RH*, *Nemergut EC*, *Lynch C 3rd*. The clinical implications of isolated alpha1 adrenergic stimulation. Anesth Analg 2011; 113: 297-304.
53. *Stokland O*, *Thorvaldson J*, *Ilebekk A*, *Kiil F*. Factors contributing to blood pressure elevation during norepineprhine and phenylephrine infusions in dogs. Acta Physiol Scand 1983; 117: 481-9.
54. *Rutlen D*, *Supple EW*, *Powell PW Jr*. Adrenergic regulation of total systemic distensibility. Venous distensibility effects of norepinephrine and isoproterenol before and after selective adrenergic blockade. Am J Cardiol 1981; 47: 579-88.
55. *Bell L*, *Hennecken J*, *Zaret BL*, *Rutlen DL*. Alpha-adrenergic regulation of splanchnic volume and cardiac output in the dog. Acta Physiol Scand 1990; 138: 321-9.
56. *Rothe C*, *Maas-Moreno R*. Hepatic venular resistance responses to norepinephrine, isoproterenol, adenosine, histamine, and Ach in rabbits. Am J Physiol 1998; 274: H777-85.
57. *Rothe C*, *Maass-Moreno R*. Active and passive liver microvascular responses from angiotensin, endothelin, norepinephrine, and vasopressin. Am J Physiol Heart Circ Physiol 2000; 279: H1147-56.
58. *Cannesson M*, *Jian Z*, *Chen G*, *Vu TQ*, *Hatib F*. Effects of phenylephrine on cardiac output and venous return depend on the

position of the heart on the Frank-Starling relationship. J Appl Physiol 1985; 2012(113): 281-9.
59. *Meng L*, *Tran NP*, *Alexander BS*, *et al*. The impact of phenylephrine, ephedrine, and increased preload on third-generation Vigileo-Flo Trac and esophageal Doppler cardiac output measurements. Anesth Analg 2011; 113: 751-7.
60. *Yamazaki R*, *Tsuchida K*, *Aihara H*. Effects of alpha-adrenoceptor agonists on cardiac output and blood pressure in spinally anesthetized ganglion-blocked dogs. Arch Int Pharmacodyn Ther 1988; 295: 80-93.
61. *Supple EW*, *Graham RM*, *Powell WJ Jr*. Direct effects of alpha 2-adrenergic receptor stimulation on intravascular systemic capacity in the dog. Hypertension 1988; 11: 352-9.
62. *MacLean MR*, *Hiley CR*. Effects of enalapril on changes in cardiac output and organ vascular resistances induced by alpha 1- and alpha 2-adrenoceptor agonists in pithed normotensive rats. Br J Pharmacol 1988; 94: 449-62.
63. *Richer C*, *Lefevre-Borg F*, *Lechaire J*, *et al*. Systemic and regional hemodynamic characterization of alpha-1 and alpha-2 adrenoceptor agonists in pithed rats. J Pharmacol Exp Ther 1987; 240: 944-53.
64. *Gelman S*, *Mushlin P*. Catecholamine-induced changes in the splanchnic circulation affecting systemic hemodynamics. Anesthesiology 2004; 100: 434-9.
65. *Zandberg P*, *Timmermans PB*, *van Zwieten PA*. Hemodynamic profiles of methoxamine and B-HT 933 in spinalized ganglion-blocked dogs. J Cardiovasc Pharmacol 1984; 6: 256-62.
66. *Rebet O*, *Andremont O*, *Gérard JL*, *Fellahi JL*, *Hanouz JL*, *Fischer MO*. Preload dependency determines the effects of phenylephrine on cardiac output in anaesthetised patients: a prospective observational study. Eur J Anaesthesiol 2016; 33: 638-44.
67. *Katz AM*. The descending limb of the Starling curve and the failing heart. Circulation 1965; 32: 871-5.
68. *Kaye AD*, *Hoover JM*, *Baber SR*, *Ibrahim IN*, *Fields AM*. Effect of norepinephrine in alpha-subtype receptors in feline pulmonary vascular bed. Crit Care Med 2004; 32: 2300-3.
69. *Gornemann T*, *Von Wenckstern H*, *Kleuser B*, *et al*. Characterization of the postjunctional alpha 2C-adrenoceptor mediating vasoconstriction to UK14304 in porcine pulmonary veins. Br J Pharmacol 2007; 151: 186-94.
70. *Lee RW*, *Raya TE*, *Gay RG*, *Olajos M*, *Goldman S*. Beta-2 adrenoceptor control of the venous circulation in intact dogs. J Pharmacol Exp Ther 1987; 242: 1138-43.
71. *Chang PI*, *Rutlen DL*. Effects of beta-adrenergic agonists on splanchnic vascular volume and cardiac output. Am J Physiol 1991; 261: H1499-507.
72. *Magder S*, *Scharf SM*. Venous return. In: Scharf SM, Pinsky MR, Magder S, editors. Respiratory-Circulatory Interactions in Health and Disease. NY: Marcel Dekker; 2001. p. 93-112.
73. *Yamaguchi N*, *de Champlain J*, *Nadeau RA*. Regulation of norepinephrine release from cardiac sympathetic fibers in the dog by presynaptic alpha and beta-receptors. Circ Res 1977; 41: 108-17.
74. *Langer SZ*. Presynaptic regulation of the release of catecholamines. Pharmacol Rev 1980; 32: 337-62.
75. *Winer N*, *Chokshi DS*, *Walkenhorst WG*. Effects of cyclic AMP, sympathomimetic amines, and adrenergic receptor antagonists on renin secretion. Circ Res 1971; 29: 239-48.
76. *Boyd JH*, *Forbes J*, *Nakada TA*, *Walley KR*, *Russell JA*. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med 2011; 39: 259-65.
77. *Kelm DJ*, *Perrin JT*, *Cartin-Ceba R*, *Gajic O*, *Schenck L*, *Kennedy CC*. Fluid overload in patients with severe sepsis and septic shock treated with early-goal directed therapy is associated with increased acute need for fluid-related medical interventions and hospital death. Shock 2016; 43: 68-73.
78. *Harrois A*, *Baudry N*, *Huet O*, *et al*. Norepinephrine decreases fluid requirements and blood loss while preserving intestinal villi microcirculation during fluid resuscitation of uncontrolled hemorrhagic shock in mice. Anesthesiology 2015; 122: 1093-102.
79. *Stadlbauer KH*, *Wagner-Berger HG*, *Raedler C*, *et al*. Vasopressin, but not fluid resuscitation, enhances survival in a liver trauma model with uncontrolled and otherwise lethal hemorrhagic shock in pigs. Anesthesiology 2003; 98: 699-704.
80. *Poloujadoff M*, *Borron SW*, *Amathieu R*, *et al*. Improved survival after resuscitation with norepinephrine in a murine model of uncontrolled hemorrhagic shock. Anesthesiology 2007; 107: 591-6.
81. *Cody R*. Haemodynamic responses to specific renin-angiotensin inhibitors in hypertension and congestive heart failure: a review. Drugs 1984; 28: 144-69.
82. *Ogilvie RI*. Comparative effects of vasodilator drugs on flow distribution and venous return. Can J Physiol Pharmacol 1985; 63: 1345-55.
83. *Ito H*, *Hirakawa S*. Effects of vasodilators on the systemic capacitance vessels, a study with the measurement of the mean circulatory pressure in dogs. Jpn Circ J 1984; 48: 388-404.
84. *Hamann SR*, *Blouin AA*, *Chang SL*, *Kalterborn KE*, *Tan TG*, *McAllister RG Jr*. Effects of hemodynamic changes on the elimination kinetics of verapamil and nifedipine. J Pharmacol Exp Ther 1984; 231: 301-5.
85. *Woodcock TE*, *Woodcock TM*. Revised Starling equation and the glycocalyx model of transvascular fluid exchange : an improved paradigm for prescribing intravenous fluid therapy. Br J Anaesth 2012; 108: 384-94.
86. *ARISE Investigators; ANZICS Clinical Trials Group*, *Peake SL*, *Delaney A*, *Bailey M*, *et al*. Goal-directed resuscitation for patients with early septic shock. N Engl J Med 2015; 371: 1496-506.
87. *ProCESS Investigators*, *Yealy DM*, *Kellum JA*, *Huang DT*, *et al*. A randomized trial of protocol-based care for early septic shock. Process trial. N Engl J Med 2014; 370: 1-11.
88. *Mouncey PR*, *Osborn TM*, *Power GS*, *et al*. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med 2015; 372: 1301-11.