REVIEWS

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From cardiac output to blood flow auto-regulation in shock

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Abstract

Shock is defined as a state in which the circulation is unable to deliver sufficient oxygen to meet the demands of the tissues, resulting in cellular dysoxia and organ failure. In this process, the factors that govern the circulation at a haemodynamic level and oxygen delivery at a microcirculatory level play a major role. This manuscript aims to review the blood flow regulation from macro- and micro-haemodynamic point of view and to discuss new potential therapeutic approaches for cardiovascular instability in patients in cardiovascular shock. Despite the recent advances in haemodynamics, the mechanisms that control the vascular resistance and the venous return are not fully understood in critically ill patients. The physical properties of the vascular wall, as well as the role of the mean systemic filling pressure are topics that require further research. However, the haemodynamics do not totally explain the physiopathology of cellular dysoxia, and several factors such as inflammatory changes at the microcirculatory level can modify vascular resistance and tissue perfusion. Cellular vasoactive mediators and endothelial and glucocalix damage are also involved in microcirculatory impairment. All the levels of the circulatory system must be taken into account. Evaluation of microcirculation may help one to detect under-diagnosed shock, and together with classic haemodynamics, guide one towards the appropriate therapy. Restoration of classic haemodynamic parameters is essential but not sufficient to detect and treat patients in cardiovascular shock.

Key words: cardiac output; shock; microcirculation; autoregulation; mean systemic filling pressure

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Cardiovascular instability is one of the commonest causes of admission to the intensive care unit (ICU). This instability is often described as an inadequate arterial blood pressure, or as unspecific signs of inadequate perfusion of organs and tissues such as metabolic acidosis, hyperlactaemia, decreased urine output and prolonged capillary repletion time. Auto-regulation refers to the ability of organs (i.e. brain and kidneys) to maintain a steady blood flow despite a great variability in blood pressure. Hence, when the blood pressure falls below the limits of auto-regulation, cardiovascular instability results firstly, in an inadequate oxygen delivery (DO_2) and secondly, in the activation of cellular mechanisms of apoptosis and organ failure. In the past John Collins Warren described shock as "a momentary pause in the act of death" and Samuel Gross defined it as "a rude unhinging of the machinery of life." Nowadays, the

particular imbalance between DO_2 and oxygen consumption (VO_2) defines the state of shock [1].

Assuming a steady concentration of haemoglobin, cardiac output (CO) is the main determinant of DO_2. However, it is not the heart itself that is the primary controller of CO [2, 3] Instead, the rate of blood flow to each organ is almost always accurately controlled by a combination of local signals in relation to, firstly, tissue needs (such as the availability of oxygen and other nutrients, the accumulation of carbon dioxide and other waste products) and, secondly, by sympathetic activity. Thus, CO is controlled by the sum of all the local tissue flows, which is essentially the venous return. Under steady conditions, the CO and venous return are equal, and any parameter that determines venous return will, therefore, also determine CO.

This manuscript aims to review the blood flow regulation from macro- and micro-haemodynamic point of view

and to discuss new potential therapeutic approaches for cardiovascular instability in critically ill patients.

MACRO HAEMODYNAMICS AND AUTOREGULATION

The goal for clinicians treating patients in shock is to increase and maintain global DO_2 ensuring an adequate CO and tissue perfusion. To achieve this, it is important to understand some concepts about blood circulation. Let us assume that blood is a Newtonian fluid, and that basic physics can explain how blood circulates around the body.

A Newtonian fluid is a fluid in which the viscosity stress arising from its flow, at every point, is linearly proportional to the local rate of change of its deformation over time. In other words, it is a fluid whose viscosity does not change with the rate of flow.

During every cardiac cycle, an amount of energy is used to push the blood into the arterial system. With every beat, an amount of volume (stroke volume, SV) is able to generate a certain amount of pressure (pulse pressure) into the arteries. During systole, most of the energy is used to push the blood into the arterial system (kinetic energy), but given that the arteries are elastic pipes, they are able to distend and store a part of this energy as elastic energy. During diastole, the arteries can return to the baseline volume, and the elastic energy stored is now transformed into kinetic energy and used to continue pushing the blood forward into the circulation, generating a continuous flow. This mechanism can be understood as the first step of auto-regulation: a healthy elastic arterial tree with normal elastic recoil can maintain a lower arterial pressure as part of the energy which is stored in the elastic component, whereas a stiff arterial tree will generate higher arterial pressures to maintain the same level of blood flow.

The elastic properties of the arterial system can be estimated using the dynamic arterial elastance. Elastance is defined by the change in pressure for a given change in volume.

$$Eadyn = \frac{PPV}{SVV}$$

The dynamic arterial elastance (E_{adyn}) is defined as the ratio between pulse pressure variation (PPV) and stroke volume variation (SVV) during a single respiratory cycle[4, 5] and it has been shown to be a good predictor of increase of arterial pressure in response to an increase in flow after a fluid challenge [6, 7]. Monge *et al.* suggest that the higher the E_{adyn} value, the more likely the arterial blood pressure is to increase after volume expansion, as long as there is an increase in stroke volume.

On the other hand, Guyton [8, 9] proposed that venous return (VR) is directly proportional to the pressure gradient of venous return and inversely proportional to the resistance to venous return (RVR). The pressure gradient of venous return is the difference between the mean systemic filling pressure (P_{msf}) and the right atrial pressure (RAP), which can be represented as follows:

$$VR = \frac{Pmsf - RAP}{RVR}$$

The P_{msf} is the pressure in the cardiovascular system when there is no blood motion and is directly proportional to the *stressed* blood volume (V_s) and inversely proportional to the compliance (C) of the cardiovascular system. The stressed volume is the volume that distends the blood vessels walls, generating an increase of intravascular pressure. It constitutes the haemodynamically effective volume and normally represents 30–40% of the total blood volume. The *unstressed* volume is inactive haemodynamically since it is the volume that fills up the intravascular space without any increase of intravascular pressure. It constitutes a blood reservoir that can be used by changes in vascular compliance (Fig. 1). P_{msf} can be easily measured at the bedside using the arterial-venous stop flow equilibrium method or by a computerised algorithm [10, 11].

From this perspective, one can see that P_{msf} can be modified by changes in the intravascular volume and/or changes in the vascular compliance. On the other hand, as the RAP represents the meeting point between the P_{msf} and the heart function [12], it can be affected in shock states that are associated with cardiac dysfunction [13]. The clinician must be aware of conditions that may falsely increase the RAP, such as increased intra-thoracic pressures related to positive pressure ventilation with high positive end-expiratory pressure (PEEP), the presence of auto-PEEP or increased intra-abdominal pressure (IAP) [14].

However, there is large lack of knowledge about the control mechanisms of the resistance to venous return, which is finely modulated by each tissue and organ according to their own active and counter-active signals.

Importantly, shock is defined at a cellular level: it is a state in which the circulation is unable to deliver sufficient oxygen to meet the demands of the tissues, resulting in cellular dysfunction.[1] Therefore, the microvascular network represents the effective site where oxygen release takes place, where the resistance to venous return is controlled and where future research should focus.

RENAL BLOOD FLOW AUTOREGULATION

The international guidelines [15] for treating septic shock recommend maintaining mean arterial pressure (MAP) at least at 65 mm Hg and emphasize that a higher blood pressure may be required for patients with known
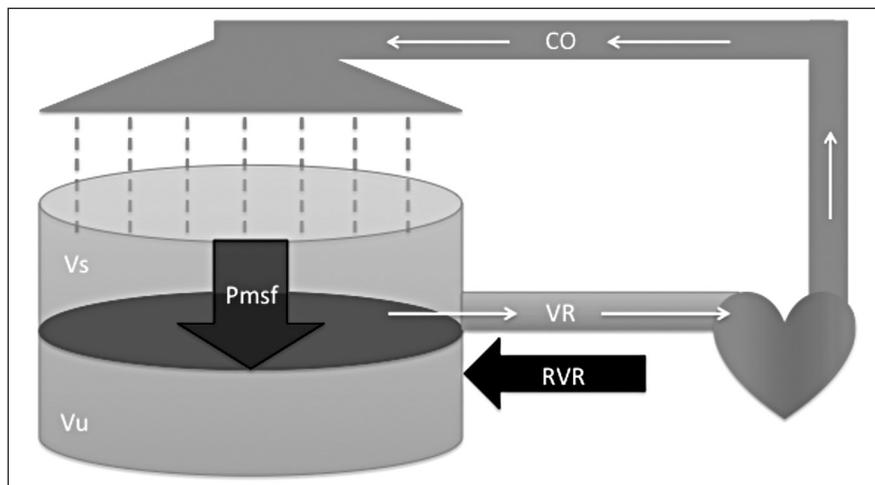
Figure 1. Schematic diagram of the cardiovascular system and the venous return. CO — cardiac output; Pmsf — mean systemic filling pressure; RVR — resistance to venous return; VR — venous return; Vs — stressed volume; Vu — unstressed volume

arterial hypertension. A recent published randomized controlled study [16] has shown no difference in mortality in septic shock patients undergoing resuscitation with a high MAP target or a low MAP target. However, among chronic hypertensive patients, those in the high-target group require less renal-replacement therapy, which suggests that septic shock patients with chronic hypertension needed higher MAP to maintain kidney perfusion.

The kidney deserves particular attention in critically ill patients as renal blood flow (RBF) can be easily monitored by urine output. Maintenance of blood pressure within an adequate range is important in order to preserve kidney perfusion. Several mechanisms are involved in the kidneys' auto-regulation process: myogenic response and tubule-glomerular feedback are able to modify pre-glomerular vascular tone. [17] In addition, the glomerular filtration rate (GFR) is dependent on changes in efferent arteriolar tone due to the release of renin from the juxtaglomerular apparatus of the afferent arteriole [18]. Thus, maintenance of RBF and GFR, after a decrease in blood pressure within the auto-regulatory range, is related to the combination of afferent arteriolar dilatation and efferent arteriolar constriction [17, 18]. An opposite vascular response occurs in cases of increased arterial pressure.

Systemic diseases may also play a role in the alteration of auto-regulation mechanisms. Auto-regulation of RBF is also impaired in critical illness [19] and during AKI [20]. There is evidence that in severe hypertensive patients, the elevated levels of blood pressure induce a displacement of the normal renal auto-regulation curve to the right. Almeida *et al.* [21] reported that although patients with severe hypertension can preserve the auto-regulatory capacity in the hypertensive range of arterial pressure, they showed substantial reductions

of effective renal plasma flow during acute normalization of blood pressure. These reductions were accompanied by decreases of a similar magnitude in glomerular filtration.

Another factor that may contribute to AKI is the impairment of venous return, i.e. under an increased IAP. The kidney is an encapsulated organ, located in the retroperitoneal space of the abdominal compartment that is especially vulnerable to the deleterious effects of increased intra-abdominal pressure (IAP) due to its anatomical position and blood supply. The kidney is often the first organ that fails when IAP is increased and can be considered the canary in the coalmine for IAH and ACS [22]. Already in 1873, E.C. Wendt from Germany stated "The higher the abdominal pressure, the less the secretion of urine". Although IAH has been associated with renal impairment for over 150 years, it is only recently that a clinically recognized relationship has been found [22]. Several animal studies have provided some insights into the mechanisms of renal dysfunction in IAH that are probably multi-factorial: reduced renal blood flow, reduced cardiac output, increased systemic vascular resistance and congestion on the venous return, together with alterations in hormonal (plasma renin activity) and neurogenic factors.[23] Renal perfusion pressure (RPP) and renal filtration gradient (FG) have been proposed as key factors in the development of IAP-induced renal failure.

$$RPP = MAP - IAP$$
$$GFR = GFP - PTP = (MAP - IAP) - IAP = MAP - 2 (IAP)$$

(where GFP = glomerular filtration pressure and PTP = proximal tubular pressure). Thus, changes in IAP have a greater impact upon renal function and urine production than changes in MAP will have.

However, although renal tissue hypoxia is considered the most important factor for development of acute kidney injury (AKI), some evidence suggests that other mechanisms are involved in the development of AKI in septic patients. For example, AKI is not always associated with frank renal hypoperfusion. Quite the opposite — it can coexist with increased RBF and a hyperdynamic circulation [24–26]. Furthermore, even when RBF reduction does occur, Prowle *et al.* [27] suggest that subtotal renal ischemia alone is not sufficient to initiate AKI.

There are, thus, other factors besides the hypoperfusion involved in the pathogenesis of AKI. Experimental and clinical observations suggest that a combination of hemodynamic and inflammatory changes within the kidney maybe responsible for reduced GFR. Although renal dysfunction in septic AKI arises primarily from changes in the balance of pre- and post-glomerular resistance[28], microcirculatory dysfunction may also contribute to renal hypoxia, even in the absence of frank renal hypoperfusion [29].

In addition, Prowle *et al.* have shown that AKI is associated with a reduction in RBF, despite normal haemodynamic parameters [20, 30]. A reduction of the percentage of CO that reaches the kidney has been described during AKI, suggesting intra-renal factors that increase renal vascular resistance. Particularly, a pre-glomerular vasoconstriction results in a greater reduction of GFR than RBF [31].

Vascular resistance in the kidney can be measured using the Renal Doppler Resistive Index (RRI).

$$RRI = \frac{Peak\ systolic\ velocity - End\ diastolic\ velocity}{Peak\ systolic\ velocity}$$

RRI is a sonographic index measured on the inter-lobar arteries that reflects the resistance to flow caused by the vascular bed downstream from the site of measurement. Since changes in intrarenal arterial waveforms were shown to be associated with urinary obstruction, several types of intrinsic renal disorders and renal vascular diseases, RRI has been use to guide differential diagnosis of renal diseases [32]. Moreover, animal studies have shown a linear relation between RRI and IAP [33]. A ureteral obstruction is characterised by a short period of vasodilation followed by renal blood flow decrease due to an increase in renal vascular resistance. Both an increased RRI and a difference greater than 0.10 between the kidneys have been associated with complete ureteral obstruction [34]. Doppler sonography has also been suggested as a useful tool for evaluating non--obstructive acute renal failure; indeed, an RRI greater than 0.70 was found to be a reliable discriminator between acute tubular necrosis and pre-renal failure [35]. Finally, the RRI has been advocated as a useful marker of diabetic nephropathy and has been also used to evaluate transplant dysfunc-

tion. Although RRI analysis is not helpful in differentiating the typical causes of transplant dysfunction (acute tubular necrosis, rejection, and immuno-suppression toxicity), it is still useful for potentially identifying vascular complications associated with transplantation [32].

Several studies have shown the usefulness of RRI to predict the occurrence and severity of AKI in critically ill patients. Corradi *et al.* showed that the RRI is altered in patients with haemorrhagic shock [36], while in critically ill patients it has been shown to be clinically useful in order to predict the reversibility of AKI [37]. An improvement of RRI has also been demonstrated after an increase of MAP with noradrenaline in septic shock patients [38]. Interestingly MAP or SV changes induced by fluid challenge did not translate into RRI variations in patients with transient, persistent or absent AKI [39].

MICROCIRCULATORY FLOW: DECOUPLING BETWEEN MACRO-HAEMODYNAMIC AND MICROCIRCULATION

The physiological function of microcirculation is to provide adequate distribution of blood flow to tissues in all metabolic conditions. This requires the ability to increase perfusion under conditions of increased metabolic demand. This adaptive function is implemented by several short and long term mechanisms, such as vessel diameter modulation due to changes in vascular tone and angiogenesis. These adaptations are triggered by biological signals related to cell metabolism, working as a negative feedback regulation. [40] This negative feedback counteracts the positive signals responsible for vessel diameter changes to haemodynamic signals that produce a maldistribution of microvascular blood flow, increasing flow in vessels with a greater wall shear stress and predisposing one to arterial-venous shunt [41, 42].

During enhanced metabolic demand, tissue cells release several vasodilatory mediators, such as pCO_2, lactate, K+ and adenosine, but also cytokines (e.g. IL-6) possibly acting via neuronal nitric oxide synthase (NOS)-derived nitric oxide (NO), prostaglandins (PGI_2 and PGE_2), H+, inorganic phosphate and reactive oxygen species. Osmolality itself may also promote vasodilation [43–46]. Red blood cells (RBCs) were also suggested to act as O_2 sensors. The mechanisms involved may include the release of ATP in response to low Hb-sO_2, [47–49] the release of NO stored in RBCs as S-nitrosohemoglobin [50, 51] and the release of NO via the reduction of nitrite [52–54].

Several clinical studies have shown that alterations in microcirculation are not always associated with classic macro-haemodynamic parameters, such as CO, in septic patients [55–58]. Impaired microvascular perfusion, in terms of reduced perfused vessels density and heteroge-

neous microvascular flow [58, 59], is responsible for organ failure even though macro-haemodynamics and blood flow have been optimized by clinical interventions. In sepsis, inflammatory mediators play an important role in decreasing vascular tone and increasing capillary permeability. Impairment of the endothelium and glycocalyx is responsible for increased leucocyte adhesion and the activation of platelets and pro-coagulatory cascades. These alterations, associated with impaired deformation of erythrocytes, are some of the causes of impaired blood flow in the microvascular network [59, 60].

For all these reasons, resuscitation of septic patients should not be targeted to optimize only macro-haemodynamic parameters as clinicians need to look at the microvascular level [61, 62]. Technologies for the monitoring of the microcirculation are progressing quickly. Recently, a third generation handheld microscope, based on incident dark field (IDF) imaging, has been introduced (CytoCam, Braedius Medical, Huizen, the Netherlands). This technique is able to provide higher quality images than side stream dark field (SDF) imaging, visualizing approximately 20–30% more capillaries than the SDF device [63]. New software for microcirculation analysis is also available and is able to automatically detect density parameters, including flow evaluation (Total Vessel Density, Perfusion Vessel Density, Proportion of Perfused Vessels). However, further research is necessary to assess the impact of the use of this technology in clinical protocols to prevent or restore an impaired microcirculation. Assessment of the glycocalyx is clinically necessary, together with other parameters measuring the extent of capillary leak in order to identify patients with fluid overload that may not progress spontaneously from the Ebb to the Flow phase of shock, as well as to help guiding the de-resuscitation phase [64]. As such, other hepato-splanchnic flow parameters, such as the indocyanine green plasma disappearance rate, may be helpful in order to avoid under-resuscitation [65].

CONCLUSION

A comprehensive approach is required to understand the resuscitation process of patients in cardiovascular shock: cellular, organ and systemic levels are affected and all of them must be taken into account in order to guide therapy.

Firstly, we should identify patients affected by shock using cellular signals of hypoperfusion (e.g. lactate, base excess). Secondly, evaluation of microcirculation may be helpful while, finally, we need to look at classic haemodynamic parameters in order to clarify the main problem and to guide one to an appropriate therapy. Although restoration of classic haemodynamic parameters is essential, it is not sufficient to guide therapy appropriately. Indeed, the previous levels must carefully guide it in order to avoid under or over treatment (or under- or over-resuscitation) of this challenging condition.

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