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Pharmacological optimization of tissue perfusion

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After fluid resuscitation, vasoactive drug treatment represents the major cornerstone for correcting any major impairment of the circulation. However, debate still rages as to the choice of agent, dose, timing, targets, and monitoring modalities that should optimally be used to benefit the patient yet, at the same time, minimize harm. This review highlights these areas and some new pharmacological agents that broaden our therapeutic options.

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Haemodynamic optimization is a daily preoccupation in the ward, emergency department, operating theatre, and critical care unit. Optimizing tissue perfusion does not simply mean improving arterial pressure, cardiac output, or both, but rather delivering oxygen from the lungs to the mitochondria in amounts adequate to sustain required metabolism. However, the wide range of available therapeutic options and haemodynamic endpoints, in addition to a relative dearth of compelling evidence as to best practice, drives impassioned debate and a variety of management stratagems. Outside the cardiac arrest/arrhythmia scenario, fluid resuscitation is universally accepted as the usual first step of haemodynamic optimization. However, the choice of fluid remains highly contentious. This particular topic is beyond the scope of our article, so the reader is referred to recent articles[32 47 81 94 106] arguing the various pros and cons and reviews.[12 87] This paper will focus on vasoactive treatments, in particular pressors and inotropes. However, rather than a drug-by-drug analysis, for which in-depth pharmacological descriptions have been reviewed elsewhere,[45 53 104 119] we shall concentrate on areas of continuing uncertainty. As much as selecting the 'best' agent, it is also incumbent to discuss how best use can be obtained from these drugs, recognizing they carry a multitude of often covert side-effects.

Tissue perfusion: are we all talking the same language?

An adequate supply of oxygen and substrate to mitochondria that enables sufficient oxidative ATP production to match metabolic demands can be considered the absolute priority of the circulation.[112] Consideration of the three components of the oxygen delivery equation (cardiac output, haemoglobin concentration, and arterial oxyhaemoglobin saturation) allows the clinician to formulate an appropriate management response in the face of a specific cardiorespiratory problem. However, tissue oxygen delivery is a global measure and does not necessarily reflect changes occurring within an organ bed, nor whether the amount delivered is adequate for metabolic needs.

At the organ level, blood flow and perfusion pressure are controlled by extrinsic factors, including neurological (e.g. sympathetic innervation), biochemical (pH, P_{CO_2}, and P_{O_2}), hormonal (renin–angiotensin system), and vasoactive mediators (e.g. nitric oxide and prostaglandins). Autoregulation represents intrinsic control, whereby afferent arteriolar tone changes as a result of modifications in perfusion pressure. However, organs do not behave in the same fashion with regard to flow dependency. The kidney, brain, and myocardium are considered to autoregulate themselves (i.e. their regional blood flow is held constant within an arterial pressure range). Consequently, below and above these thresholds, organs may encounter ischaemia or, conversely, a luxury perfusion that could potentially increase oedema formation and jeopardize perfusion.

Acute disease pathology can compromise normal complex physiological responses so conventional concepts such as autoregulation may not necessarily apply. For example, septic shock is associated with increased spatial and temporal microcirculatory heterogeneity,[20] whereas perfusion thresholds may be blunted.[97] Age and chronic diseases such as hypertension are also associated with circulatory remodelling. As a consequence, little is known

about the best perfusion pressure to target in an individual patient, particularly one who is critically ill.

Which target, using what monitor?

Vital signs are the first available clinical indicators of well-being in the ward or emergency department. Low arterial pressure, tachycardia, impaired mental status, chest pain, delayed capillary refill, decreased urinary output, or both should trigger an urgent attempt to diagnose and correct the impaired circulation. Yet even the apparently simple goal of adequacy of arterial pressure is a matter of lively debate. On the basis of normal human physiology and animal studies,[8 50] a mean arterial pressure 65 mm Hg has been widely adopted as the minimum acceptable level.[19] However, this takes no account of the individual's pre-morbid arterial pressure, as described earlier. Acute renal insufficiency has been the most studied 'failure', owing to its easily accessed parameters. Although initial studies suggested benefit from maintaining higher arterial pressure levels, especially in previously hypertensive patients,[21 22 37 84] more recent reports demonstrate failure to improve clinical outcomes through this strategy.[10 52] Mean arterial pressures of 60 mm Hg (or even lower) could be adequate in most critically ill patients, as shown by Dünser and colleagues[27] in a retrospective study of patients in septic shock. The lower target did not worsen clinical outcomes, although kidney function was compromised to some extent. Thus, both global and regional circulations should be simultaneously considered, accepting the fact that current tools do not lend themselves to monitoring of regional vascular beds. Furthermore, there is a trade-off in terms of the potentially harmful effect of the increased dose of vasopressor needed to achieve higher values.

Arterial pulse pressure variation, an increasingly popular tool for guiding fluid responsiveness, is also subject to several crucial limitations that are frequently overlooked, including the requirement for large tidal volume,[16] and possible confounding by the concurrent use of PEEP, vasopressors,[72] and the presence of arrhythmias or any spontaneous breathing effort.

Similarly, the utility of central venous pressure (CVP) monitoring is increasingly questioned, because static measurements of filling pressure correlate poorly with right ventricular end-diastolic volumes, and are poorly predictive of fluid responsiveness unless the CVP is low (<5 mm Hg).[82] Furthermore, there is often a poor relationship between right and left heart filling pressures, both in the critically ill patient and those with chronic cardiorespiratory disease. More useful and valid information is obtained from assessing the dynamic response in CVP to a therapeutic intervention such as a fluid challenge.

Central venous oxygen saturation (Scv_{O_2}) has recently gained attention as a monitoring modality, predominantly through the work of Rivers and colleagues[85] where survival benefit was achieved through the use of a threshold Scv_{O_2} value of 70% as a primary target for the early resuscitation of septic patients. This variable reflects the balance between oxygen supply and demand to the upper body, as it is usually sampled from the superior vena cava. However, Scv_{O_2} does not necessarily reflect whole-body 'mixed' venous oxygen saturation measured in the pulmonary artery.[111] Increased values are often encountered in established sepsis, and may reflect increased microvascular shunting, metabolic shutdown with decreased utilization of oxygen, or both.[86]

A range of continuous/intermittent cardiac output monitoring devices are now available, ranging from highly invasive (the pulmonary artery catheter) to minimally invasive (e.g. thoracic bioimpedance and transthoracic echocardiography), with numerous technologies (e.g. oesophageal Doppler and calibrated/uncalibrated pulse contour analysis systems) sitting in between. Each and every technique carries its own inherent limitations, ranging from validity in specific population subsets, reliability, ease of use, cost, necessary expertise, and risk profile. As underlined by the various non-protocolized multicentre pulmonary artery catheter studies,[40 41 92 99] placement of the monitoring tool in itself does not directly affect outcomes. Even protocolized studies[9 67] failed to show outcome benefit in patients in established organ failure, though a number of perioperative studies have shown reductions in mortality, morbidity, and hospital stay through the use of stroke volume or oxygen delivery-targeted optimization.[11 101] Clearly, how and when the clinician uses the added information from flow monitoring dictates the degree of accrued benefit.

The final monitoring modality to consider relates to tools that can assess cellular well-being. This is the Holy Grail of tissue perfusion monitoring, though, as highlighted above, responses in different organ beds do vary. Specific biochemical markers are released on organ injury, such as troponin or B-type natriuretic peptide for the myocardium, and a variety of biomarkers for the kidney, including urinary interleukin-18, plasma cystatin C, and plasma and urinary neutrophil gelatinase-associated lipocalin.[44 70 79 110] At present, plasma lactate, arterial base deficit, and mixed venous oxygen saturation are the only biomarkers of whole-body tissue perfusion, and these are neither particularly specific nor, in some situations, sensitive. For example, hyperlactataemia may represent an exaggerated aerobic glycolysis with excess production of pyruvate that is stimulated by endogenous[55] or exogenous[66] catecholamines. A high lactate level should thus not be considered automatically as an indicator of a tissue oxygen debt mandating an increase in systemic oxygen transport.

In which setting?

Context is crucial. For example, the inflammatory response, fluid losses, and capillary leak occurring both

during and after extensive major surgery will generally far exceed those seen during minor surgery. Likewise, a young, fit patient will generally tolerate a given insult far better than a patient with severe co-morbid illness and limited cardiorespiratory reserve. However, many controversies remain; for example, the desirability of restrictive *vs* liberal perioperative fluid regimens or the use of supranormal oxygen delivery targets.[12 39 48] All aspects of the patient, surgical procedure, illness, or both should be taken into account, including iatrogenic factors that affect oxygen delivery and consumption such as the use of blood transfusion, sedation, mechanical ventilation, and temperature modulation. For example, oxygen consumption (VO_2) increases by 15% per 1°C increase in temperature. During cardiopulmonary bypass surgery, there is the added component of non-pulsatile flow affecting tissue perfusion.[63 78]

To what benefit?

As described earlier, haemodynamic optimization has only been shown to be beneficial in selected populations. The concept of supranormal oxygen delivery was introduced by Shoemaker and colleagues[95] who proposed that supranormal values of oxygen transport and consumption could result in fewer postoperative complications. However, although this practice benefits high-risk surgical patients[56 115 117] and those presenting with early stage sepsis,[85] it proved singularly ineffective[38] or even harmful[42] in critically ill patients with established organ failure. This may relate simply to timing. The failed organs may have moved into a phase of metabolic shutdown as a consequence of prolonged inflammation and mitochondrial dysfunction,[1] and beyond the point whereby restoring perfusion could reverse the organ failure rapidly. In a retrospective analysis of their data, Hayes and colleagues[43] could identify specific patterns relating to eventual survival or non-survival, with non-survivors being unable to increase VO_2 in response to aggressive augmentation of oxygen delivery.

To what harm?

Vasopressors and inotropes are frequently used in serious and often life-threatening situations. Catecholamines and related compounds (e.g. phosphodiesterase inhibitors and dopaminergic drugs) have long been the mainstay of such treatment and have evolved as an integral part of patient management with relatively little validation of comparative safety and efficacy. The primacy of catecholamines has only been challenged in recent years, particularly with the utilization of agents from different classes, including vasopressin and its longer-acting analogue terlipressin and, the calcium sensitizer, levosimendan. Comparisons between these different agents will be drawn in a later section, but it is initially worth focusing on the harm these agents carry as these may have a significant deleterious impact on patient survival. Although tachyarrhythmias and digital, cardiac, or mesenteric ischaemia are well-recognized side-effects of catecholamine therapies, there are many other equally, if not more, sinister complications.[96] These include increased myocardial work yet decreased metabolic efficiency, increased oxygen expenditure,[29 30] thermogenic effects,[23 24] and cellular injury. Indeed, a standard laboratory model to induce myocardial injury or damage is to infuse adrenergic or dopaminergic agents. Reactive oxygen species generation also increases with catecholamine administration. Neri and colleagues[69] showed that even short-term administration was associated with myocardial damage, cell death, an initial increase in cytokine production followed by a later decline, and reduced anti-oxidative defences. Increased superoxide radical production was also shown using norepinephrine in *ex vivo* heart preparations.[89] Catecholamines also have effects on the splanchnic circulation[54 62] that may lead to ileus, malabsorption, stress ulceration,[98] and deranged liver function.[114] Numerous studies have also demonstrated a thrombogenic effect through the use of adrenergic agents.[113]

Further pernicious effects of catecholamines include promotion of bacterial growth[34–36 59 68] and accelerated biofilm formation.[59] Combined with their immunomodulatory properties[74–76 106 107 108 116] that will vary depending on dose and duration, this will markedly increase the risk of nosocomial infection. Some studies suggest that norepinephrine also impairs the energy metabolism of human circulating monocytes, thus contributing to their dysfunction.[7 58]

Catecholamines will also induce insulin resistance and hyperglycaemia and stimulate lipolysis; these features are all detrimental to outcomes in critically ill patients.[109] Dopamine also has well-known hypophysial effects; even low 'renal' doses can reduce the blood concentrations of anterior pituitary-dependent hormones except cortisol (e.g. prolactin),[4] with consequent effects on immune function.[105]

Remarkably, there have been relatively few randomized, controlled studies of inotropes compared against non-inotropic medical management. In two studies, the use of different phosphodiesterase inhibitors resulted in worse outcomes.[14 15] A recent cohort revealed that perioperative use of dobutamine in cardiac surgery was independently associated with major cardiac morbidities[31] while analysis of a large registry of patients in decompensated heart failure also revealed worse outcomes in patients given catecholamines compared with nitrates, even after adjustment for illness severity.[2]

Which drug?

Norepinephrine is currently recommended as the first-line catecholamine for use in septic shock[19] and haemorrhagic shock.[18] However, recent large-scale studies failed to

demonstrate any superiority (alone or in combination with dobutamine) over epinephrine, either in septic shock[3] or in ICU patient requiring vasopressor support for any reason.[65 66] There is also an increasing awareness of the potential harm of catecholamines[96] allied to studies in both animal models and patients suggesting that, paradoxically, beta-blockers can be used successfully to reduce sympathetic tone in sepsis.[73 93] A variety of options have emerged over the last decade that holds promise for the future.

Vasopressin's story began more than a decade ago with the recognition that low doses that would not affect healthy people caused a profound vasopressor effect in patients with inflammation. Numerous papers have reported its use in septic shock,[28 46 51 80] ischaemic and postcardiotomy cardiogenic shock,[64] vasodilatory shock,[26] and in unstable brain-dead patients.[13] Though the rationale for the exogenous use of this hormone is based on the concepts of relative vasopressin deficiency and altered baroreflex sensitivity, there does appear to be increased sensitization peripherally on V1 receptor-mediated calcium signalling in vascular smooth muscle.[6] Despite its endogenous role as an antidiuretic hormone (acting on renal V2 receptors), it improved urine output when given to septic shock patients.[80] The recent VASST study[91] comparing norepinephrine and vasopressin failed to demonstrate overall survival benefit from vasopressin; however, the *a priori* defined subset with less severe shock did show a statistically significant reduction in mortality. A recent retrospective analysis of the VASST study database suggested a beneficial synergy between vasopressin and corticosteroids.[90] An alternative to vasopressin is its synthetic, longer-acting analogue, terlipressin, which has greater specificity for the V1 receptor.[77] The main safety concerns regarding vasopressin and terlipressin relate to excessive vasoconstriction causing ischaemia of limb extremities, the heart, and the splanchnic circulation. However, the complication rate was similar to norepinephrine in the VASST study where only low doses of vasopressin were used.

Nitric oxide is produced in excess in sepsis and other shock states, including cardiogenic and haemorrhagic shock. This causes excessive vasodilatation, vascular hyporeactivity, and myocardial depression. A multicentre study of a non-specific NO synthase inhibitor, L-NMMA, in septic shock was terminated prematurely because of increased harm.[57] The same drug used in a multicentre study of cardiogenic shock showed no benefit over placebo.[103] At present, a phase III trial of pyridoxalated haemoglobin polyoxyethylene, a NO scavenger, is underway after promising results in a phase II trial.[49]

Levosimendan, the first of a new class of drug,[100] is a calcium sensitizer which increases stroke volume without a corresponding increase in cardiac work.[17] It also has a peripheral effect on opening ATP-sensitive potassium channels, causing vasodilation. Despite promising early studies in patients with decompensated heart failure,[33 71 83] a more recent trial failed to show outcome benefit.[61] Importantly, levosimendan does enable ongoing use or introduction of beta-blockade into this patient population,[60] suggesting superiority of levosimendan over dobutamine. A preconditioning dose of levosimendan improved outcomes after cardiac surgery[102] while early studies report its successful use in myocardial depression,[5] splanchnic perfusion impairment,[25] or renal failure[118] related to sepsis. This likely relates to calcium desensitization being a major mechanism of cardiac dysfunction in sepsis.[88] While a generally safe agent, hypotension has been reported during initial bolus dose loading.

Conclusion

Many areas of uncertainty still exist about how to best monitor tissue perfusion, what specific goals to target in individual patients, and how to manage them optimally with fluid and drugs. Our ever-increasing understanding of underlying pathophysiology, coupled with the development and investigation of novel techniques and drugs, will undoubtedly result in improved treatments and outcomes. In the meantime, we should remain cognizant of the potential harm of our current therapies.

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