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Review Article

Microcirculatory dysfunction and resuscitation: why, when, and how

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Abstract

Cardiovascular resuscitation is a cornerstone of critical care practice. Experimental advances have increased our understanding of the role of the microcirculation in shock states and the development of multi-organ failure. Strategies that target the microcirculation in such conditions, while theoretically appealing, have not yet been shown to impact upon clinical outcomes. This review outlines the current understanding of microcirculatory dysfunction in septic, cardiogenic, and hypovolaemic shock and outlines available treatments and strategies with reference to their effects upon the microcirculation.

Key words: blood, flow; complications, multiple organ dysfunction syndrome; intensive care, CVS; microcirculation; resuscitation

Editor's key points

- In this narrative review, the authors explore the human microcirculation's physiology and pathology.
- The authors consider the defects in the microcirculation in various shock states and discuss therapeutic options.

The cardiovascular system is an elaborate transport system whose major function is the supply of oxygen to metabolizing tissues. Macrocirculatory function is tightly controlled to ensure that bulk oxygen delivery is matched to the metabolic demands of the whole organism. Systemic perfusion pressure is a key element of the macrocirculatory system but is strongly influenced by vascular tone within the microcirculation. Individual organs adjust their microcirculatory perfusion to regulate the local supply of oxygen in order to meet their metabolic needs. In times of pathological and physiological stress, the microcirculation is likely to be a key player in the development of critical illness.

Clinicians are hindered by their inability to assess the microcirculation and the balance of metabolic supply and demand at the bedside. Hence, more readily available macrocirculatory measures, such as cardiac output, mean arterial pressure, central venous pressure, serum lactate, and mixed venous oxygen saturation, are used as surrogates, with the necessary assumption that microcirculatory perfusion is coupled to the macrocirculation. In shock states, however, this relationship is disrupted such that microcirculatory organ perfusion may be abnormal despite restitution of seemingly adequate macrocirculatory parameters. Some authorities suggest that disordered perfusion alone is sufficient in itself to play an important role in critical illness and trigger the development of multi-organ failure.[1 2] Although these associations may simply be epiphenomena, the quest for adequate monitoring to manipulate the microcirculation more precisely may prove key in improving resuscitation of the critically ill.

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Purpose and structure of the microcirculation

The microcirculation and its endothelium represent the largest organ in the body. It comprises functional units of vessels <100–150 μm in diameter, namely arterioles, venules, and capillaries (Fig. 1). The arteriolar network develops from a terminal artery via a series of bifurcations. The nomenclature of each arteriole corresponds to the generation number of the immediately distal bifurcation; thus, the A1 arteriole precedes the first bifurcation after the terminal arteriole. This form of branching is the most common, although arteriolar branch length and number vary within and between organs. The specific functional requirements of the kidney, gut, and liver result in unique microcirculatory architecture within these individual organs.

Microcirculatory perfusion is subject to myogenic, metabolic, and neurohumoral mechanisms that control locoregional blood flow (Fig. 2). Myogenic autoregulation is the intrinsic ability of a blood vessel to constrict or dilate in response to a change in intraluminal pressure and is tempered by shear stress-induced release of nitric oxide (NO).[4] Myogenic responses, mediated by changes in vascular smooth muscle contractility, serve to regulate capillary pressure and flow across a wide range of systemic perfusion pressures. These responses, combined with neurogenic and temperature factors, not only provide a basal level of tone but also interact with other vascular control mechanisms to influence locoregional perfusion.[4]

The metabolic theory of autoregulation describes the matching of local capillary blood flow to the metabolic needs of the underlying tissue.[5] Hypoxia results in rapid, endothelium-mediated[6 7] vasodilation[8] via release of vasodilating prostaglandins, NO, and the putative endothelium-derived hyperpolarizing factor.[9–11] Erythrocyte NO release is also likely to play an active role in endothelial responses to hypoxia.[12 13] The release of metabolites, such as adenosine, lactate, H^+, and K^+, from the underlying tissues induces a more delayed vasodilatory response.[14]

The degree of arteriolar vasodilation is subject to neurohumoral modulation dependent on vessel size and the distribution of adrenergic receptors particular to a given organ. First-order arterioles control total regional flow as defined by the Hagen–Poiseuille equation. These are also the primary site of pressure reduction within the circulation as a whole and the locus of control for systemic mean arterial pressure. Local capillary flow is controlled by third-order, small-sized terminal arterioles that alter the distribution of flow within a functional unit. Terminal arteriolar tone and on–off capillary perfusion, rather than flow within an individual capillary, will affect substrate supply to respiring tissues. The number of capillaries that red blood cells traverse at a given time is termed 'functional capillary density' (FCD).[15 16] Changes in FCD reduce the surface area for capillary exchange, increase diffusion distance,[17] and alter the degree of arteriovenous shunting of blood through tissues.[15] Variations in FCD are coupled to cellular metabolic requirements such that increased requirements result in decreased terminal arteriolar tone, increased FCD, and increased substrate supply. Once FCD is maximal, more proximally located arterioles dilate, increasing the bulk flow of substrate.[15] The recruitment of a given capillary also depends upon the interplay between blood rheology (i.e. haematocrit, viscosity, cellular factors, immune function, and coagulation function) and the structural nature of the given capillary and its endothelium. Disruption of microcirculatory perfusion has been linked to severity of organ failure and poor outcomes[18–20] and has been specifically described in haemorrhagic,[21] cardiogenic,[20] and septic shock.[19]

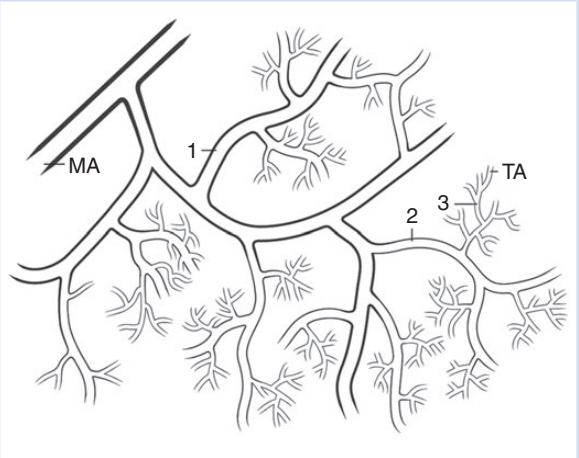

Fig 1 The structure of the microcirculation typically takes the form of arborescence and comprises vessels ranging in diameter from <100 to 150 μm. Abbreviations: 1, first-order arteriole; 2, second-order arteriole; 3, third-order arteriole; MA, main artery; TA, fourth terminal or fourth-order arteriole.

Monitoring the microcirculation

Several techniques are available to assess microcirculatory perfusion; these incorporate a range of different indices and are comprehensively reviewed by De Backer and colleagues.[22] The ideal technique would allow quantification of vascular recruitment and the magnitude, heterogeneity, responsiveness, and efficiency of oxygen transfer to the tissues. Hand-held sidestream dark-field imaging produces high-resolution video of the microcirculation and can be used non-invasively on the sublingual mucosa or invasively on a wide variety of tissues. The indices of microcirculatory perfusion generated with this technique provide an estimate of capillary density, magnitude of blood flow, and heterogeneity of perfusion.[23] Moreover, impaired perfusion as defined by these indices is correlated with poor clinical outcomes.[24] Sidestream dark-field imaging remains semi-quantitative; at present, analysis is only partly automated and needs to be performed offline. The technique is susceptible to movement and pressure artefact, although this may be less with newer generations of device. It also lacks a means to assess vascular responsiveness and reserve dynamically, such as has been developed for other monitoring techniques. For example, transient forearm vascular occlusion with a pneumatic cuff allows assessment of the return of vascular flow on release of occlusion that can be quantified by laser Doppler flowmetry.[25] An adequate restoration of blood supply requires a microcirculation that is functional enough to recruit vascular beds in response to metabolic need after mild ischaemia. Laser Doppler flowmetry, however, provides no measurement of flow in individual vessels or of vascular heterogeneity.

Near-infrared spectroscopy[26] is a non-invasive technique that assesses the redox state of microcirculatory haemoglobin; the use of a similar forearm occlusion test allows quantification of the rate of decay of microcirculatory oxygen saturation, thus representing the metabolic status of the underlying tissue. The rate of return of normal microcirculatory saturation is hypothesized to represent microcirculatory reserve. Microvascular oxygenation as assessed by near-infrared spectroscopy is dominated by the oxygen status of the venous system; the oxygen tension of underlying tissues can only be inferred. In contrast, transcutaneous oxygen probes allow for direct assessment of

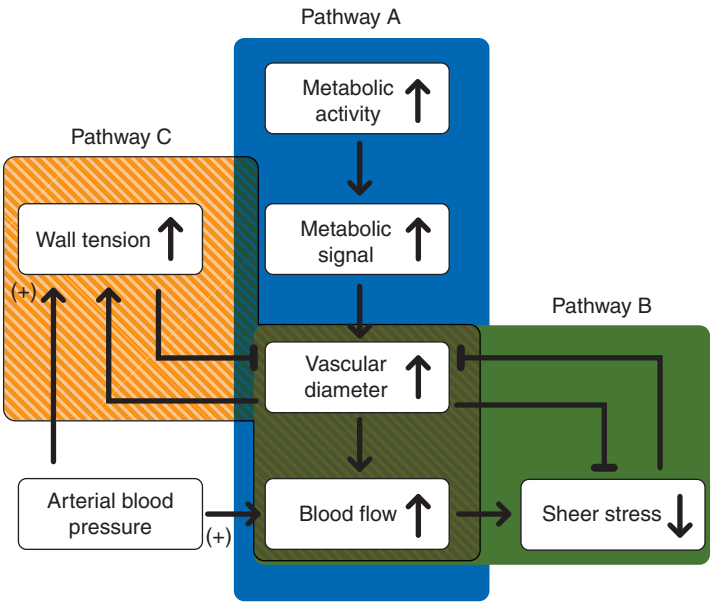

Fig 2 Schematic diagram illustrating interactions between factors involved in regulation of blood flow. Blunt-ended lines denote negative effects. Bold lines and arrows show the primary effects in the system. Vertical arrows show the effects of increasing metabolic demand on the indicated quantities in the presence of metabolic, shear-dependent, and myogenic responses. Pathway A shows the vasodilatory effect of the metabolic response resulting from increased metabolic demand. Pathway B highlights the increase in tone attributable to net reduction in shear stress in the system because of an increased vascular diameter. This effect is partly opposed by the simultaneous increase in blood flow. Pathway C shows the vasoconstriction caused by increased diameter and vessel wall tension. (Adapted from Arciero and colleagues,[3] with permission from The American Physiological Society.)

interstitial oxygen tension reflective of the oxygen supply–demand balance at the local tissue level. If combined with an oxygen challenge test, this not only assesses the ability of the microcirculation to transduce an increased blood oxygen tension to the tissues but may also offer some insight into the underlying tissue metabolic state.[27]

Hypovolaemic shock

The haemodynamic responses to haemorrhage are well described; increased sympathetic output results in augmented inotropy and chronotropy, while central blood volume is defended via aldosterone- and vasopressin-induced salt and water retention and arteriolar vasoconstriction. Arteriolar responses vary within different tissues; for example, cerebral perfusion is preserved given its unique metabolic requirements and fundamental importance to survival.[28] Conversely, perfusion of the splanchnic and cutaneous circulations is partly sacrificed.[29] This difference is mediated by variable expression of adrenergic receptor subtypes.[30 31] In skeletal muscle, adrenergic nerve stimulation of A1 and A2 (70–150 μm) arterioles results in vasoconstriction. Smaller vessels (A3–A4) exhibit more complex responses, with initial constriction followed by a return to the resting state within seconds.[32] In contrast, circulating catecholamines have dose-dependent effects, causing dilatation at low doses and constriction at high doses in both large and small arterioles.[32] The net effect of the neurohumoral components of sympathetic activity is A1 vessel vasoconstriction[33] and an inversely linked pattern in smaller (A4) vessels. A4 dilatation in particular occurs during periods of significantly reduced systemic perfusion pressure;[33] this has been postulated to be a final attempt to preserve capillary perfusion in the face of profound hypovolaemia. Similar changes are likely to occur in tissues other than skeletal muscle, including gut,[33 34] pancreas,[34] and kidney.[33] Venular responses are poorly defined and controversial[35 36] but are likely to involve constriction in response to circulating catecholamines[32] in an 'attempt' at compensatory autotransfusion.[37]

The endothelium is a key component of the vasculature. Haemorrhage will result in endothelial swelling, reducing capillary cross-sectional area by up to 20%.[38] The inflammatory response to tissue injury results in endothelial activation, partly mediating vascular hyporesponsiveness via upregulation of inducible NO synthase and endothelin-1.[39 40] The activated endothelium then becomes an adhesive surface to which activated white cells attach. The slowly rolling leucocytes are consequently exposed to inflammatory cytokines released at the site of ischaemia or injury and diapedese through the widening gap junctions of the capillary endothelium.[41] These leucocytes create a positive feedback loop of microcirculatory and cellular dysfunction[42] by further stimulating endothelial activation[43] and causing obstruction of the capillary lumen.

The impact of the cellular components of the blood upon microcirculatory flow is not limited to leucocytes. Erythrocytes are ~7 μm in diameter and can pass through much smaller capillaries because of their ability to deform. In conditions of stress, deformability is rapidly diminished; in combination with endothelial swelling, this reduces capillary erythrocyte perfusion[44] and switches off capillary recruitment. Functional capillary density is thereby reduced, as are oxygen delivery and the efficiency of effluent removal.[37]

Microcirculatory compromise despite adequate macrocirculatory resuscitation and thus uncoupling from local tissue requirements is a common theme within the shock literature.[18 33 45–47]

The ability to resuscitate the microcirculation is a marker of the severity of the haemorrhage, with milder degrees of haemorrhage being more responsive.

Cardiogenic shock

Cardiogenic shock has been relatively less investigated than hypovolaemic shock, but they share significant similarities. The aetiology of microcirculatory dysfunction in cardiogenic shock has not been fully elucidated, but vascular responsiveness to metabolic need appears damped.[48] Based on the ability of acetylcholine to reverse the observed microvascular constriction, it has been theorized that a sympathetic–vagal imbalance plays a significant role in reducing microvascular perfusion via arteriolar vasoconstriction.[49] This in turn may be compounded by augmented sensitivity to an already increased sympathetic output. There may also be a systemic reduction in NO production as a result of reduced activity of the endothelial isoform of NO synthase, as is seen in chronic left ventricular failure.[50 51] Given that the majority of patients are managed early in the disease with revascularization, anticoagulants, antiplatelet drugs, or a combination of these, microvascular thrombosis is less likely to be involved significantly.[49]

In addition to the changes in vascular tone, there are also rheological changes associated with cardiogenic shock, with early increases in viscosity because of increased protein and fibrinogen concentrations, increased red cell aggregation, and reduced red cell deformability.[52] The driving factors for such endothelial and rheological changes may be mediated by a combination of increased concentrations of circulating catecholamines, reperfusion injury, and a systemic inflammatory response.[53] Data from the SHOCK[54] registry point to a distributive component of cardiogenic shock,[55] which supports the notion of an inflammatory response or immune activation as part of these patients' clinical presentation. It is likely that the excess inducible NO synthase-derived NO released after myocardial infarction is a major contributor to this vasodilatory component of cardiogenic shock.[56] A trial of the non-selective NO synthase inhibitor tilarginine (L-N^G-monomethylarginine) failed to improve outcomes,[57] perhaps as a result of blockade of the non-inducible forms of NO synthase. Of interest, two groups have reported that standard medical treatment alone is successful in restoring microcirculatory flow in decompensated, but not shocked, heart failure patients.[58 59] Perhaps in parallel with findings in hypovolaemic or haemorrhagic shock, there is a tipping point in heart failure beyond which the reduction in cardiac output induces microcirculatory decompensation. As a consequence, the microvasculature may uncouple from the macrocirculation, marking the transition to a decompensated form of shock.

Sepsis

Septic shock occurs as a result of a rampant systemic activation of inflammatory pathways by constituent parts of microorganisms collectively known as pathogen-associated molecular patterns. Excessive production of NO and other mediators leads to varying degrees of myocardial depression, vasodilation, loss of vascular tone, and hyporesponsiveness to catecholamines. The microcirculation is likely to be a key locus of haemodynamic compromise in septic shock.[60] However, microcirculatory abnormalities in sepsis and its links with organ dysfunction are not fully understood, particularly in organs other than skeletal muscle and sublingual tissues. Mechanisms are multifactorial and include a combination of vascular autoregulatory dysfunction, increased blood viscosity,[61] neutrophil activation,[62] and reduced red cell deformability.[61] Notably, despite marked activation of the various coagulation pathways and depletion of endogenous anticoagulants, widespread microvascular occlusion by clots is a surprisingly unusual phenomenon.

Early sepsis is characterized by a hyperdynamic vasodilatory state, often accompanied by a relative hypovolaemia and a concurrent reduction in FCD. The preservation of venular flow[63] supports the presence of arteriovenous shunting.[64 65] Importantly, residual capillary perfusion becomes increasingly heterogeneous; in mathematical models, this is shown to be less efficient than homogeneous flow (Fig. 3).[66] These findings, in parallel with the observed reduction in capillary oxygen tension and preservation or elevation of venous oxygen tension [termed the oxygen partial pressure (P_{O_2}) gap],[65] suggest a deficiency in oxygen supply.

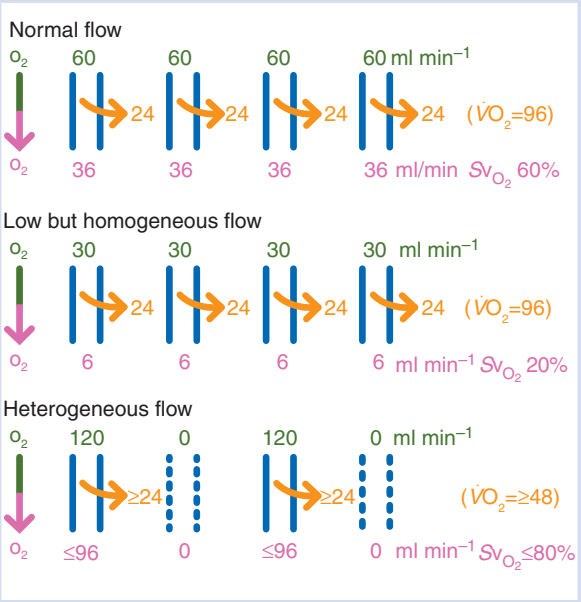

Fig 3 Impact of heterogeneous perfusion on tissue metabolism and venous oxygen saturation (Sv_{O_2}). In the normal situation (top panel), O_2 is delivered at 240 ml min^{-1} in four perfused capillaries. The tissues extract oxygen to meet cellular oxygen consumption ($\dot{V}O_2$). In the presence of low-flow but homogeneous perfusion (middle panel), half the O_2 is delivered to the tissue but all the capillaries are perfused. The amount of oxygen is sufficient to meet the oxygen requirement of the cells; hence, $\dot{V}O_2$ is preserved even though Sv_{O_2} is severely decreased. In the presence of heterogeneous flow (bottom panel), even though total oxygen delivery is preserved (240 ml min^{-1}), only 50% of the capillaries are perfused. Cells close to the perfused capillaries consume the normal amount of oxygen. Cells too far away from perfused capillaries do not receive enough O_2 to meet their O_2 requirements and become hypoxic. It is possible that the proportion of O_2 extracted from perfused capillaries increases in order to compensate for those which are poorly perfused. The degree of any compensation is uncertain, but it is unlikely to restore normal oxygen delivery to the vascular bed as a whole. As a consequence, hypoxic zones can be encountered in the presence of an elevated Sv_{O_2}. Note that this schematic presentation is simplified. In normal conditions, recruitment of the microcirculation is not maximal, and a mild degree of heterogeneity can be observed. In response to systemic low flow, such as illustrated in the middle panel, the microcirculation tends to adapt by recruiting previously unfilled capillaries and decreasing perfusion heterogeneity. When endothelial dysfunction occurs and heterogeneity develops, such as in the bottom panel, these adaptive mechanisms are lost. (Adapted from De Backer and colleagues,[22] with permission of Springer Science+Business Media.)

Microcirculatory dysfunction in sepsis has been demonstrated in stomach, small intestine, colon, liver, and kidney.[34] Global coronary blood flow is elevated[67] and, although there appears to be an oxygen extraction deficit, net lactate consumption argues against significant ischaemia.[67] While microvascular heterogeneity[68] could result in ischaemia, this has not been reliably identified.[69–72] The role of the microcirculation in septic cardiomyopathy remains poorly defined. This has been postulated to be a cytokine- and NO-mediated adaptive response to reduced ATP production that prevents irreversible ischaemic damage;[73] secondary reductions in microvascular supply may follow the decrease in local oxygen demand.

Some authors have postulated that the microcirculatory dysfunction of septic shock is a key trigger in the development of shock and multi-organ failure, and therefore, its reversal should be a priority during resuscitation of critically ill patients.[74] The validity of this hypothesis has been questioned because of the absence (or minimal presence) of necrotic or apoptotic cell death in multiple organs in sepsis, including heart, liver, kidney, and brain,[75] which would be expected with significant tissue hypoxia. Furthermore, the traditional notion that hyperlactataemia is a specific indicator of anaerobic metabolism attributable to tissue hypoperfusion has been successfully challenged. Although recommended as a resuscitation end point by the Surviving Sepsis Campaign,[76] an increased lactate clearance is no better than other markers of global oxygen supply–demand imbalance.[77] In a randomized trial of lactate-based goal-directed therapy in sepsis, an increase in the aggressiveness of resuscitation in response to hyperlactataemia led to improved patient survival[78] but failed to reduce lactate concentrations effectively. This implies that while the presence and persistence of lactataemia confers a poor prognosis,[79 80] it is likely to be an association rather than a true marker of hypoperfusion. Hyperlactataemia in sepsis is far more complex than a simple oxygen supply–demand mismatch. Other important mechanisms include impaired hepatic clearance[81] and excess activation of the skeletal muscle Na^+ pump driven by catecholamine-stimulated aerobic glycolysis, rather than anaerobic metabolism attributable to an oxygen deficit.[82 83]

A counter-suggestion to the theory of microcirculatory dysfunction being the motor of multi-organ failure is the induction of a cellular metabolic shutdown akin to hibernation that is postulated to preserve cell viability and thereby reduce the necessity for the vasculature to supply as much oxygen.[84] This is supported by several strands of data, including the lack of significant cell death described above, the fact that tissue oxygen tension is normal or even elevated in septic patients,[85–87] and that increases in local tissue oxygen consumption precede improvements in microcirculatory perfusion in resolving sepsis.[88] Taken together, experimental studies of sepsis show significant variations in tissue oxygen tension (representing local oxygen supply–demand balance) within different organs.[89] Six hours after induction of sepsis, and notwithstanding aggressive fluid resuscitation, profound and persistent reductions in tissue P_{O_2} were seen in hepatic and renal beds that were not reflected by similar changes in muscle beds. Global oxygen delivery had also decreased concurrently. Yet by 24 h, when organ dysfunction was established, tissue P_{O_2} values in all beds had normalized. Clearly, the direct relevance to human sepsis is uncertain, but these findings do highlight an early oxygen supply–demand mismatch that may subsequently be reversed by a reduction in cellular metabolism, perhaps consequent to a reduction in mitochondrial ATP provision.[90]

Arguably, when tissue metabolism has uncoupled from the microcirculation, as evidenced by the normalization or elevation of tissue P_{O_2}, attempts to normalize microcirculatory flow and oxygen delivery may well be futile or even detrimental. Some authorities contend that microcirculatory dysfunction late in the phase of septic shock and multi-organ failure may even serve as an adaptive and protective mechanism, protecting the underlying tissues from the damaging effects of hyperoxia.[91–93] New data suggest that microcirculatory shunting may represent a vascular aspect of innate immunity, diverting blood away from infected areas and opposing the haematogenous spread of that infection.[94]

Treatments

In haemorrhage, erythrocytes are transfused with the aim of improving tissue oxygen delivery. While successful in the stable anaemic outpatient,[95] findings in the critically ill are less encouraging.[96] Indeed, a recently published study showed no benefit from targeting a higher haemoglobin concentration in septic shock patients.[97] Red cells in stored blood have a reduced capability to deform and enter capillaries. Oxygen-carrying capacity is reduced, while ATP depletion and the NO-scavenging effect of haemoglobin promote vasoconstriction. These changes will predispose to reduced microcirculatory perfusion. Indeed, the efficacy of blood to improve microvascular perfusion is uncertain in both haemorrhage and sepsis[96 98 99] but is recognized to worsen with an increasing age of stored blood.[100] Taken alongside other data,[101 102] the potential increased risk profile from aged red cells is a major issue that is under further study.[103]

The use of modest fluid administration and permissive hypotension in trauma is becoming more common[104] and may improve microcirculatory perfusion.[105] Colloids and hypertonic saline are attractive options to prevent the sequelae of both blood transfusion and isotonic fluid use. In terms of microcirculatory perfusion, they may not be superior to isotonic crystalloid solutions,[33] and their use in trauma patients remains controversial.[106 107]

Few studies have targeted microcirculatory dysfunction in cardiogenic shock states. Veno-arterial extracorporeal membrane oxygenation and ventricular assist devices can restore microvascular flow and FCD, either alone[108 109] or in combination with an intra-aortic balloon pump.[110] The effectiveness of intra-aortic balloon pump therapy alone has recently been called into question because of the lack of improvement in clinical outcomes;[111] data pertaining to its microvascular effects are also limited.[112–114] Conversely, improvements in microcirculatory perfusion during a temporary pause in intra-aortic balloon pump therapy may mark a readiness to discontinue this intervention.[115] Potentially, a measure of microcirculatory function could be incorporated into the assessment of patients undergoing weaning from more invasive modes of cardiac support. The low numbers recruited and the heterogeneity of clinical presentations in studies related to mechanical support make it difficult at present to draw firm conclusions; nevertheless, this does hold promise and merits further investigation, perhaps using validated large animal models.[116]

From a pharmacological standpoint, Den Uil and colleagues[117] showed that glyceryl trinitrate improved microcirculatory function in cardiogenic shock despite unchanged macrocirculatory parameters. This suggests that the peripheral microcirculation is a key site of action of nitrates, perhaps mediated by venular dilatation and secondary increases in transcapillary perfusion pressure. In sepsis, this effect is not present; indeed, one study reported an increase in mortality in patients treated with nitrates.[118] Dobutamine may recruit a poorly perfused

microcirculation independent of its haemodynamic effects,[119] but catecholamine-based therapy is not without risk and has been linked to poor outcomes.[120] Surgical patients, while not suffering from sepsis *per se*, do suffer a similar significant inflammatory response and impaired microvascular perfusion.[121] In this patient group, the timing of the insult is easily defined, a limitation of many clinical sepsis studies. In a group of patients undergoing major gastrointestinal surgery, the use of dopexamine as part of a haemodynamic optimization protocol resulted in improved microcirculatory perfusion.[121] The subsequent randomized controlled trial of cardiac output-guided therapy did not realize a mortality benefit.[122] As an alternative to catecholamine therapy, the calcium sensitizer levosimendan does recruit the microcirculation in sepsis[123] and cardiogenic shock[124] and shows promise in the management of low-output states. In tandem with this, recent studies offer encouraging data on the use of β-blockade in septic shock in terms of both microcirculatory resuscitation and reduced mortality.[125 126] Other than limited use of catecholamines, in particular dopamine,[127] no combination of inotrope or vasopressor is superior in lowering mortality in patients with septic shock.[128–130]

In sepsis, there have been several notable failures of putative therapies, including NO inhibition,[131] drotrecogin alfa[132] (despite its ability to recruit the microcirculation),[88 133] supranormal goal-directed therapy,[134] early goal-directed therapy,[135 136] and corticosteroids.[137] These failures may stem from an indiscriminate application of therapies without consideration of either the phase of illness or the degree of microcirculatory dysfunction present in an individual patient. If the microcirculation is not significantly affected by the disease or if it has been normalized, uncoupled from metabolism, or both, then therapies targeting the microcirculation would not be expected to offer any benefit and may even expose the patient to increased risk. With late presentation of the patient or a delay in instituting therapy, microcirculatory dysfunction and organ dysfunction may already be established,[138] at which point such use of therapies may be futile.

Protocol-based resuscitation strategies in sepsis have shown promise.[139] However, the applicability of the Rivers' early goal-directed trial[140] to everyday clinical practice remains contentious, especially in light of the recent ProCESS and ARISE multicentre studies.[135 136] The results from the UK-based PROMISE trial are keenly awaited, but the data do not currently support the use of early goal-directed therapy in sepsis. However, it is important to note that the resuscitation protocols in these studies incorporate macrocirculatory end points, which offer little information as to the perfusion state of the microcirculation.[63] The microcirculation and macrocirculation are uncoupled early after the onset of sepsis,[141 142] and adequate early microcirculatory resuscitation may improve patient outcomes[24] either by prompting appropriate therapies or by avoiding potentially detrimental ones. Hence, integrating a measure of microcirculatory function into resuscitation protocols may be desirable. Yu and colleagues[27] used an oxygen challenge test as a marker of microcirculatory function to this end, with significant morbidity and mortality benefit. Interestingly, this benefit may have been achieved by avoidance of higher doses of catecholamines. There is currently a small suite of bedside tools available for microcirculatory analysis, of which sidestream dark-field imaging is the most promising. Unfortunately, none has yet been validated as part of an overall resuscitation strategy. Once a bedside microcirculatory and metabolic resuscitation end point is available, the re-examination of previously unsuccessful therapies may be possible.

Conclusion

The microcirculation is an important part of the cardiovascular system, vital for the normal delivery of oxygen. In health, its function is coupled to the requirements of underlying tissues such that supply exceeds demand, regardless of variations in macrocirculatory variables, such as blood pressure and cardiac output. In pathological conditions, beyond certain limits and despite homeostatic mechanisms, the microcirculation ceases to be perfused normally and the clinical entity of shock develops. If resuscitation of the microvasculature is rapid and complete, microvascular perfusion can be normalized and poor outcomes obviated; if not, the microcirculation remains hypoperfused despite normalization of macrocirculatory parameters (i.e. uncoupled). After this point, the occurrence of multi-organ failure is more likely, with a concordant increase in mortality. If microcirculatory monitoring could be added to standard haemodynamic measures, a return of normal perfusion may serve as a superior marker of the adequacy of resuscitation. This may allow more measured resuscitation which, given the concern regarding the deleterious effects of catecholamines, fluids, or blood products,[143 144] would seem prudent. The role of monitoring the microcirculation in established shock or multi-organ failure is less certain. Uncoupling from the macrocirculation in this clinical context may be a result of a shift in priorities to preventing damage to underlying organs. Evidence is robust that cellular metabolism reduces in multi-organ failure[84] such that supply of oxygen at physiological levels may be, at best, useless or even potentially harmful,[145] as inferred from models of ischaemia–reperfusion injury.[91 92 93] In established organ failure, the abnormal microcirculation may reflect an adaptive response to limit damage inflicted by infection, inflammation, or oxidative stress. Therefore, the degree of microcirculatory resuscitation required may vary depending upon the type and phase of critical illness. Currently available haemodynamic and oxygen-derived measures are relatively insensitive to events happening at the tissue level. Technologies to monitor the microcirculation at the bedside still await both full validation and the ability to deliver online data that would encourage more widespread uptake. Furthermore, end points for microcirculation-focused resuscitation have not yet been defined.

Authors' contributions

J.P.R.M.: literature review and overall authorship. A.D.: contribution to manuscript preparation. M.S. and J.F.F.: critical review of manuscript and contribution to its preparation.

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Declaration of interest

None declared.

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