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Vascular content, tone, integrity, and haemodynamics for guiding fluid therapy: a conceptual approach‡

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Editor's key points

- The authors propose a new approach to diagnose and manage shock.
- They suggest consideration of each of: blood flow, vascular content, the vascular barrier, and vascular tone.
- The promised advantages include harmonized approach across micro- and macro-vascular disturbance.
- The authors caution that their approach needs prospective, clinical testing.

Background. Despite many clinical trials and investigative efforts to determine appropriate therapeutic intervention(s) for shock, this topic remains controversial. The use of i.v. fluid has represented the cornerstone for the treatment of hypoperfusion for two centuries.

Methods. As a part of International Acute Dialysis Quality Initiative XII Fluids Workgroup meeting, we sought to incorporate recent advances in our understanding of vascular biology into a more comprehensive yet accessible approach to the patient with hypoperfusion. In this workgroup, we attempted to develop a framework that incorporates key aspects of the vasculature into a diagnostic approach.

Results. The four main components of our proposal involve the assessment of the blood flow (BF), vascular content (vC), the vascular barrier (vB), and vascular tone (vT). Any significant perturbation in any of these domains can lead to hypoperfusion at both the macro- and micro-circulatory level. We have termed the BF, vC, vB, and vT diagnostic approach the vascular component (VC) approach.

Conclusions. The VC approach to hypoperfusion has potential advantages to the current diagnostic system. This approach also has the distinct advantage that it can be used to assess the systemic, regional, and micro-vasculature, thereby harmonizing the approach to clinical vascular diagnostics across these levels. The VC approach will need to be tested prospectively to determine if this system can in fact improve outcomes in patients who suffer from hypoperfusion.

Keywords: blood volume; cardiac output; fluid management; fluids; micro-circulation; resuscitation; vascular content; vascular integrity; vascular tone; volume

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The characterization of shock is fundamentally a cellular definition wherein the oxygen requirements of parenchymal cells to sustain respiration needed to produce ATP are exceeded by that being delivered by the circulation.[1] Hypovolaemia is one type of shock where this can occur and is described by the condition where there is inadequate tissue perfusion as a consequence of reduced vascular content (vC). It can occur because of the systemic loss of volume such as in haemorrhagic shock but also to a defect of a normal or even elevated cardiac output resulting in absolute or regional hypovolaemia. In such conditions, fluid administration is the optimal therapy to increase the vC in the expectation of promoting tissue perfusion and improve oxygen transport to the tissues.

Despite many clinical trials and investigative efforts to determine appropriate therapeutic intervention(s) for shock, this topic remains controversial and there remain broad areas where no consensus exists. The use of i.v. fluids for the treatment of hypoperfusion goes back more than 70 yr, and represents the cornerstone of the treatment of hypoperfusion.[2] However, the question of the appropriate use of fluid in the treatment of hypoperfusion remains contentious. Prompt resuscitation of patients with hypoperfusion with i.v. fluids

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has been shown to improve outcomes, but excessive fluid administration is associated with worse outcomes.[3–5] In addition, recent large-scale clinical investigations have demonstrated that both colloid and crystalloid i.v. fluids have potential toxicity.[6–8] Taken in totality, the generic response is that clinicians must give the correct amount of the appropriate fluid promptly, but not give too much.

Therefore, the mandate for clinicians is to determine when, how, and what to give, and when to remove fluid from patients during the course of their illness. The current approach to fluid administration and fluid removal tends to be focused primarily on cardiac output and haemodynamic stability.[9] The pre-eminence of cardiac output in the assessment and treatment of hypoperfusion in particular can be misleading and lead to excessive volume administration. All patients who are 'volume responsive' do not necessarily require volume. If perfusion is adequate, the fact that an infusion of volume increases cardiac output should not necessarily result in the administration of more volume. That is why the true circulatory defect, which requires correction with fluid therapy, should be regarded as lack of tissue perfusion.[10] There is a broad realization that fluid is a drug, and that clinicians lack the tools to determine the appropriate dose of these drugs. As a part of International Acute Dialysis Quality Initiative (ADQI) XII Fluids Workgroup meeting, we sought to incorporate the advances in our understanding of vascular biology and develop a more comprehensive yet accessible approach to the patient with hypoperfusion that would lead to improved outcomes.

Methods

We used the Delphi methods to achieve consensus. The Delphi method has been used to harness the opinions of diverse groups of experts on practice-related problems. The process is based on a review, performed by a group of field experts, of a survey concerning the issue in question. In the traditional Delphi method, a group of experts reviews the available literature to answer a question by scoring these surveys. Several rounds of this process are required to reach a consensus. In the present study, the experts were asked to use their personal knowledge of the literature and skills to individually consider observations reported by other experts.

Expert group

A group of international experts was established; this group included critical care physicians, anaesthesiologists, nephrologists, surgeons, and emergency room physicians who were recruited based on their expertise in fluid management in critically ill and perioperative patients. The group consisted of 31 international physicians from five continents.

Process

In this ADQI XII subgroup, each expert was required to submit to the group questions related to vascular health and microcirculation. The questions were then submitted to other experts in the group who were invited to comment individually on the questions.

We searched the Cochrane Controlled Trials Register, the Cochrane Library, MEDLINE, and EMBASE from 1966 to present. A co-author familiar with literature search protocol of the Cochrane Collaboration designed and conducted the electronic search strategy with input from members of the expert panel. The search was limited to human trials but not limited by language. Duplicate records were deleted. The search results were screened by the authors in a stepwise manner to identify the eligible studies. In the first step, we screened the titles, and irrelevant papers were excluded. In the next step, we read the abstract or full text of the papers for inclusion. The number of and reason for excluded studies in this step was recorded. The following search terms are used (Appendix 1).

Results

Based on the literature identified before the conference, the following key questions were considered:

(i) What are the key elements of vascular biology that enable the vascular barrier (vB) to remain intact?
(ii) Which biomarkers exist that inform on the integrity of the vB, specifically the glycocalyx and endothelial cells?
(iii) What are the key elements of the vC?
(iv) Can the blood volume be objectively measured in humans in health and disease?
(v) What are the key elements and aspects of vascular tone (vT) which comprise vascular responsiveness, tone, and shunting? Can these metrics be measured in humans in health and disease?
(vi) What are key elements for measuring blood flow (BF), and can these metrics be measured at the systemic, organ, and micro-vascular level?
(vii) Can BF, vC, vB, and vT be incorporated into a diagnostic system to assess patients suffering from hypoperfusion?

Discussion

Research advances in our understanding of vascular biology in health and disease have demonstrated that the vasculature is more dynamic and complex than previously understood. In particular, the discovery that the endothelial glycocalyx is a critical component of vascular integrity has demonstrated that vascular health and function is dynamic and has a significant impact on tissue perfusion.[11] In order to apply the current advances of our knowledge of vascular biology to the clinician at the bedside, we attempted to develop a framework that incorporates key aspects of the vasculature into a diagnostic approach. Some aspects of the approach will require better bedside tools than are currently available. This manuscript represents an initial 'roadmap', and as with any proposal of this nature, it will require further study and validation.

The four main components of our proposal involve the assessment of the BF, vC, vB, and vT. Any significant perturbation in any of these domains can lead to hypoperfusion at both the

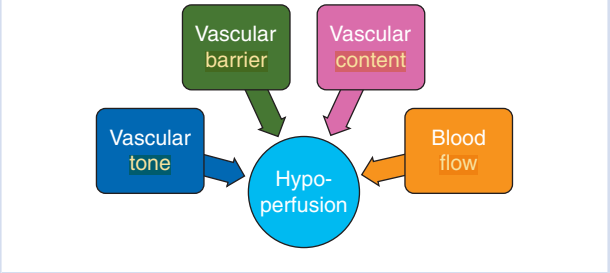

Fig 1 Vascular components that can lead to hypoperfusion.

macro- and micro-circulatory level (Fig. 1). We hypothesize that by interrogating each of these domains, a clinician can ascertain the dominant pathology in a patient that is suffering from hypoperfusion. This will then enable the clinician to have a better understanding of the aetiology of hypoperfusion thereby guiding the therapeutic approach. Each domain that we describe below can be applied to the systemic, regional (organ level), and the micro-circulation.

Vascular content

The blood volume and the portion of the volume containing red cells represent the vital elements of the vC. The common vernacular at the bedside is that a diminished vC equals 'hypovolaemia'. However, it is important to point out that the vC may be in the normal range, but a patient given a vasodilator (e.g. hydralazine, nitroglycerin) or in response to drugs with vasodilatory effect (e.g. propofol) may no longer have an adequate vC to 'fill' the increased vascular space (the potential vascular space increases as a consequence of vasodilation). In this example, the patient would develop evidence of hypoperfusion and would be clinically assessed as hypovolaemic, when in fact the vC is normal and the primary defect is poor vasomotor tone resulting in an enlarged vascular space that the vC does not adequately fill. Instead of volume therapy, this patient may in fact require a therapeutic response more directed at restoring vasomotor tone instead of one that is driven by volume therapy (Fig. 2). Clinically, an important feature of any clinical assessment is 'the patient's volume status'. The output of this assessment is typically hypo, hyper, or euvolaemia with a separate caveat about the intravascular volume status (i.e. patient is hypervolaemic but intravascularly depleted). However, the intravascular volume (vC) is not the same as the total body volume status, which includes the interstitium and the lymph content. In this proposal, the vC would be assessed in an objective quantifiable manner. The separate evaluation of these different domains allows for a more accurate assessment of the patient.

Currently, the measurement of whole blood volume can be measured accurately with a variety of techniques. The two best validated techniques utilize indocyanine green (ICG) and I_{131}.[12 13] Early attempts to measure blood volume by dilution techniques used 'Evans blue' as a label for the plasma protein albumin; however, a possible mutagenic potential brought it to an end.[14] In the 1980s, it became obvious that in order to determine blood volume a double tracer approach independently measuring plasma and red cell volume was necessary for exact and reproducible values.[13] Common tracers at that time were radioiodinated serum albumin for measuring plasma- and radiochromium-labelled red blood cells (RBCs) for measuring red cell volume. However, the disadvantages of radioactive contamination, along with plasma half-life of 60 days and dye accumulation, especially in repeated measurements, called for alternative tracers. In 1968, ICG, a relatively stable dye with an initial distribution volume comparable with that of Evans blue and labelled albumin, was used for the first time. Together with fluorescein-stained erythrocytes, it can reliably determine blood volume.[15] It is not radioactive, safe, reliable, and quickly eliminated. Meanwhile, it is seen as the gold standard; however, it is personnel-intensive, time-consuming, expensive, and elaborate for incorporation into clinical routine. Therefore, several trials have tried using the 'bed-side' haematocrit (haemoglobin) dilution technique.[16] The main drawbacks of this method are that it only measures the circulating part of blood, depends on a 'normal' vT and a constant thickness of the glycocalyx (see below). Destruction of this structure which contains a large fraction of non-circulating plasma increases the circulating plasma volume without changing total plasma volume.[11]

In the micro-circulation, vC can also be determined. Unlike the 'macro' circulation, the micro-circulation consists of networks of capillaries all of which contain plasma, but not all capillaries contain RBCs. Capillaries often preclude the entry of RBCs because of vasoconstriction and shunting effects. Because the physiological volume responsible for convective transport of oxygen is RBC-carrying component of the micro-circulation, the non-RBC-containing capillaries do not contribute significantly to oxygen transport. The key metrics that are used to assess the micro-circulatory vC are capillary density and micro-circulatory haematocrit.[17] These variables, in addition to micro-circulatory flow, can be directly measured by the use of hand-held video microscopy.[18] It is important to note that plasma water has $<3\%$ oxygen carrying capacity, thus, although the administration of fluid during resuscitation may improve systemic haemodynamic variables, it may not significantly provide oxygen delivery to the parenchymal cells.[19]

As described above, systemic vC (blood volume and haematocrit) can be objectively and accurately assessed in humans; however, bedside devices that are less cumbersome that enable these data to be acquired rapidly and easily represents an important unmet need. Bedside devices (such as video microscopy) that can assess vC in the micro-circulation are currently available. The various types of micro-circulatory monitoring devices have been extensively reviewed elsewhere.[20–22]

Vascular tone

For this domain, an objective assessment of the degree of vasoconstriction and vasodilation are assessed. At a systemic level, these metrics can be assessed with measures such as the systemic vascular resistance (SVR). At a regional level, a similar

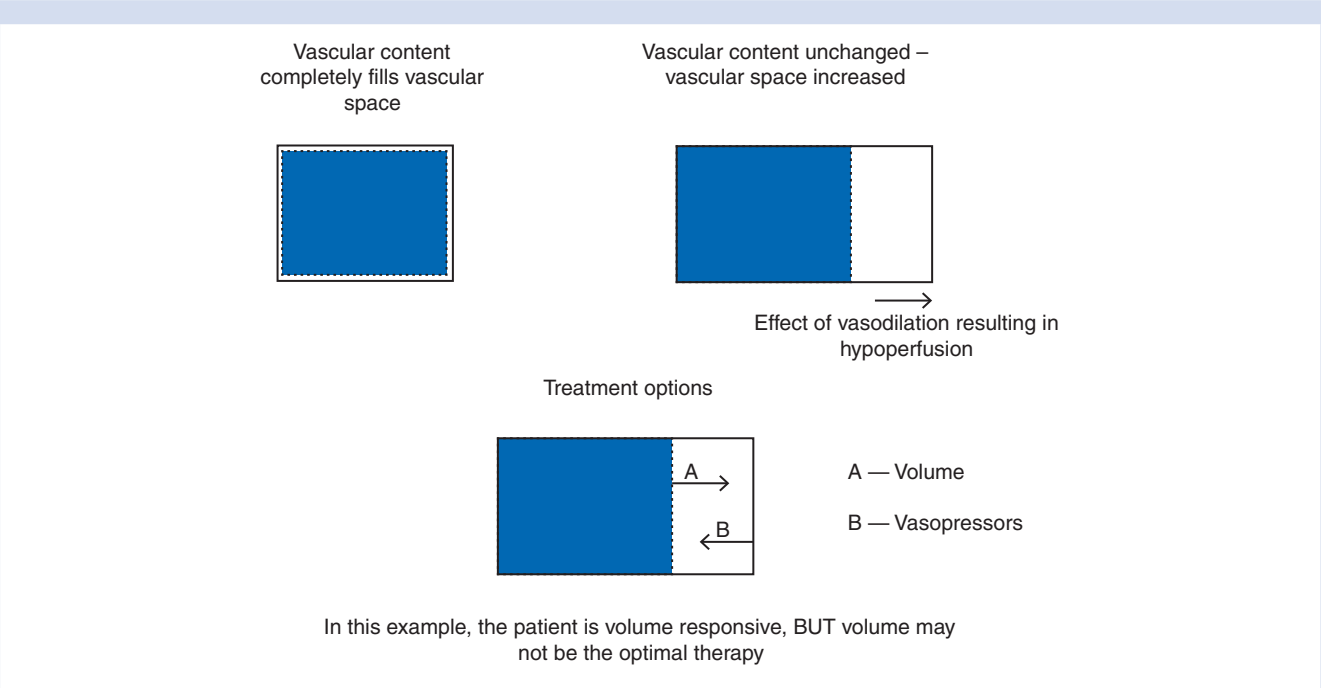

Fig 2 Dynamic changes between vC and the vascular space. Reproduced with permission from ADQI (www.ADQI.org).

strategy of measuring BF, arterial pressure, and venous pressure can allow organ vascular resistance (Ohms law approach). An example of this regional approach is the ascertainment of the pulmonary vascular resistance (PVR) with measurement of the cardiac output, pulmonary artery occlusion pressure, and the mean pulmonary artery pressure. For the micro-circulation, imaging is available that quantifies vasomotor tone (vT). For example, changes in arteriolar diameter have been measured in patients being administered vasodilators.[23] Because within any circulatory bed, there is always some degree of heterogeneity for each of these assessments, the quantitative assessment will represent net degree of vascular resistance.

Vascular barrier

For this domain, the endothelial glycocalyx and endothelial cells form the primary constituents of the vB. The endothelial glycocalyx is a gel-like fringe covering the intravascular side of every healthy vessel (although there is considerable variations between the glycocalyx compartment in the various organs) of substantial dimension (estimated average thickness 1 μm).[11 24] It participates in numerous physiological processes, such as regulating vascular permeability, preventing firm adhesion of leukocytes to the vessel wall, transmission of shear stress, or modulating inflammatory and haemostatic processes. It also contains many receptors which as a consequence of glycocalyx shedding, resulting in activation of immune cascades. In addition, the glycocalyx contains many anti-oxidative molecules such as superoxide dismutase. Thus, the glycocalyx is a central player in endothelial function and its preservation must be considered in any resuscitation strategy.[24]

Various biomarkers can be used to assess the integrity of the glycocalyx. The main components of the glycocalyx can be measured in human plasma using conventional ELISA kits. This includes the membrane-bound syndecans and glypicans and their negatively charged heparan- and chondroitin-sulphate side chains which account for much of the biophysical properties. The non-sulphated, receptor-attached long-chain molecule hyaluronan is considered to be an essential part of the surface lining. Early manifestation of endothelial injury after ischaemia–reperfusion, sepsis, atherosclerosis, cardiopulmonary resuscitation, and trauma has been shown to cause the disruption of the glycocalyx with increased plasma levels of glycocalyx components.[11] The main pathogenic component common to these insults is oxygen radical species which directly attack the integrity of the glycocalyx, thereby resulting in shedding.[25] The objective ascertainment of the integrity of the vB would be very useful for a clinician. In essence, vB measurement would allow the clinician to assess the degree of 'capillary leak' and would inform a clinician on the potential pathophysiology and may assist in the selection of an appropriate i.v. fluid. If the vB is sufficiently intact, then a colloid may be a better choice as it is more likely to remain intravascular, but if the vB is not intact, a colloidal infusion tends to diffuse into the interstitium, which is not desirable. In this scenario, a crystalloid or a blood product may be a better choice. Clinical studies in patients with sepsis, a disease that is associated with vB disruption, suggest that colloids (i.e. albumin and starch) may be superior than crystalloid solutions in patients with sepsis and evidence of hypoperfusion.[26 27] Currently, the assessment of vB is not objectively determined, and the clinician must make an informed

guess as to the integrity of the vB. Moreover, there are data to suggest that excessive fluid infusion may in fact damage the vB.[28]

Blood flow

This domain is well characterized and multiple tools are available to quantify BF. At a systemic level, BF is assessed as cardiac output for which the pulmonary artery catheter remains the bedside 'gold-standard'. However, many less invasive techniques can also provide cardiac output metrics with accuracy and precision. At a regional level, BF would be the organ BF. An example of this would be the placement of a thermodilution catheter in the renal vein, which allows the bedside clinician to assess renal BF.[29] At the level of the micro-circulation, pressure and resistance are the two variables which directly determine BF. Mass transport (flow) of blood together with oxygen content determine the oxygen availability at the parenchymal level. The resistance is determined by vessel tone and the viscosity of the blood and is described by the Law of Poiseuille. It must be kept in mind however that the vascular bed is a highly heterogeneous resistive network and is continuously changing. Its inability to match oxygen supply by demand as a result of defect in vascular reactivity results in functional shunting and is characteristic of distributive shock. The driving pressure of BF to the micro-circulation where oxygen is transported to is the difference between the input and output pressure of the micro-circulation. Arteriolar and venular tone determine this driving pressure difference, which defines the flow of blood in the micro-vasculature.[30]

The hierarchy of the circulation: systemic, regional, and the micro-circulation

The concept that we have outlined, considering BF, vC, vT, and vB, enable a systematic assessment of any vascular circuit from global systemic vasculature down to the micro-circulation level. There are advantages to assessing these areas individually as not all patients have systemic disease. For instance, patients with severe acute respiratory distress syndrome (ARDS) may have severely impaired pulmonary vasculature, but a relatively intact systemic vasculature. Thus, for an organ level assessment, determining the BF, vC, vT, and vB may allow the clinician to have a better understanding of the disease. By integratively assessing the different compartments comprising the hierarchy of the circulation, one may obtain a differential diagnosis as to the origin of the circulatory defect during shock, thereby guiding the clinician to provide the most appropriate therapy. ARDS is usually the result of severe alveolar injury leading to hypoxaemia, but the pulmonary endothelium is often highly disrupted as well, and an assessment of vB and vT in particular might be useful in guiding care.

A similar approach can be used to assess the micro-circulation. When the micro-circulation is imaged and assessed, the BF (convection) is a critical determinant of micro-vascular health. The vC assessment of the micro-circulation would be more focused on micro-vascular haematocrit and capillary filling. Akin to the vC, the vT would be an assessment of the capillary vasomotor tone and the capacity for red cells to transit the micro-circulation appropriately. Perhaps most valuable in the assessing the micro-circulation would be the vB wherein

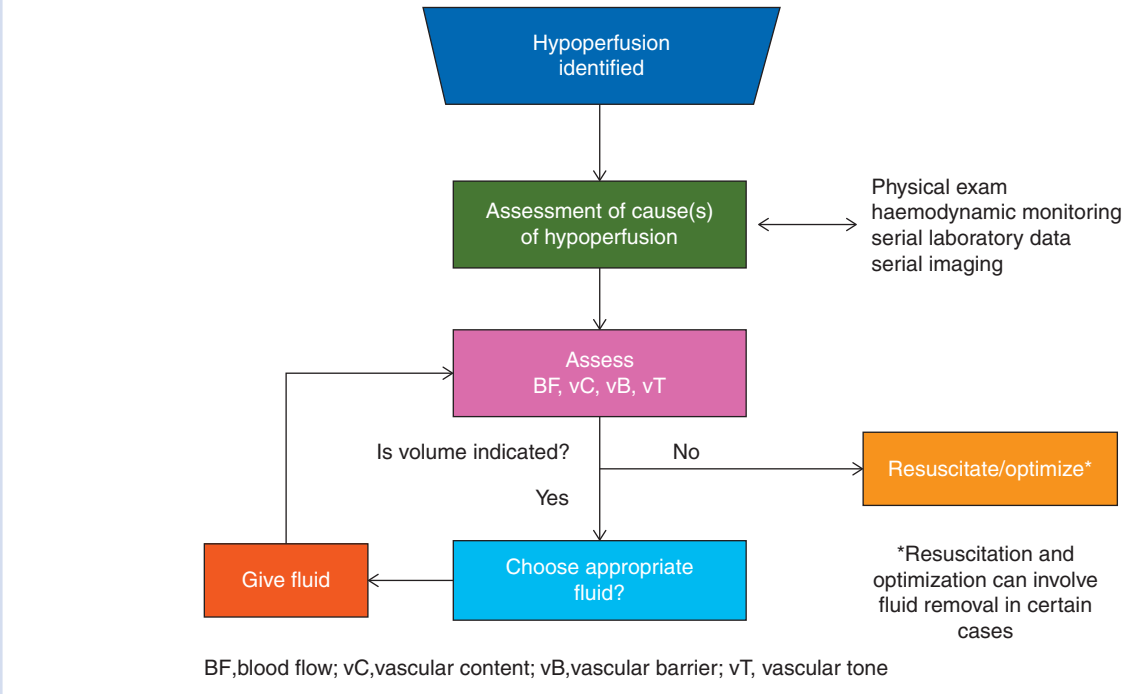

Fig 3 Flowchart of how to guide fluid management with the vascular component approach. Reproduced with permission from ADQI (www.ADQI.org).

Table 1 Vascular components in different forms of shock. BF, blood flow; vC, vascular content; vT, vascular tone; vB, vascular barrier. †Within the 'Distributive Shock' classification, there exist multiple subtypes (e.g. spinal shock, septic shock). A potential advantage of the VC approach is that the vB, vT, and vC can identify distributive shock subtypes. For instance, septic shock and spinal shock would be characterized by decreased vT and vC. However, in spinal shock, the vB would be expected to be largely intact when compared with septic shock. Thus, the VC approach may allow for more rapid diagnosis of the various subtypes of distributive shock[1]

	BF	vC	vB	vT
Cardiogenic shock	Macro/micro decreased	Normal	Intact	Intact
Haemorrhagic shock	Macro/micro decreased	Decreased	Impaired (macro)	Intact
Obstructive shock	Macro/micro decreased	Normal	Intact	Intact
Distributive shock†	Macro normal micro decreased	Normal/decreased	Impaired†	Impaired†

Table 2 Vascular components at the systemic, regional, and micro-circulatory level. SVR, systemic vascular resistance; OVR, organ vascular resistance

	vC	vT	vB	BF
Systemic	Blood volume	SVR	Biomarker panel	Cardiac output
Regional	Arterial Hb/Ht	OVR (reactive hyperaemia)	Indocyanine green	Pulse pressure variation, peripheral temperature, NIRS, laser Doppler
Micro-circulation[31]	Capillary Ht Functional capillary density Glycocalyx volume[24]	Arteriolar diameter[23]	VEGF, Syndecan 1 or 4, thrombomodulin, hyaluronic acid, heparin sulphate Glypican 1 (all glycocalyx markers) malondialdehyde (oxidative stress), myelo peroxidase, nitrate/nitrite (nitroso stress)	Capillary BF, heterogeneity of BF, rolling sticking leucocytes

metrics of diffusion and distance between capillaries can offer important insight into condition and integrity of the vB.

Implementation and future research

We have termed the BF, vC, vB, and vT diagnostic approach the vascular component (VC) approach. An approach to hypoperfusion utilizing the VC system is shown in Figure 3. The identification of hypoperfusion is followed by a standard clinical work-up. For those patients in whom more granular data are required to fully ascertain the cause of extremis, VC elements would be objectively assessed using bedside techniques. We believe that for patients in whom distributive shock appears to be the primary phenotype, this approach will be able to rapidly and reliably discriminate different forms of distributive shock (e.g. neurogenic, anaphylactic, *vs* septic). A summary of the expected metrics for various forms of shock and their respective VC is provided in Table 1.

An obvious limitation to testing this approach at the systemic level is the lack of bedside tools that can provide the high-fidelity data for each domain. Currently, BF and vT can be effectively assessed at the bedside. As described above, there are multiple biomarkers that are indicative of the status of vB, and more tools would be needed for more granular assessment of the vB. In addition, quantitative measures of capillary leak, specifically how quickly does plasma water exit the vascular space would be useful in guiding fluid therapy. Currently, the objective measures for vC are cumbersome, and bedside measures of vC are not yet available, although they are in active development and testing. A summary of the tools, some of which are available for use for assessing the systemic, regional, and microvasculature, is outlined in Table 2.

Summary

The VC approach to hypoperfusion has potential advantages to the current diagnostic system. The concept of 'volume responsiveness' tends to be the focus of current resuscitative strategies.[15] Thus, when a patient is evaluated and diagnosed as being volume responsive, they receive volume. As outlined above, an approach that integrates BF and these vascular domains is likely to result in a more complete understanding of why a patient is 'volume responsive' and likely to result in appropriate volume being given more judiciously.

This approach also has the distinct advantage that it can be used to assess systemic, regional, and micro-vasculature, thereby harmonizing the approach to clinical vascular diagnostics across these levels. The VC approach will need to be tested as these bedside tools become available to determine if this system can in fact improve outcomes in patients who suffer from hypoperfusion.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Authors' contributions

L.S.C., C.I., D.C., and T.J.G.: conceived the vascular component approach, wrote the manuscript, made the figures, and edited the final manuscript. M.M., J.A.K., and A.D.S.: wrote the manuscript, made the figures, and edited the final manuscript.

Declaration of interest

L.S.C. reports receiving fees for serving on steering committees from AbbVie and AM-Pharma, fees for serving as an adjudicator for a clinical end-point study from Alere, fees for device development from Covidien, Baxter, Bard Medical, and NxStage Medical, fees for serving as a principal investigator for trials sponsored by Astute Medical, fees for clinical-trial development and planning from Ikaria. C.I. has received honoraria and independent research grants from Fresenius-Kabi, Bad Homburg, Germany; Baxter Health Care, Deerfield, Illinois; AM-Pharma, Bunnik, The Netherlands; Novartis, Basel, Switzerland; Hutchinson, Hutchinson, Minnesota; B. Braun, Melsungen, Germany; Covidien, Dublin, Ireland; and Eli Lilly, Indianapolis, Indiana. C.I. has developed SDF imaging and is listed as inventor on related patents commercialized by MicroVision Medical (MVM) under a license from the Academic Medical Center (AMC), The Netherlands. He has been a consultant for MVM in the past, but has not been involved with this company for more than five years now, except that he still holds shares. Braedius Medical, a company owned by a relative of dr Ince, has developed and designed a hand held microscope called CytoCam-IDF imaging. C.I. has no financial relation with Braedius Medical of any sort, i.e., never owned shares, or received consultancy or speaker fees from Braedius Medical. D.C. reports receiving consulting fees from BBRaun, Fresenius Kabi, and Grifols. T.J.G. reports receiving research support from Acacia, Covidien, Fresenius and honoraria from Cadence, Edwards and Pacira. J.A.K., M.M., and A.S.: Chaired the entire ADQI XII meeting and reviewed and edited the Pharmacological Management of Fluid Overload Work Group drafts and figures.

References

1 Vincent JL, Ince C, Bakker J. Clinical review: circulatory shock—an update: a tribute to Professor Max Harry Weil. *Crit Care* 2012; **16**: 239–43

2 Awad S, Allison SP, Lobo DN. The history of 0.9% saline. *Clin Nutr* 2008; **27**: 179–88

3 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

4 Arikan AA, Zappitelli M, Goldstein SL, Naipaul A, Jefferson LS, Loftis LL. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. *Pediatr Crit Care Med* 2012; **13**: 253–8

5 Wiedemann HP, Wheeler AP, Bernard GR, *et al.* Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; **354**: 2564–75

6 Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *J Am Med Assoc* 2012; **308**: 1566–72

7 Myburgh JA, Finfer S, Bellomo R, *et al.* Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; **367**: 1901–11

8 Perner A, Haase N, Guttormsen AB, *et al.* Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012; **367**: 124–34

9 Vincent JL, Weil MH. Fluid challenge revisited. *Crit Care Med* 2006; **34**: 1333–7

10 Pranskunas A, Koopmans M, Koetsier PM, Pilvinis V, Boerma EC. Microcirculatory blood flow as a tool to select ICU patients eligible for fluid therapy. *Intensive Care Med* 2013; **39**: 612–9

11 Becker BF, Chappell D, Jacob M. Endothelial glycocalyx and coronary vascular permeability: the fringe benefit. *Basic Res Cardiol* 2010; **105**: 687–701

12 Haller M, Akbulut C, Brechtelsbauer H, *et al.* Determination of plasma volume with indocyanine green in man. *Life Sci* 1993; **53**: 1597–604

13 Recommended methods for measurement of red-cell and plasma volume: International Committee for Standardization in Haematology. *J Nucl Med* 1980; **21**: 793–800

14 Robertson JA, Harris WJ, McGregor DB. Mutagenicity of azo dyes in the Salmonella/activation test. *Carcinogenesis* 1982; **3**: 21–5

15 Rehm M, Haller M, Orth V, *et al.* Changes in blood volume and hematocrit during acute preoperative volume loading with 5% albumin or 6% hetastarch solutions in patients before radical hysterectomy. *Anesthesiology* 2001; **95**: 849–56

16 Awad S, Dharmavaram S, Wearn CS, Dube MG, Lobo DN. Effects of an intraoperative infusion of 4% succinylated gelatine (Gelofusine®) and 6% hydroxyethyl starch (Voluven®) on blood volume. *Br J Anaesth* 2012; **109**: 168–76

17 Boerma EC, Ince C. The role of vasoactive agents in the resuscitation of microvascular perfusion and tissue oxygenation in critically ill patients. *Intensive Care Med* 2010; **36**: 2004–18

18 De Backer D, Hollenberg S, Boerma C, *et al.* How to evaluate the microcirculation: report of a round table conference. *Crit Care* 2007; **11**: R101

19 Legrand M, Mik EG, Balestra GM, *et al.* Fluid resuscitation does not improve renal oxygenation during hemorrhagic shock in rats. *Anesthesiology* 2010; **112**: 119–27

20 Scardina GA, Ruggieri A, Messina P. Oral microcirculation observed in vivo by videocapillaroscopy: a review. *J Oral Sci* 2009; **51**: 1–10

21 Roustit M, Cracowski JL. Non-invasive assessment of skin microvascular function in humans: an insight into methods. *Microcirculation* 2012; **19**: 47–64

22 De Backer D, Ospina-Tascon G, Salgado D, Favory R, Creteur J, Vincent JL. Monitoring the microcirculation in the critically ill patient: current methods and future approaches. *Intensive Care Med* 2010; **36**: 1813–25

23 Atasever B, Boer C, van der Kuil M, *et al.* Quantitative imaging of microcirculatory response during nitroglycerin-induced hypotension. *J Cardiothorac Vasc Anesth* 2011; **25**: 140–4

24 Van Teeffelen JW, Brands J, Stroes ES, Vink H. Endothelial glycocalyx: sweet shield of blood vessels. *Trends Cardiovasc Med* 2007; **17**: 101–5

25 Rubio-Gayosso I, Platts SH, Duling BR. Reactive oxygen species mediate modification of glycocalyx during ischemia–reperfusion injury. *Am J Physiol Heart Circ Physiol* 2006; **290**: H2247–56

26 Annane D, Siami S, Jaber S, *et al.* Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. *J Am Med Assoc* 2013; **310**: 1809–17

27 Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; **350**: 2247–56

28 Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. *Anesthesiology* 2008; **109**: 723–40

29 Redfors B, Bragadottir G, Sellgren J, Sward K, Ricksten SE. Effects of norepinephrine on renal perfusion, filtration and oxygenation in vasodilatory shock and acute kidney injury. *Intensive Care Med* 2011; **37**: 60–7

30 Taylor AE, Moore TM. Capillary fluid exchange. *Am J Physiol* 1999; **277**: S203–10

31 Bauer A, Kofler S, Thiel M, Eifert S, Christ F. Monitoring of the sublingual microcirculation in cardiac surgery using orthogonal polarization spectral imaging: preliminary results. *Anesthesiology* 2007; **107**: 939–45

Appendix 1

plasma volume
plasma volume assessment
plasma volume measurement
plasma volume and methods
blood volume assessment
blood volume measurement
blood volume and methods
cardiac output
cardiac output monitor
stroke volume
stroke volume variation
pulse pressure variation
Doppler
bioimpedance
bioreactance
lithium dilution
carbon dioxide indicator
thermodilution
picco
transesophageal
transesophageal echo
echocardiogram
pulse contour
fick principle
non-invasive
hemodynamic monitor
indocyanine green
labeled albumin
radioisotopes
hematocrit dilution
fluorescein
fluid and volume effects
microcirculation
circulation
vascular
vascular health
regional blood flow
organ blood flow
renal function
capillary blood flow
tissue perfusion
cellular function
cellular oxygenation
diagnostic
imaging

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