Experience teaches that to place reliance upon a single sign is precarious. Compare this sign and that, and confident recognition of the patient’s state grows as these signs group themselves together to form a harmonious picture.

Sir Thomas Lewis

One of the biggest critical care challenges is a septic patient with massive apparent fluid losses. The losses result from increased capillary permeability and third space sequestration, confounded by reduced vascular tone mediated through induced nitric oxide production, which might be associated with myocardial dysfunction. These changes lead to a fall in cardiac output and profound hypotension, which result in poor organ perfusion, multiple organ failure and death. It would probably come as a surprise to most scientists, therefore, that, whereas clinicians have good techniques for measuring cardiac output, there are no easily undertaken bedside methods for measuring total circulating blood volume.

Circulating volume is a major determinant of cardiac output and it has been the response of the latter to fluid challenges that provides us with proxy assessments of circulating volume. Furthermore, it has been the achievement of good cardiac output rather than circulating volume which has consistently been related to better outcomes.

Given the complex cause of changes in volume, blood pressure and cardiac output in sepsis, how should they be restored? Start by providing large quantities of intravenous fluid (6–10 litres of crystalloid or 2–4 litres of colloid) in order to obtain a blood pressure and a hyperdynamic state. The type of fluid probably does not matter, but colloids tend to be less likely to cause pulmonary oedema at higher filling pressures. Once volume resuscitation is ‘complete’, organ perfusion should be restored by increasing blood pressure to pre-morbid values with vasoconstrictors, because organ autoregulation is lost and perfusion becomes pressure dependent. Norepinephrine on a full circulation seems to be in favour if dopamine is ineffective or has caused side-effects. The resulting improved global circulatory state should provide a sustainable cardiac output for adequate organ function while specific therapies such as timely surgery and antibiotics prevent further insult.

What about the effect of all that fluid on systemic oedema and tissue oxygenation? Systemic oedema is an inevitable late development that follows fluid loading in patients with disturbed tissue permeability. It should not be a distraction to the prime target of achieving a full circulation. Furthermore, the effect of tissue oedema on tissue oxygenation is not necessarily deleterious.

What about haemodynamic targets and monitoring? Use clinical end-points of perfusion in the first instance and insert an arterial line. If cardiac output is low, some measurement of pre-load and cardiac output is appropriate to guide inotrope requirements and avoid cardiac overload.

The foregoing guide sounds simple and should sound familiar. These are some of the latest evidence-based recommendations of the American College of Critical Care Medicine (ACCM) for the treatment of septic shock.

The paper by Stephan and colleagues in this issue therefore comes as a timely reminder that clinical assessment of circulating volume as a first aim to adequate cardiac output in an individual still has a role. But how can we seamlessly merge clinical art form and scientific measurement?

The importance of generous volume replenishment in septic shock was first seriously promoted by William Shoemaker and colleagues. Shoemaker’s approach at the time was brave considering that most intensivists were focused on drying patients to improve $P_{aO_2}$ in order to reduce $F_{IO_2}$ to <0.6. Now most would agree that Shoemaker was right. However, when he suggested numerical haemodynamic targets that were subsequently applied prospectively in controlled studies the results were ambiguous.

Where patients did badly the proponents of goal-directed...
therapy suggested that the targets had been achieved with far too much use of inotropes. Unwittingly, the proponents had struck on the real problem, namely that the targets were population based rather than individually tailored, leading to some patients being driven with inotropes (possibly with insufficient volume) beyond their normal physiological limit. A recent study confirms the importance of physiological reserve for outcome.23

The effect of these studies was to tilt the emphasis towards volume resuscitation and to use inotropes to achieve pre-morbid blood pressure rather than specific oxygen transport targets. Then a spanner was thrown in the works when Connors and colleagues demonstrated that patient management guided by pulmonary artery flotation catheter, the current tool for guiding volume replacement, was associated with a poorer outcome.24 At the time it was thought unlikely that this was due to complications of catheter placement,25 which are relatively low,26 27 but was more related to the way in which the information it provided was used.28–31 So, paradoxically, after having been told that our clinical ability to assess haemodynamics is poor,32 33 it seems that clinicians without the flotation catheter get better results.24 Perhaps it is no longer time to ask what is the cardiac output but rather, is cardiac output effective?

How can we define an effective cardiac output (ECO)? The great Paul Wood, doyen of circulatory clinical assessment, firmly established the value of applying Ohm’s law to bedside assessment and physiological measurement.34 Blood pressure, which is directly related to the product of cardiac output and systemic vascular resistance, if compromised by fluid loss, stimulates sophisticated neuroendocrine compensatory activity. When acute this activity is revealed through clinical signs such as vasoconstriction, tachycardia and sodium retention (oliguria) in order to restore an effective cardiac output and, consequently, blood pressure. Chronic forms of compensated ineffective cardiac output are well recognized in conditions such as cirrhosis, nephrosis and chronic congestive cardiac failure where a sustained state of fluid retention and neuroendocrine activity coexists with a constant risk of organ failure at any further change in circulating volume status.35

An effective cardiac output, on the other hand, should have little need for compensatory mechanisms and individuals should be able to simultaneously have toes that are warm to the touch, and sustain their normal blood pressure preferably with a heart rate below 100 beats min−1.36 37 The absolute cardiac output is irrelevant in such circumstances. In the context of critical illness, a reasonable aim for an individual would be to achieve these same clinical end-points with some combination of fluids, vasoactive agent and inotrope. The advantage of clinical end-points for global perfusion is that they remain the same regardless of the phase of illness. The ACCM recommends additional end-points such as urine output and cerebral function; these could be included in a definition of ECO but may be unrelated to global perfusion due to previous established damage. Inevitably, clinical assessment is likely to vary with observer experience and therefore should be used with markers of improving cellular respiration. Furthermore, some patients, particularly those with poor cardiac function, may never reach these end-points; this is perhaps an omen of the likely outcome.

Do clinical end-points mean we can safely abandon all physiological measurement? Almost certainly not.16 Measurements complement clinical assessment but do not replace it. They sometimes provide immediate diagnostic information, can provide confidence to undertake fluid challenges and help monitor trends towards the clinical target. Most significantly, measurement provides us with a language for information exchange. Whereas pulmonary artery catheter data may have been criticised for being poorly acquired, badly used or misleading,38 alternative techniques have not yet been so tainted. Modern continuous methods such as oesophageal Doppler19 40 and thermodilution-calibrated arterial pulse wave contour cardiac output41 are widely used. These techniques might not confirm warm feet from their derived calculations but, when combined with clinical examination, might provide an appropriate numeric target for planning management during that specific phase of the illness.

Improved global perfusion should be associated with improving cellular metabolism. In spite of some well known problems such as lead time bias42 43 and lack of specificity, indicators such as mixed venous oxygen saturation, acid–base balance and blood lactate are widely accepted as measures of anaerobic metabolism.16 Progressive acidosis in spite of adequate global perfusion is suggestive of concealed regional ischaemia such as ischaemic hepatitis or bowel infarction. These conditions easily overwhelm buffering capacity and are rarely reversible by further increases in cardiac output. Perhaps the most successful tool for regional perfusion has been gastrointestinal tonometry,44 which with hepatic venous flow and saturation changes45–47 might find a niche for monitoring intestinal ischaemia particularly following vasoconstrictor therapy.

So where does the work of Stephan and colleagues17 fit in? They have attempted to correlate clinical indicators—four markers of fluid overload and three suggestive of volume loss—with measurements of absolute circulating blood volume. They carefully selected stable critically ill patients to minimize confounding variables and defined hypovolaemia as a 10% deviation from expected calculated values for normal circulating blood volume. Their study concluded that a score based on clinical indicators of extracellular volume status reasonably predicted measured circulating hypovolaemia when that loss was approximately 1 litre. The study might be criticised for having some overlap in clinical indicators, using a nomogram as the control for circulating volume or possibly for assuming that a stable vascular compliance allows one to equate absolute circulating volume with effective circulating volume.
However, the message is clear: clinical assessment can be reasonably used to indicate volume status.

So might now be the time to apply a similar methodology to assessment of effective cardiac output? A daring start might be to break with tradition and assume this time that physical signs are the gold standard for an individual, and make the measurements in the presence and absence of signs. The volume and inotrope requirements to return to ECO might provide interesting and relevant information, particularly as we embark on outreach critical care.

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