

## Commentary

# Shockingly complex: the difficult road to introducing new ideas to critical care

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### Abstract

Resuscitation of critically ill patients with trauma or sepsis continues to challenge clinicians. Early imperatives include diagnostic judgment as to the presenting problem – sepsis or trauma. Subsequently, the clinician decides on the phase of resuscitation required for support – ‘ebb’ versus ‘flow’. Finally, the clinician needs to determine what therapeutic strategies to employ and then judge when resuscitation is complete. Shortcomings of current approaches to determining the adequacy of circulatory resuscitation have prompted the evaluation of new technologies purported to directly assess microcirculatory flow as a clinical endpoint for the adequacy of resuscitation. While early studies are intriguing, this technology requires much more study before it can be considered for widespread adoption by the clinician.

**Keywords** circulatory resuscitation, microcirculatory, resuscitation, sepsis, therapeutic strategies

In their review, Spronk and colleagues [1] address some of the very real dilemmas faced by clinicians during the resuscitation of critically ill patients with trauma or sepsis. Having made a diagnostic judgment as to the presenting problem – sepsis or trauma – the clinician must next decide on the phase of resuscitation that the patient is in – ‘flow’ phase versus ‘ebb’ phase [2]. Finally, the clinician must determine what therapeutic strategies to employ and judge when resuscitation is complete. In this commentary I take the clinician’s perspective in attempting to translate what we have learned from many years of preclinical study. Additionally, I identify areas where evidence remains elusive, and therefore where the clinician’s judgment, incorporating ‘the art of medicine’, must dominate the treatment plan.

The clinician must first determine whether they are dealing simply with the resuscitation of a traumatized patient in whom, in the absence of direct cardiac injury, the prevailing pathophysiologic disease mechanism is intravascular volume loss. Alternatively, are they dealing with the more complex problem of a patient with the sepsis/systemic inflammatory

response syndrome (SIRS) continuum, in which dysregulation of tissue oxygen delivery occurs because of abnormalities at all three levels of the circulation: the cardiac output, the distribution of blood flow, and blood flow distribution within organs [3]. In the former situation, resuscitation must include early diagnostic strategies that identify the cause of intravascular volume loss. For the latter, resuscitation must include strategies that identify whether the patient is infected (is it sepsis or SIRS?), and if the patient is infected then where. Debating the adequacy of and novel approaches to resuscitation in either trauma or sepsis is a moot exercise if the clinician fails to remember that source control must occur in parallel with resuscitation. Unfortunately, there remain examples in the clinical literature of patients being committed to the study of novel treatment approaches while the underlying cause of the problem remained untreated [4].

For the critical care basic scientist, there remain elusive issues about the underlying pathophysiology of these diseases, especially sepsis. An understanding of the

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SIRS = systemic inflammatory response syndrome.

mechanism of multiple organ dysfunction in sepsis (and in SIRS) could be critical to determining ancillary therapeutic approaches that could improve intensive care unit related outcomes from this syndrome. As Spronk and coworkers note [1], animal studies have taught us that impaired microcirculatory perfusion is a crucial finding in many organs in sepsis [5,6]. In addition, although a primary cause remains unknown, Spronk and colleagues summarize many possible reasons for reported derangements in microcirculatory flow in sepsis, including abnormal leukocyte–endothelial interactions, impaired deformability of red cells, alterations in viscosity and increases in microvascular permeability leading to tissue edema. The presumed pathway to organ dysfunction in this scenario would be ischemic tissue injury complicating an imbalance between tissue oxygen needs and microvascular oxygen delivery – so-called ‘circulatory’ hypoxia [7]. What we do not know yet is whether therapy directed at any or all of these problems would either improve microvascular flow or, even if flow were to be improved, whether improved clinical outcomes would result [8]. In fact, it was the observation that cell injury and death could occur in septic animal models with normal microvascular perfusion that led us to conclude that other causes of multiple organ dysfunction in sepsis warrant consideration [9]. Other investigators came to the same conclusion through different lines of reasoning, thus leading to the hypothesis that mitochondrial dysfunction leading to cell injury could occur in sepsis, independent of alterations and microvascular flow – referred to as ‘cytopathic’ hypoxia [7,10].

Whether it be trauma or sepsis, ‘ebb’ phase resuscitation (in which the goal is restoration of perfusion pressures) takes precedence over all else, and includes the ‘ABCs’ of resuscitation [11]. In this phase, the clinician’s tools to achieve completeness of resuscitation of the circulation are probably adequate, namely monitoring the arterial pressure to ensure it is restoration to pre-injury levels (thus consistent with ensuring core organ perfusion monitored by changes in sensorium and urine output). The clinical challenge is whether circulatory resuscitation is ‘adequate’ – a question that defines what has been referred to as ‘flow’ phase resuscitation. Here, Spronk and coworkers [1] noted the clinician has a few diagnostic tools available including arterial lactates, mixed venous oxygen saturation and tonometric partial pressures of carbon dioxide – tools with reported strengths and weaknesses. It is because of the perceived shortcomings of current diagnostic technologies for assessing the adequacy of ‘flow’ phase resuscitation that Spronk and colleagues raised the intriguing possibility direct measurement of microcirculatory flow might be a clinical end-point for resuscitation. As an unabashed advocate of the crucial role of microcirculation in critical illness, I am intrigued by this possibility, but remind the reader there are a number of questions that must be addressed in the evaluation this new technology.

In previous work [12,13] we discussed the phases of evaluation that new technologies need to go through before they can be considered for routine use; this is even more important in today’s environment. With regard to the hypothesis that microcirculatory perfusion should be measured as an end-point of resuscitation, we suggest that further preclinical studies, in acceptable animal models conducted with the same rigor as clinical trials demand, must be carried out to determine whether measurement of microcirculatory flow is an acceptable surrogate of cellular oxygen availability, and whether restoration of microcirculatory perfusion in septic animal models improves an outcome that could be considered a surrogate of a clinical end-point. Furthermore, these studies must establish what quantitative measure of microvascular perfusion (e.g. perfused vascular density, total blood flow) is adequate for use as a resuscitation end-point. Finally, translated to the bedside, does the application of therapies demonstrated to improve microcirculatory flow in preclinical studies, conducted in appropriate animal models and monitored by changes in directly measured microcirculatory flow, lead to improve outcomes?

Spronk and colleagues have begun an important dialogue regarding the use of exciting new technologies with the potential to improve the clinician’s ability to monitor adequacy of ‘flow’ phase resuscitation. For advocates of the introduction of new diagnostic technology to the critical care setting, the road to widespread clinical acceptance is challenging but needs to have a beginning. In the nonhealth sector, this direction begins with development of a business case and careful implementation of its various steps, with the courage to challenge assumptions critically with focused study. The real challenge for colleagues who wish to introduce diagnostic technologies to the critical care setting is to ensure that their business case is sufficiently funded for the long trip to adoption, which we believe has been the reason why other technologies have not reached their full clinical potential.

## Competing interests

The author(s) declare that they have no competing interests.

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