Commentary

Recently published papers: New evidence for old debates, new drugs and some timely reminders

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The present article provides a brief synopsis from the past 2 month's critical care literature.

Sepsis

There has been a longstanding debate in the fields of sepsis and multiple organ dysfunction syndrome regarding the relative importance of microcirculatory failure versus mitochondrial failure. This debate stems from the observation that in the presence of supranormal oxygen delivery there is frequently a failure to achieve normal levels of consumption, and there is an association between the magnitude of this discrepancy and outcome. Accordingly, measures of global oxygen consumption, such as mixed (or central) venous oxygen saturations, plasma lactate and base deficit, are widely considered the best markers of the adequacy of resuscitation.

Using a novel method of intravital microscopy of the sublingual mucosa, de Backer and colleagues have demonstrated that microcirculatory perfusion is reduced by ~50% despite normal global haemodynamic parameters, and that shunting by larger vessels is commonplace [1]. This confirms previous animal and tissue studies, and despite the excellent pictures (see http://ajrccm.atsjournals.org/cgi/content/full/166/1/16/DC1) is unsurprising. Of note, the authors found that the degree of severity correlated with the outcome. What is remarkable, however, is the demonstration, using this intravital microscopy technique of the preservation of local vascular responsiveness to the vasodilatory mediator acetylcholine, and indeed the restoration of local microcirculatory function achieved by its administration. Whether this reflects a local imbalance between vasoconstrictors and dilators remains speculative but, of note, 18 of the 21 patients were receiving exogenous catecholamine vasopressors to maintain a target mean arterial pressure.

Enthusiastic conclusions were drawn regarding the utility of this intravital microscopy technique in an accompanying editorial [2], and a proposal was made that semiquantitative measures of the sublingual microcirculation be added to the goals of the adequacy of resuscitation. Intravital holds considerable promise as a research tool but, like gastric tonometry, its universal application appears to lack foundation, for the present at least.

In a complementary study, Brealey and colleagues report on their investigations of mitochondrial function in the muscles of patients with severe sepsis [3]. They found convincing evidence of mitochondrial failure and found a strong correlation between the degree of failure and adverse outcome.

What these two studies [1,3] demonstrate is that both the microcirculatory failure and the mitochondrial failure are important pathophysiological processes in sepsis, and indeed it seems probable that the former precipitates the latter. What makes both of these studies noteworthy is that they represent some of the most eloquent demonstrations of these processes in critically ill patients to date. Let us hope that ongoing research identifies successful strategies to modify these processes. One such strategy may be the potentiation of the paracrine messenger adenosine [4], although previous successes in mice have all too often failed to translate to humans.

Similarly, extrapolating the observation that a low serum granulocyte–macrophage colony-stimulating factor is prognostic of a poor outcome in sepsis [5] to the efficacy of exogenous supplementation [6] is an oft trodden path with a poor track record.

FEV_1 = forced expiratory volume in 1 second; NIPPV = face mask positive pressure ventilation.

Finally, the keenly awaited French 'steroid replacement' trial in sepsis has been published [7]. The first important finding was a very high incidence of adrenal insufficiency in 229 of the 299 patients (77%) studied, albeit that interpreting corticotrophin studies in such patients is controversial. Interestingly, corticotrophin responsiveness did not predict outcome. Intensive care unit, hospital, 28-day and 1-year mortality were very high in all groups (53–77%). In the responder groups, randomisation to the treatment group conferred no benefit. In the nonresponders, treatment conferred a statistically significant survival advantage to 28 days that persisted but ceased to be significant at 1 year (although the study was not powered to test 12-month mortality). There were no detectable adverse events associated with treatment. The regimen of intravenous hydrocortisone (50 mg, 6 hourly) plus daily enteral fluorocortisone (50 μg) is arguably too high, and no doubt future studies will address this. Annane *et al*. conclude by advocating universal corticotrophin testing followed by treatment, which should be withdrawn in responders.

Cardiac failure

There has been growing interest in the natriuretic peptides for sometime. July saw the publication of a paper by Maisel *et al*. demonstrating the diagnostic potential of a bedside assay for B-type natriuretic peptide in the differential diagnosis of acute dyspnoea [8]. That study and two studies from last year [9,10] suggest that levels of these peptides correlate with the severity of cardiac failure but, as with troponins as markers of myocardial damage, caution in the interpretation of results is likely to be required [11].

On the subject of troponin, it is encouraging to find a little light being shed on the difficulties of its meaningful interpretation. It has been observed that troponin levels are elevated in the presence of renal impairment, making interpretation and therefore diagnosis of acute coronary syndromes difficult in the critically ill. To investigate this, Aviles *et al*. [12] studied whether troponin T levels were predictive of outcome, a composite of death and myocardial infarction within 30 days, in a large cohort of patients ($n = 7033$) with suspected acute coronary syndrome and both normal and reduced creatinine clearance. After adjustment for potential confounding factors, an abnormally elevated troponin T level (>0.1 ng/ml) was found to be predictive of myocardial infarction or death regardless of renal function.

It is sobering to be reminded that the use of inodilators in the treatment of acute cardiac failure has never undergone a large-scale, randomised, controlled trial. However, with the advent of the novel calcium-sensitising agent levosimendan, one such trial has now been reported [13]. This trial randomised 2003 patients with acute or acute on chronic heart failure to receive 24 hours of either dobutamine or levosimendan. A higher proportion of those patients who received levosimendan (29% versus 15%) achieved target improvements in haemodynamic parameters. More impressively, a lower proportion of these patients died over the following 6 months (26% versus 38%). Although cardiogenic shock and multiorgan failure were exclusion criteria in this trial, it surely provides evidence to justify similar studies in critically ill patients with low cardiac output.

On a related point, a thought-provoking if methodologically suboptimal study of the significant association between the administration of dopamine and the incidence of delirium [14] will hopefully result in a more thorough examination of the neuropsychiatric sequelae of all the commonly used doperminergic drugs.

On a final cardiac note, the encouraging results of a trial of ibutilide as second-line therapy in the treatment of atrial fibrillation in the critically ill [15] suggests that this novel class III anti-arrhythmic may provide a much needed treatment for this common condition, which all too often proves difficult to control.

Respiratory

Attention to simple details is as important, if not more, than complex and novel interventions. A semirecumbant or upright posture has been repeatedly demonstrated to result in superior respiratory and overall outcome. Despite these demonstrations, however, the implementation of this intervention appears to be poor. Cook and colleagues have published a timely survey on this issue [16]. They conclude that a classic case of system failure exists with regard to patient positioning, and they suggest a number of useful strategies to overcome this and similar problems.

At the other extreme of patient positioning, the study by Lee *et al*. [17] suggests that instigating the prone position early in the course of acute lung injury to patients with a larger shunt and a more compliant chest wall predicts success. Their study contributes further confirmatory evidence of the clinical benefit of prone positioning but does nothing to answer the vital questions regarding how long patients should be in the prone position for maximum benefit, and indeed whether improving gas exchange translates into better outcomes.

Against the advancing wave of enthusiasm for face mask positive pressure ventilation (NIPPV), a significant negative study has been published [18]. The authors randomised a heterogeneous group of patients who developed respiratory distress within 48 hours of extubation to receive standard therapy or standard therapy plus NIPPV. They found no benefit from this intervention. To their credit, the authors acknowledge that more experienced units or targeting specific patient groups might have achieved a positive outcome, but they conclude that they cannot recommend NIPPV as an intervention in this setting. We would argue from both personal experience and trial evidence that NIPPV

in this setting can prevent the need to reintubate, and that a trial of NIPPV is sometimes warranted, not least as a failed trial is unlikely to harm the patient.

Ventilator-associated pneumonia remains a major cause of morbidity and mortality. The optimal diagnostic technique is controversial, with some studies suggesting that invasive methods improve outcome while others have been unable to demonstrate any benefit from these expensive and time-consuming investigations. To further this debate, Wu and colleagues have compared quantitative culture of endotracheal aspirates, protected specimen brushings and bronchoalveolar lavage to investigate whether bacteriological findings correlated in patients with suspected ventilator-associated pneumonia [19]. They demonstrated that the less invasive and less work-intensive technique of quantitative culture of endotracheal aspirates correlated well with both protected specimen brushings and bronchoalveolar lavage findings, allowing early definitive antibiotic choice or cessation of antibiotics in the case of negative results. Criticism of their investigation might include the small study number and lack of any outcome benefit demonstrated, although this was not the aim of the study. However, a significant impediment to this approach is the inability to obtain routine quantitative cultures in many hospitals. With mounting evidence in favour of quantitative assessment of specimens, this problem may need addressing.

Magnesium is known to be a bronchodilator and has been anecdotally reported as having beneficial effects in acute severe asthma. However, these findings have not been consistently reproduced in well designed, randomised, controlled trials. In a welcome attempt to address this issue, Silverman and colleagues [20] have conducted such a trial and found that the addition of intravenous magnesium to standard therapy resulted in a significant improvement in FEV_1, at 4 hours, in those with the most severe airway obstruction (baseline $FEV_1 < 25\%$ predicted). Given that magnesium is safe and inexpensive, and that there is now good evidence to support its routine use in the severest cases, it only remains for the optimal dose and duration of therapy to be established.

Other noteworthy papers

Nasogastric feeding is found to be at least as good as, if not better than, nasojejunal feeding in the hands of Neumann and DeLegge [21], essentially because nasojejunal tube placement results in a significant delay in the start of feeding. Surely the pragmatic approach is to start with a nasogastric tube and to only employ the alternatives in cases of failure.

The long-term success of renal allografts from nonheart-beating donors is reported by Weber and colleagues [22]. Sadly, adoption of this technique, in the UK at least, awaits the deliberation of the government and judiciary.

Finally, if you have been seduced by the attractive qualities of alcohol-based hand rubs to reduce crossinfection while avoiding hand washing, then be warned: your gel may not be all its cracked up to be [23,24].

In addition to the aforementioned studies, we would also recommend the following commentaries and reviews [25–28].

Competing interests

None declared.

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