Commentary

Recently published papers: Treating sepsis, measuring troponin and managing the obese

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Abstract

Sepsis and septic shock continue to contribute to our workload and stimulate our research activities although many fundamental questions remain. Studies reported on here focus on inotrope use and a novel way of predicting inotrope response. Continuing this theme more fundamental work is reported examining the mitochondrial respiratory chain and the effects of sepsis coupled with interesting work on lactic acidosis. Troponin raises its head again and we are still left quizzing over its value in the ICU. Finally we discuss a paper on the outcome of the obese patient on a general ICU. Like sepsis a continuing challenge.

Medicine is the only profession that labours incessantly to destroy the reason for its own existence.

James Bryce (1914)

Choosing the inotrope

Sepsis and septic shock in the intensive care unit (ICU) still contribute significantly to our workload and, unfortunately, account for significant mortality. Consequently, they continue to provide much interest in the literature as our understanding of the processes involved become ever more complex. An interesting physiological short term study performed by Albanese and colleagues [1] addresses a far more basic aspect to the treatment of septic shock: that is, the choice of inotrope. In 20 patients, the vasopressors terlipressin and norepinephrine were compared. The aim of this study was to compare the two inotropes given the known undesirable effects of norepinephrine and the observed diminished vasoreactivity to catecholamines in sepsis [2]. Patients were recruited if they had a mean arterial pressure (MAP) <60 mmHg, two or more organ dysfunctions and fulfilled criteria for septic shock. Norepinephrine was given at a predetermined incremental rate whereas those randomised to terlipressin were given a bolus (1 mg). The main findings (well presented in the discussion) were that both agents effectively increased MAP and improved renal function. Terlipressin resulted in a decrease in heart rate and cardiac index but no change in stroke volume index. Oxygen delivery and consumption index were also decreased with terlipressin. This observation was probably a reflection of decreased chronotropic drive with terlipressin. Is this important? Given the small sample size, no firm conclusions can be made, although the lack of detrimental effect on oxygen delivery suggests not. One wonders if the use of terlipressin may soon become commonplace in this interesting but difficult group of patients. On the same theme, Levy and colleagues from France report an interesting and rather brave study in septic shock [3]. In this prospective study, 110 patients with septic shock as a presumptive initial diagnosis were treated, following adequate volume resuscitation, with an incremental dopamine 'challenge'. An initial dose of 10 μg/kg/minute was employed for 10 minutes and increased to 15 μg/kg/minute after 10 minutes followed by a further increase to 20 μg/kg/minute; the aim was a MAP of 70 mmHg. 'Dopamine responders' were defined by an increase of >15% of cardiac output after vascular loading. Those deemed resistant were treated with alternative agents. Overall mortality was approximately 54% (similar to that in the report by Albanese *et al.*). Risk of death was associated with the usual suspects, including simplified acute physiology score (SAPS II), sepsis-related organ failure assessment (SOFA), MAP <60 mmHg, increased lactate and, surprisingly, the use of hydrocortisone, although as the authors point out this study was performed before low-dose steroid recommendations were applied. They did observe, however, a rather dramatic difference in the groups. Those deemed 'responders' had an overall mortality of 16% whereas those deemed 'non-responders' had a mortality of 78%. Granted, the study is open to some minor criticisms (mainly some differences in the baseline characteristics of the two groups as well as non-standardisation of volume

AMI = acute myocardial infarction; ICU = intensive care unit; MAP = mean arterial pressure.

resuscitation) but it does open some interesting doors. It would seem intuitive that patients who respond to treatment quickly may have better outcomes and it is well established that catecholamine resistance is associated with a bleak prognosis [4]. This study, however, provides a rapid means by which the overall outlook of a patient can be assessed quickly. What we do with these data is somewhat more difficult. The mortality in the non-responders was 78% and not 100%. They may, therefore, identify individuals who could benefit from aggressive escalation of other aspects of our armoury. They may also provide us with useful information with which to discuss possible outcomes with relatives. We await the first paper on terlipressin responsiveness with interest!

Sepsis and mitochondria

From treatment of sepsis we turn to more fundamental questions. Much attention has focused recently on microcirculatory and mitochondrial dysfunction in sepsis [5] and a study reported in the *American Journal of Respiratory Critical Care Medicine* expands our knowledge further [6]. Employing an endotoxin mediated rodent model of sepsis, the authors examined changes in mitochondrial protein expression and mitochondrial function. Mitochondria were isolated from the diaphragm following endotoxin administration, which resulted in a marked reduction (approximately 50%) in mitochondrial oxygen consumption. Moreover, reductions in NADH oxidase activity and uncoupled respiration were seen. Uniquely, the authors also demonstrated a significant depletion in the protein subunits of complex I, III, IV and V, most of which are iron-sulphur cluster containing. The implication is, therefore, that specific proteins integrally involved in electron transport are selectively depleted, resulting, presumably, in impaired mitochondrial function and hence ATP production. As the authors point out, an important goal for further studies will be to try and elucidate the exact biochemical processes responsible for this observation. We may achieve the sepsis magic bullet after all. Associated with a potential derangement in mitochondrial function is the process, well known among intensivists, of lactic acidosis. Revelly and colleagues [7] provide us with some new insights into this process. Patients with either septic shock or cardiogenic shock were infused with ^{13}C-labelled sodium lactate; lactate clearance and metabolism were compared to those in normal individuals. The conclusions, in keeping with other work, suggest that lactate clearance is similar in all groups and that hyperlactaemia relates to increased production [8]. The observed hyperlactaemia seemed to be related to increased glucose turnover. This provides further evidence for the theory that lactic acid *per se* is not responsible for the acidosis but is a marker of enhanced glycolysis. The initial step of proton production, namely hydrolysis of fructose 1,6 diphosphate, occurs but the 'normal' process of proton elimination through conversion to the weak acid with the volatile anhydride (i.e. carbonic acid) does not. This results in the ensuing acidosis. No doubt this debate will continue to run and run.

Yet more on troponin

We all recognise the poor cardiac performance seen in sepsis and the introduction of the measurement of serum troponin I seemed to offer us a definitive answer to this conundrum. Since those heady days of nearly 20 years ago thousands of papers have been published on the use, abuse and misuse of this test. The problem with any investigation is the interpretation and nowhere is this more so than in the ICU where elevated troponin concentrations have been observed in up to a third of admissions [9]. Increasingly, elevations in troponin are recognised as a prognostic indicator in the absence of myocardial infarction and the study by Quenot *et al*. [10] addresses the role of troponin as an independent prognostic indicator in the ICU rather than a diagnostic test. They examined all medical admissions over a six month period excluding all with electrocardiographic changes or symptoms of an acute myocardial infarction (AMI), those who had received cardiac massage and patients with significant systolic dysfunction (ejection fraction <50% on echocardiography). Of the 217 patients included, 69 (32%) had raised troponin I levels. This group were older, had higher SAPS II scores and had a higher incidence of mechanical ventilation. Multivariate analysis seemed to support the view that raised troponin was indeed a marker of poor outcome as defined by in-hospital mortality. How this relates to practice is difficult to assess. Lim *et al*. [11] adopted a thoughtful approach to the troponin/infarction debate. They performed a prospective cohort study on all patients admitted to a single unit over a two month period. Where AMI was suspected, all electrocardiographs (ECGs), troponin levels and echocardiographic results for these patients were collected. Evidence of myocardial infarction was based on standard guidelines plus either a rise or fall in troponin T and any regional wall abnormality demonstrated on echocardiography. Of 115 pateints selected, 81% had both ECGs and troponin levels determined at least once: 24 of these were deemed to have had an AMI as defined by their own criteria. These patients had, unsurprisingly, a poorer outcome. In a very honest discussion, the authors acknowledge the limitations of their study while highlighting the important questions that warrant further thought. Firstly, that diagnosis of AMI with the current guidelines is difficult in a critical care setting as they are designed for a non-ICU population. Their unilateral amendments to the diagnostic criteria certainly need to be refined to be of use, but are a welcome step in the right direction. Secondly, diagnosing an AMI is essential as conventional treatments may provide huge morbidity and mortality benefits, whereas the same treatments in patients with non-ischaemic rises in troponin may be disastrous. Finally, they argue strongly for clinicians to think before requesting a troponin test and to ensure that the other criteria for AMI are at least being looked for. A troponin test has no chance of being interpretable if it has no accompanying ECG. The questions that need to be answered as regards positive troponin tests in the ICU

setting have been succinctly summarised [12]. It is important to differentiate between thrombotic acute coronary syndromes and other causes of troponin elevation wherever possible, as the management and prognosis may be so different for the two subsets. Once again, the question of what to do even if it is a true acute coronary syndrome is not yet known – conventional treatments for AMI have yet to be fully evaluated in the context of the critically ill patient. For the moment, we should be giving ourselves a chance to make the diagnosis by correlating the troponin test with other tests – certainly the ECG – in all patients.

Treating the obese in ICU

A subject rarely out of the popular press these days is that of the obesity epidemic and it is somewhat staggering that in 1998, 55% of the adult North American population were deemed as being overweight or obese [13]. Increasingly, this patient population finds its way to the ICU and practicing clinicians are often concerned with regard to the special problems these patients present. The underlying ventilation-perfusion mismatch causing hypoxia is well known as are the difficulties associated with mechanical ventilation, weaning and the risk of ventilator associated pneumonia [14,15]. Given this knowledge, perhaps there is a general feeling that the obese, and particularly the morbidly obese, fare badly in the intensive care setting. The prospective study by Ray *et al*. [16] examined 2,148 patients admitted to a 9 bed general ICU/high dependency unit and classified patients into groups based on the calculated body mass index. This study provides some interesting insights into this issue. This cohort accounted for 76% of admissions over the study period of 44 months. Groups were compared by age, APACHE II score, mortality, ICU length of stay, need for ventilation and length of ventilation. The significant finding was that the morbidly obese (body mass index >40) were more frequently female and younger. Adverse events included evidence of infection, problems with intubation, haemorrhage, prolonged paralysis, deep vein thrombosis or pneumothorax and showed no statistical significance. These were expressed on a per-patient basis as opposed to a per-procedure basis, which may obscure a true difference in rates. Also of note is that only 50% of the patients required mechanical ventilation, the area of most concern in obese patients. An interesting observation was that the severely obese were female and younger, although the age difference was only present in those surviving to hospital discharge, confirming one prejudice at least. The overall findings are interesting in that this study did not demonstrate any significant problems in the obese over and above those for the rest of the population. We were slightly confused, however, with the conclusion that "studies using larger populations were needed to confirm these observations"!

Competing interests

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

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