

## Commentary

# Recently published papers: Changing bandwagons, innovations and questioning dogma

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Published: 22 June 2009

This article is online at <http://ccforum.com/content/13/3/157>

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*Critical Care* 2009, **13**:157 (doi:10.1186/cc7897)

### Abstract

This issue's Recently published papers commentary considers the popular and muddy waters of glycaemic control, stops briefly to ponder the incidence of pulmonary embolus in acute exacerbations of chronic obstructive pulmonary disease, promotes novel studies in the areas of traumatic brain injury and extracorporeal circuits, and rounds off with a potentially dogma-challenging study in cardiac arrest.

### And the answer is ...?

Optimal glycaemic management continues to be the focus of many authors' research efforts, with at least seven noteworthy papers published during the past 2 months. Despite this burgeoning body of work many controversies remain.

The first study to consider is the so-called NICE-SUGAR collaboration between the Canadian, Australian and New Zealand trials groups [1]. An excellent and pragmatic design was employed, and 6,104 patients were recruited and randomized to glycaemic targets of 4.5 to 6.0 mmol/l (80 to 110 mg/dl) or <10.0 mmol/l (<180 mg/dl). An evidence-based feeding guideline was used that favoured enteral nutrition, and glycaemic monitoring was preferentially performed by arterial blood analysis. A myriad of end-points and analyses were performed but the headline result was a statistically significant higher 90-day mortality in the group with the 4.5 to 6.0 mmol/l target (27.5% versus 24.9%), predominantly attributed to cardiovascular causes. The Kaplan-Meier curves show that the groups separate roughly between days 20 and 40. The authors' conclusion rightly stresses that a universal target of 4.5 to 6.0 mmol/l cannot be recommended over the target of <10 mmol/l. However, the explanation for the apparent excess mortality remains highly speculative, with the authors and many commentators focusing on the higher incidence of hypoglycaemia in this group.

To add weight to their argument, the same group added the data from the above trial to all of the other published trials and conducted a meta-analysis [2]. Unsurprisingly, given the patient numbers in the NICE-SUGAR study, that analysis reached the same conclusion.

However, the story doesn't end there. The investigators from Belgium who conducted the original glycaemic control study have reported another study of their tight control protocol, on this occasion in a paediatric population [3]. As with their first trial, the majority (75%) of patients were admitted after cardiac surgery. They recruited 700 patients and demonstrated statistically significant improvements in the protocol group in terms of inflammatory markers, secondary infection rates (29.2% versus 36.8%) and 30-day mortality (2.3% versus 5.1%). The incidence of hypoglycaemia was 24.9% in the protocol group versus 1.5% in the control group. Long-term developmental follow up is planned to investigate possible sequelae.

The explanation for the success of this group's studies remains contentious. The predominance of elective cardiac surgical patients and greater use of parenteral nutrition are often considered, but these lack a clear pathophysiological basis. Perhaps a more important point is the glycaemic target in their control group, which was set at <11.9 mmol/l (<215 mg/dl). Emerging work has suggested that the threshold for glycaemic toxicity may well be in the 8.0 to 12.0 mmol/l (140 to 215 mg/dl) range and may differ between tissues.

Indeed, this group have also just reported a very detailed animal study, further elucidating the pathophysiology of hyperglycaemia in a rabbit model of 7-day critical illness secondary to extensive tissue injury [4]. The study identified a cytopathic and mitochondrial injury that was associated with

HSL = hypertonic sodium lactate.

glucose levels of 13.9 to 19.4 mmol/l (250 to 350 mg/dl), with the liver being the worst affected organ. Myocardium was also severely affected but skeletal muscle was relatively spared. Hyperinsulinaemia in the context of normoglycaemia was of no benefit. Hyperinsulinaemia in the context of hyperglycaemia significantly worsened the mitochondrial and tissue injury observed. Toxic products of glycolysis appear to be responsible for the tissue injury.

Continuing on the glycaemic control theme, Savioli and colleagues [5] investigated the effects of tight control on fibrinolysis and the Sequential Organ Failure Score in patients with severe sepsis or septic shock. This was a small study, recruiting only 90 patients. Thirty-four of the patients were found to have inhibition of fibrinolysis, which was associated with a doubling of 90-day mortality (44% versus 21%). The patients randomized to tight glycaemic control demonstrated minor biochemical and overall score benefits, which manifested only after several days of therapy. Most notable, however, were the average blood glucose levels in the two groups, which were about 8.5 mmol/l (153 mg/dl) versus about 5.8 mmol/l (105 mg/dl). In short, the minimal benefits identified in the tightly controlled group arguably represent the minimal differences in glycaemic control between the groups.

Moving onto a very large observational study (66,184 patients), Bagshaw and colleagues [6] present the results of a database of average blood glucose level during the first 24 hours of ICU admission. They divided patients into quartiles of <5.60 mmol/l (<100 mg/dl), 5.60 to 8.69 mmol/l (100 to 157 mg/dl), 8.69 to 11.79 mmol/l (157 to 121 mg/dl) and >11.79 mmol/l (>212 mg/dl), and they found hospital mortality rates of 17.5%, 13.9%, 20.3% and 24.4%, respectively.

Overall, what does seem to be emerging is that blood glucose levels in the critically ill probably do have an optimal but narrow range, and that perhaps this range is slightly but significantly higher than the 4.5 to 6.0 mmol/l originally described.

Finally, on the subject of glycaemic control is a study looking at iatrogenic hypoglycaemia. One of the purported mechanisms by which tight glycaemic control may confer harm is by the near universal increase in the incidence of hypoglycaemia. As with the emerging case for trying to define the optimal blood glucose range, which probably shifts with patient condition, defining what level and for what duration hypoglycaemia inflicts end organ damage remains undefined. In order to address this question, an American group has reported a study interrogating a clinical database of 7,820 patients admitted with acute myocardial infarction. The database recorded all incidences of hypoglycaemia, defined as blood glucose below 3.3 mmol/l (<60 mg/dl) together with administration of insulin. Patients who had one or more episodes of hypoglycaemia had an in-hospital mortality of 12.7% versus 9.6% in those who did not. However, patients

who received insulin had near identical in-hospital mortality rates (10.4% in the hypoglycaemic group versus 10.2% in the group without hypoglycaemia). In contrast, in the patients who did not receive insulin therapy, the in-hospital mortality associated with hypoglycaemia was 18.4% versus 9.2% in those without. Thus, iatrogenic hypoglycaemia does not appear to be detrimental, whereas spontaneous hypoglycaemia is at least a marker of severity of illness, if not a contributory factor. What this study does not address is the long-term neurocognitive outcome of iatrogenic hypoglycaemia.

### Why so breathless?

To investigate the proportion of acute exacerbations of chronic obstructive pulmonary disease that are due to an acute pulmonary thrombo-embolic event, Rizkallah and colleagues [7] performed a meta-analysis of the available literature. The studies that they identified are heterogeneous and none is without methodological issues, but they found a surprisingly high prevalence rate in hospitalized patients of 24.7% (95% confidence interval 17.9% to 31.4%). They describe that pre-imaging probability models had rarely been used, and in the one study that did the model performed inadequately in this patient population. They demonstrated a trend toward a lower rate of deep vein thrombosis than pulmonary embolism and hypothesize that *in situ* pulmonary thrombosis, rather than embolus, may be a largely unrecognized but significant phenomenon. They conclude that a well designed prospective study is warranted.

### Innovations

Two recently published papers describe novel approaches to common clinical problems.

In an eloquent phase II study, Ichai and colleagues [8] compared the use of hypertonic sodium lactate (HSL) with mannitol for the treatment of intracranial hypertension after severe traumatic brain injury. The trial used a randomized design with rescue crossover. Thirty-four patients were recruited. Those who received HSL, either initially or as rescue therapy, had better short-term physiological outcomes. Five of the 17 who received HSL first required mannitol rescue therapy, as compared with eight of 17 in the mannitol group, who received lactate rescue. One-year Glasgow Outcome Scores were significantly better in the patients who received HSL either as primary or rescue therapy, although the study was too small for this difference to be regarded as reliable. A phase III study of HSL is certainly justified on the basis of the data presented, not least given the burden of death and severe disability after traumatic brain injury and the contradictory trial evidence surrounding all therapies, including mannitol, hypertonic saline, mild therapeutic hypothermia and decompressive craniectomy.

The second thought provoking innovation is reported by Krouzicky and colleagues [9], who present their successful implementation of cooling as a means of achieving effective

anticoagulation in an extracorporeal renal replacement circuit. They took 12 normal pigs and randomized half of them to the cooled circuit and half to 'isothermia'. They used an arteriovenous system at 150 ml/minute with no pre-dilution. In the cooled protocol the arterial side was reduced to 20°C and the venous side re-warmed to 38°C. The cooling technique was very successful in preserving the circuit for 6 hours and had no detrimental effects. Further trials with prolonged exposure should be forthcoming.

### **Primum non nocere**

Finally in this round up, yet another example has emerged of a potentially dogma-busting study. Ristagno and colleagues [10] have investigated the effects of cardiopulmonary resuscitation with and without adrenaline (epinephrine) on cerebral microvascular flow, tissue oxygenation and carbon dioxide tension. In their pig study they investigated four protocols. All groups had ventricular fibrillation induced with no intervention for 3 minutes followed by standard cardiopulmonary resuscitation. Group 1 received a placebo, group 2 received adrenaline, group 3 received adrenaline after pre-treatment with an  $\alpha_1$  and  $\beta$  blocker, whereas group 4 received adrenaline after pre-treatment with an  $\alpha_2$  and  $\beta$  blocker. The cerebral perfusion was adversely affected by the adrenaline. This effect was prevented by  $\alpha_1$  blockade. This study raises many issues, most important of which is whether adrenaline is the right drug to optimize cerebral and cardiac perfusion after cardiac arrest. This is a difficult area to investigate and, despite the many limitations, this study should provoke considerable debate and further studies.

### **Competing interests**

The author declares that they have no competing interests.

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