Review

Year in review 2008: *Critical Care* - metabolism

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Abstract

In 2008, the interest in metabolic and endocrine issues and their consequences in critically ill patients was high. A large proportion of the research papers related to these issues was related to the metabolism of glucose and its control and to the changes in body composition, including muscular weakness. In *Critical Care*, original reports from investigations of glucose physiology and clinical data from observational and interventional studies were published. Important reports of the effects of hormone analogues, such as vasopressin and hydrocortisone, and early antioxidants in selected subpopulations were also available in 2008.

In 2008, interest in endocrine and metabolic disturbances occurring during critical illness was still growing. New clinical and experimental data have been published and some of these provide exciting links between pathophysiological changes to functional outcome variables. This review intends to summarise the new data published in these areas in 2008 in *Critical Care* and elsewhere. The fields covered will include 'Glucose metabolism and control', 'Body composition and muscular weakness' and 'Other interventions'.

Glucose metabolism and control

The physiology of glucose and the effects of glucose control represented major fields of investigation, fuelled by the discrepancy between the results of the pioneering 'Leuven I' study [1] and later reports. In 2008, three major prospective trials of glucose control were published by teams from Colombia [2], Germany [3] and Saudi Arabia [4]. All of these trials were consistently unable to reproduce the benefits reported from the Leuven I study; that is, survival was not increased in patients randomly assigned to tight glucose control by intensive insulin therapy. The discordances between these data and those from the Leuven I study [1] underlie the numerous unanswered issues and the need for pre-clinical and clinical investigations in the field. In *Critical Care* in 2008, we had the privilege of publishing one of the prospective trials [2] and other papers related to the issues of glucose physiology and control in the critically ill, which can be pooled into physiological insights and reports of clinical data.

Physiological insights

As reported in *Critical Care*, in a very detailed investigation of a set of 37 patients scheduled for cardiac surgery, Lehrke and colleagues [5] sought to better understand the determinants of insulin resistance, the major mechanism of stress hyperglycaemia [6,7]. These investigators hypothesised that both inflammatory mediators (the cytokines interleukin-6 [IL-6] and tumour necrosis factor) and hormones (cortisol, resistin, leptin and adiponectin) independently increased the insulin resistance. This hypothesis is appealing as it is based on robust recent evidence [8] from data recorded in obese patients and in inflammatory situations. The resistance to insulin was assessed by both the insulin requirements to maintain 'euglycaemia' and an insulin glycaemic index deduced from the result of the multiplication of blood glucose by the circulating insulin concentration (the sum of exogenous and endogenous insulin). Using a likelihood ratio test, these authors could elegantly show that cortisol was the best predictor of insulin resistance, followed by IL-6, leptin and adiponectin. Daily clinical practice could be influenced in the future as these data can serve to identify additional risk factors for the development of insulin resistance, namely before surgery is scheduled [9].

Another interesting physiological approach was published last year by Otto and colleagues [10]. These investigators sought to discriminate the effects of insulin from those of hyperglycaemia in a cell culture system of human polymorphonuclear cells stimulated with a low dose of lipopolysaccharide. The outcome variable recorded included the release of IL-1 and IL-6, the phagocytosis activity, the oxidative burst and a flow cytometric analysis. The most salient finding was the induction of IL-6 release after incubation of cells, already with 250 mg/dL of glucose, a concentration that can be found in clinical situations. The release of IL-1 needed higher glucose concentrations and the hyperglycaemia-induced production of both cytokines was partially inhibited by insulin. Both the oxidative burst and the phagocytic activity were decreased by hyperglycaemia and

ICU = intensive care unit; IL = interleukin.

by hyperosmolarity. From a clinical standpoint, these data can be viewed as a partial explanation of the susceptibility of hyperglycaemic patients or poorly controlled diabetics to infections and ischaemia.

Clinical data

Data reported from clinical investigations in *Critical Care* last year can be regarded as either 'observational' or 'interventional'. In the first category, two different teams investigated particular aspects of glucose metabolism during moderately strict glucose control (target blood glucose of 4.4 to 8.0 mmol/L) in selected populations of critically ill patients. The first study was performed in 31 patients with subarachnoid haemorrhage [11]. In these patients, several indices of brain metabolism and damage (glucose, lactate, pyruvate, glycerol and glutamate) were continuously measured by microdialysis, and correlations with the blood glucose levels were followed. Basically, the authors found that the glucose concentration measured in the cerebral tissue was much lower than the plasma concentration. In spite of the low brain glucose levels, there was no evidence of brain energy failure, as the lactate and pyruvate concentrations remained unchanged. However, the glycerol level tended to increase, consistent with cell membrane damage. These important findings in a selected group of patients are consistent with earlier work from Vespa and colleagues [12], who performed a similar study in a broader population of brain-injured patients. The data presented by Schlenk and colleagues [11] are consistent with the recent report of Oddo and colleagues [13], who reported a risk of brain energy deficit (defined by an elevated lactate-to-pyruvate ratio) in a population of 20 brain-injured patients when blood glucose fell to below 6.7 mmol/L. The data presented by Schlenk and colleagues [11] will definitely contribute to the development of recommendations for blood glucose targets in the specific population of 'neurocritical care patients' in whom both hyperglycaemia and hypoglycaemia, even moderate, can induce detrimental effects, as recently reviewed by Bilotta and colleagues [14].

In another setting, but using the same intermediate glucose target, Waeschle and colleagues [15] compared the severity of sepsis with the time course of glycaemia, including the incidence of hyperglycaemia and hypoglycaemia and glucose variability, in a population of 191 patients. This thorough analysis was clearly needed to confirm the long-held belief that the incidences of both hyperglycaemia and hypoglycaemia, and hence glucose variability, increased as a function of the severity of sepsis. Interestingly, the multivariate analysis indicated that the frequency of hypoglycaemia and the amplitude of glucose variability were correlated and represented predictors of poor prognosis. These important findings corroborate other data recorded in septic patients (that is, the association between high glucose variability and poor outcome in septic patients) [16]. The correlation between hypoglycaemia and higher mortality was reported in each of the prospective trials on glucose control [17] and was found as an independent predictor of mortality in a large cohort of critically ill patients [18]. However, this correlation may not imply a direct toxicity of insulin treatment, as recently suggested in patients after myocardial infarction [19].

Two important interventional studies and a detailed analysis of the indices of the quality of glucose control were also published last year in *Critical Care*. The first interventional study [2], performed in Colombia as a single-centre trial in a mixed (medico-surgical) intensive care unit (ICU), was designed to confirm the external validity of the Leuven I study [1]. Twenty-eight-day mortality was the primary outcome variable, and 504 patients were enrolled and randomly assigned to intensive insulin therapy (target of 4.4 to 6.1 mmol/L) versus a 'standard' target of 10.0 to 11.1 mmol/L. Even though there was an overlap between blood glucose achieved in both groups, no advantage in favour of intensive insulin therapy was found. This study, like several other prospective randomised controlled trials [3,4,20,21], including one study in very-low-birth-weight infants [22], was unable to confirm the survival benefit afforded by tight glucose control by intensive insulin therapy reported in the pioneering study [1]. The results of two recent meta-analyses [23,24] indeed show no survival benefit but a fivefold increase in the rate of hypoglycaemia in the patients randomly assigned to intensive insulin therapy. However, these trials should not discourage the intensive care community from searching for improvements in glucose control, possibly using different glucose targets [25]. In this regard, the data provided by Chase and colleagues [26] are of major importance. Using a combined strategy of adaptation of insulin infusion and feeding rates in a cohort of 371 patients, these investigators reported remarkable results in terms of percentage of blood glucose values within the desired range. This represents a major improvement as compared with the previous performance of this centre, assessed in a retrospective cohort of 413 matched patients. Very importantly, this improvement in glucose control was associated with decreased hospital mortality in patients who stayed in the ICU for more than 3 days. These very impressive data suggest that the degree of achievement of a pre-defined glucose target is the key factor of any strategy used to control glycaemia. In fact, there are several indicators of the success and 'quality' of glucose control. The long list of published quality indicators was systematically reviewed by Eslami and colleagues [27]. As stated by the authors, there is a clear need for an unambiguous indicator reference subset rather than a jungle of potential indicators. This important article will probably be very helpful for many investigators in the field of glucose control when designing interventional studies and selecting end points and indices of quality of any intervention.

Body composition and muscular weakness

Long-term critically ill patients are at very high risk of developing severe malnutrition, even when nutrition support is

adapted using the usual monitoring tools. The consequences of this severe malnutrition on body composition are mostly unknown. Last year in *Critical Care*, Reid and colleagues [28] reported a carefully monitored 12-month course of body composition and functional capacity recorded in a young woman recovering from an episode of extrapontine myelinolysis. In spite of an intensive rehabilitation program, muscle wasting and functional compromise were still very impressive after 1 year. This report is needed to promote and foster further research to improve the physical and nutritional management of chronically critically ill patients!

Indeed, the aspects of muscular rehabilitation following long-term critical illness are frequently overlooked. A comprehensive report by a multidisciplinary task force of the European Respiratory Society and the European Society of Intensive Care Medicine [29] underlined the need to standardise the practice of physiotherapy and to increase the awareness of the benefits of prevention and treatment of immobility and muscular de-conditioning. In fact, the understanding and knowledge of the pathophysiology and management of critical illness polyneuropathy and myopathy are progressively increasing. A comprehensive and thorough review of this topic was published in *Critical Care* in 2008 [30]. Among novel and efficient interventions, the early mobility systematic protocol performed by a specialised team is efficient [31] and was found to be particularly cost-effective in patients with acute respiratory failures admitted to a medical ICU as it reduced the lengths of stay in the ICU and in the hospital without increasing the costs [32].

Other interventions

In 2008, several large trials designed to test the hypotheses of improved outcomes following administration of analogues of hormones, presumably deficient during septic shock (that is, vasopressin and hydrocortisone), were conducted. In the first study, the Vasopressin and Septic Shock Trial (VSST) [33], 778 patients underwent random assignment to receive noradrenaline or vasopressin titrated and tapered to maintain a target blood pressure. There was no difference in the primary end point (28-day mortality) or in any of the rates of adverse events. Similarly, in the Corticosteroid Therapy of Septic Shock (CORTICUS) trial [34], 499 patients were randomly assigned to hydrocortisone or to placebo during the early phase of septic shock. Even though the reversal of shock was hastened in the patients treated with hydrocortisone, there was no difference in survival but an increased incidence of secondary septic shock. Finally, based on a high probability of elevated oxidative stress [35], three groups of critically ill patients (postoperative cardiac or respiratory failure after cardiac surgery, major trauma or severe subarachnoid haemorrhage) were randomly assigned to a combination of antioxidants (trace elements and vitamins) or placebo [36]. The primary outcome variable of the study was a change in the acute kidney injury score, and 200 patients were enrolled. Although the antioxidant therapy was able to restore circulating values of its different components within the normal range, only the inflammatory response (estimated by the C-reactive protein level) in the trauma and in the subarachnoid haemorrhage groups was improved. Large studies using different doses of different combinations of antioxidants administered in different populations at different times will definitely be needed to accurately define the place of antioxidants in the treatment of critically ill patients [35]. The 'negative' results of these three large trials are very important as they stress the complexity of manipulating the hormonal and oxidative pathways during critical illness and the need for further pre-clinical research.

Competing interests

The author declares that they have no competing interests.

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