CRITICAL CARE

REVIEW

Year in review 2009: *Critical Care* – metabolism

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Abstract

Novel insights into the metabolic alterations of critical illness were published in *Critical Care* in 2009. The association between early hypoglycaemia/high glycemic variability and poor outcome was confirmed. Improvements in the understanding of the pathophysiological mechanisms of stress hyperglycemia and potential progress in the bedside management of glucose control were presented. With regard to enteral nutrition, some alterations of gastrointestinal physiology were better delineated. The relationship between the achievement of nutritional goals and outcomes was further investigated. Finally, understanding of some critical-illness-related endocrine and neuromuscular disorders improved through new experimental and clinical findings.

Several important contributions in the field of metabolic alterations of critical illness were published in *Critical Care* in 2009. These articles can be gathered into three areas of interest: the physiology and clinical management of glucose control; enteral nutrition and gastrointestinal disorders; and critical-illness-related endocrine and neuromuscular alterations.

Glucose metabolism and control

Since 2001 and the publication of the 'Leuven I' study [1], the metabolism and control of blood glucose is an area of intense research in intensive care medicine. The contrasting findings of subsequent prospective randomized controlled trials of glucose control fostered research in several different fields: epidemiological insights came from association studies between blood glucose and outcome; endocrinological pathways were investigated as potential contributors to stress hyperglycaemia; and computer-assisted decision systems and continuous glucose monitoring were assessed in clinical conditions.

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Association between blood glucose levels and outcome

An association between high admission blood glucose concentration and worse vital outcome has been known of for several decades. Interestingly, an analysis of a database of more than 250,000 patients allowed further categorisation of the type of patients in which the relationship between blood glucose and mortality was the strongest after acute myocardial infarction, arrhythmia, unstable angina or pulmonary embolism [2]. Likewise, the presence of hypoglycaemia at the time of admission or during critical illness is also associated with increased mortality, as reviewed recently [3]. An important article published in 2009 in *Critical Care* summarises the analysis of a 5-year database from the Australia New Zealand Intensive Care Society including 66,184 adult admissions [4]. These authors indeed reported that the presence of early hypoglycaemia is common and associated with lower survival rates, especially in some subsets of patients. High early blood glucose variability (that is, during the first 24 hours of ICU stay) was also associated with higher adjusted ICU and hospital mortality.

Physiopathology of stress hyperglycaemia

New important insights into the physiopathology of stress hyperglycaemia were also reported in *Critical Care* last year. In particular, the underlying mechanisms of insulin resistance were investigated by Langouche and colleagues [5] in a set of 318 critically ill patients. These authors recorded the circulating blood levels of adiponectin, retinol binding protein 4 and leptin, three adipokines known to be involved in the modulation of insulin sensitivity and action. The levels of all three adipokines were lower than in normal subjects and intensive insulin therapy influenced the concentrations of adiponectin and retinol binding protein 4. Similarly, Venkatesh and colleagues reported in *Critical Care* [6] decreases in the mean plasma adiponectin concentration of 23 critically ill patients compared to historical control subjects. Interestingly, a correlation was found between adiponectin and plasma cortisol levels, and an inverse correlation was found between adiponectin and C-reactive protein levels. Circulating levels of resistin, another recently reported hormone released by adipocytes and macrophages, were found to be increased in a population of 170 critically ill patients [7]; a correlation

with the magnitude of insulin resistance was also reported. These important findings are quite consistent with recent progress in understanding the changes in adipose tissue gene expression during critical illness [8,9].

Another potentially important pathophysiological insight was reported by Preissig and colleagues in *Critical Care* in 2009 [10]. The pancreatic endocrine function of critically ill children admitted to a paediatric ICU with respiratory or cardiovascular failure was studied by the simultaneous analysis of blood glucose and plasmatic C-peptide levels. A severe primary beta-cell dysfunction reflected by inappropriately low levels of C-peptide was found in children with both respiratory and cardiovascular failure; in contrast, high insulin resistance appeared as the prominent cause of stress hyperglycaemia in cases of respiratory failure only. These intriguing findings of different and apparently unrelated pathogenetic mechanisms of stress hyperglycaemia prompted several different interpretations of the adequacy of the beta-cell response [11,12].

In any case, impairments of glucose metabolism could differ between children and adults. The important paediatric Leuven study published in 2009 by Vlasselaers and colleagues [13] confirmed some benefit of insulin therapy dosed to reach 'age-adjusted normoglycaemia.'

Clinical management of glucose control

The failure to reproduce the results of the Leuven I study [1] in different settings, including two large-scale prospective randomised international trials published in 2009 [14,15], raised a number of important issues directly relevant to daily practice [16].

The two most recent meta-analyses [17,18] were unable to demonstrate an advantage of tight glucose control by intensive insulin therapy compared to a more conservative approach. As a consequence, the guidelines for glucose control were re-assessed in 2009 [19,20] and now recommend that blood glucose be kept below 180 mg/dl (10.0 mmol/L).

Whatever therapeutic target is chosen, quality of performance is a key factor needed to interpret the outcome variables of studies on tight glucose control [21]. Several approaches are currently under investigation, not only to improve the quality of glucose control, but also to increase safety and to decrease glycaemic variability. The use of continuous or near-continuous monitoring devices and closed-loop systems for insulin infusion based on systematic algorithms based on multiple-compartment models are currently being tested. In *Critical Care*, Juneja and colleagues [22] report their experience of the use of a computerized insulin IV protocol program in 4,588 patients over 21 months. In essence, this study validated the efficacy of this software as the target glycaemic range was rapidly achieved, with a very low rate of hypoglycaemia. However, frequent checks of glucose are required, implying an adapted nurse to patient ratio. Similar findings were reported by others using other computerized approaches [23-25]. The use of continuous blood glucose monitoring systems is another area of intense investigation [26,27].

Enteral nutrition and gastrointestinal disorders

The importance of early enteral nutrition was highlighted in 2009 by the publication of a meta-analysis in which a significant reduction in mortality occurred when enteral nutrition was instituted within 24 hours after admission [28]. However, difficulties in providing efficient early enteral nutrition are frequent and prevent its institution in many situations. Clinical studies carried out and published in *Critical Care* in 2009 addressed the issues of digestive physiology during critical illness and the influence of enteral nutrition on outcome.

Digestive physiology

Chapman and colleagues [29] published a study concerning the relationship between gastric emptying, glucose absorption and glycaemia in critically ill patients. Using a 3-O-methyl-glucose test, they found that delayed gastric emptying decreased glucose absorption in a group of 19 mechanically ventilated patients compared to 19 healthy subjects; conversely, blood glucose concentration affected gastric emptying.

The relationship between digestive physiology and glucose was further investigated by Deane and colleagues [30]. The effects of exogenous glucagon-like peptide-1 on the glycaemic response to small intestinal nutrients was studied in critically ill patients. Glucagon-like peptide-1 is a hormone exerting an 'incretin' effect (that is, it stimulates insulin secretion), thereby offering a novel therapeutic approach to reduce the magnitude of glycaemic responses during enteral feeding.

Enteral nutrition and clinical outcome

Of the unresolved issues regarding enteral nutrition, the best site of infusion has still to be determined. White and colleagues [31] addressed this question by comparing the outcomes of ventilated critically ill patients randomised to early post-pyloric or gastric feeding. In essence, early post-pyloric feeding did not provide any advantage over gastric feeding but did delay the achievement of the nutritional target. In terms of outcomes, there were no differences between the two groups.

A relationship between the achievement of nutritional goals and vital outcome was investigated by Strack van Schijndel and colleagues [32] in a prospective observational cohort study of 243 ventilated critically ill patients. The caloric and protein targets were analysed separately: enteral nutrition was calculated according to indirect calorimetry and the protein intake was 1.2 g of protein/kg/

day. Reaching the nutritional goals was associated with significant decreases in ICU and 28 day mortality in the female population, while the difference was not significant in males. These challenging findings are of interest when designing interventional trials. Similarly, another observational study reported an association between energy and protein intake and vital outcome in subsets of obese and lean patients [33].

The addition of pharmaconutrients is another area of research. For instance, glutamine could be of particular interest in cases of sepsis as it could attenuate inflammation and increase the heat-shock protein response. These pathways were investigated in healthy volunteers receiving endotoxin [34]. Even though endotoxin reduced plasma glutamine concentrations, there was no measurable effect on cytokine levels, nor on the expression of heat-shock proteins.

Thyroidal and neuromuscular alterations

Both endocrine and neuromuscular changes are now identified as important contributors to the poor functional outcome of patients with prolonged critical illness. For instance, the 'low T3 syndrome' has been recognised for a long time and its involvement in the need for prolonged mechanical ventilation has recently been revisited [35], although the pathophysiology of this frequent disorder is still incompletely elucidated. Mebis and colleagues [36] investigated the expression of genes in the hypothalamus of an animal model of chronic critical illness and found decreased mRNA levels of thyrotropin releasing hormone and increased mRNA levels of type II diodinase and thyroid hormone transporters.

The neuromuscular consequences encountered in patients with prolonged critical illness are responsible for several complications [37], including dysfunction of the diaphragm muscle [38]. The pathophysiology of ICU-acquired weakness or critical illness polyneuromyopathy is complex and involves increased oxidative stress, impaired microcirculation, proteolytic status, cytokine-related inflammation, altered calcium homeostasis, and hyperglycaemia [39]. Hermans and colleagues [40] published a study in *Critical Care* that focused on electrophysiological data from patients in their ICU before and after implementation of intensive insuline therapy. In their experience, intensive insulin therapy reduced the electrophysiological incidence of critical illness polyneuromyopathy and the duration of mechanical ventilation. This effect was not found for other therapeutic modalities [41]. The potential mechanisms are partially speculative and were discussed in *Critical Care* [42].

Conclusion

The area of critical-illness-associated metabolic and endocrine changes received increased attention in 2009, as reflected by the articles published. The issues of stress hyperglycaemia and glucose control were also further investigated. The nutritional aspects of critical illness, particularly derangements of the gastrointestinal physiology and the neuromuscular changes found in critically ill patients, were re-addressed using new approaches. Altogether, new areas of research were opened by the high-quality articles published in *Critical Care* in 2009.

Competing interests
The authors declare that they have no competing interests.

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