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Give me less sugar: how to manage glucose levels in post-anoxic injury?

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Despite recent advances in the management of comatose survivors after cardiac arrest (CA), a high proportion of these patients will eventually die because of severe cardiovascular failure or extended brain injury [1]. The combination of these haemodynamic and neurological alterations with a post-CA systemic inflammatory response, similar to that observed in sepsis, is commonly defined as the “post-cardiac arrest syndrome” [2]. However, beyond these abnormalities, the development of metabolic derangements, such as hyperglycaemia, can also potentially contribute to secondary brain injury and poor neurological outcome [3]. Indeed, experimental studies suggest that elevated blood glucose levels after the return of spontaneous circulation may exacerbate post-anoxic injury [4, 5]; nevertheless, the impact of hyperglycaemia in this specific clinical setting remains unclear.

Retrospective analyses of patients after resuscitation from out-of-hospital CA (OHCA) showed that hyperglycaemia was common during the post-resuscitation period and might have been associated with poor outcome

[6, 7]. However, interventional studies of tight glucose control (TGC) in CA patients showed that this strategy was not associated with improved outcomes when compared to a less strict glycaemic management [8]. Moreover, TGC could determine a higher incidence of hypoglycaemia, and in a multicentre cohort of CA patients the lowest blood glucose was associated with hospital mortality [9]. There are also two other factors that complicate glycaemic control in such a patient population. First, the use of targeted temperature management (TTM) after CA can further alter glucose metabolism because of reduced glucose utilization, decreased insulin sensitivity and impaired secretion of endogenous insulin due to cooling procedures [3]. Second, blood glucose variability (BGV), i.e. the degree at which a patient’s blood glucose fluctuates between high and low levels, was a stronger predictor of poor outcome than absolute glucose level itself in these patients [3, 10]. Taken together, these data suggest the need for large cohort studies to better understand the pathogenesis of the alterations of glucose homeostasis as well as the impact of elevated glucose and/or large BGV concentrations in post-anoxic injury.

In this issue of *Intensive Care Medicine*, Daviaud et al. [11] report on their evaluation of the relationship between blood glucose levels and outcome in a large cohort ($n = 381$) of OHCA patients admitted over a 5-year period and treated with moderate glycaemic control (target glucose: 5.1–7.7 mmol/L). Median glucose levels and median BGV, defined as the difference between the highest and the lowest blood glucose concentrations ($\Delta_{\max} - \min$) over the first 48 h, were lower in patients with a good outcome than in those with a poor outcome (7.6 vs. 9.0 mmol/L, $p < 0.01$; 7.1 vs. 9.6 mmol/L, $p < 0.01$, respectively). In their multivariate analysis, increased median glucose levels, but not BGV, were independently associated with poor outcome at hospital discharge. These authors suggest that a strategy

combining both glucose control and minimization of glycaemic variations might improve outcome in CA patients.

This study has a number of strengths which need to be highlighted. First, the authors included a sample size of nearly 400 patients, which allowed them to apply several statistical approaches in their analysis of the possible link between glucose levels and outcome in this cohort. Second, no missing data on glucose level measurements were reported, thus limiting the potential bias of retrospective data collection. Third, most patients were treated with TTM, while in previous studies the patients were analysed before the era of hypothermia implementation [6, 7].

Although the study of Daviaud et al. [11] clearly challenges the role of BGV on poor outcome after CA, a number of important issues need to be discussed to identify possible explanations for the differences with previously reported results, including study limitations. First of all, the best method to assess BGV remains to be defined. Even if high BGV can be associated with increased oxidative stress, neuronal damage and mitochondrial alterations, studies conducted in critically ill patients have used different definitions of BGV, such as the standard deviation (SD) of all glucose measurements, the coefficient of variation, the concomitant presence of both hyper- and hypoglycaemia or other indices, such as the glucose variability index, the glycaemic lability index or the mean amplitude of glycaemic excursion [12]. In previous studies on CA patients, BGV was assessed using the difference between the $\Delta\text{max} - \text{min}$ over a 24-h period [3] or the SD and mean absolute glucose change per patient per hour [10]. It is clear that the diversity of the indicators used hampers the comparability of these studies and hence limits any potential recommendations on glucose management strategies aiming to control BGV in CA patients [3, 10, 11]. Moreover, the relationship between BGV and mortality could be blurred by the frequency of observations (i.e. less frequent measurements of glucose levels lead to an underestimation of BGV) and the use of TGC [13]. Both glucose sampling methods and the glucose levels that were targeted with continuous insulin infusions were different among the three studies evaluating BGV after CA [3, 10, 11], thus increasing the number of confounders on the evaluation of patients' outcome in this setting (Table 1).

Second, regarding mortality, a convincing relationship with BGV and outcome has been clearly demonstrated in non-diabetic critically ill patients [14]. As such, Beiser et al. [15] showed that in non-diabetic CA patients both minimum glucose values outside the range of 3.9–9.4 mmol/L and maximum values outside the range of 6.2–13.3 mmol/L were associated with an increased risk of poor outcome. In the study of Daviaud et al. [11], diabetes mellitus was associated with high

Table 1 Summary of clinical studies evaluating the role of blood glucose variability on outcome after cardiac arrest

References	Type	Patients, <i>n</i> (period)	OHCA (%)	Blood glucose sampling	Target glucose (mmol/L)	Definition BGV	Evaluation (h)	Therapeutic hypothermia (%)	Outcome	Main findings
Cueni-Villoz et al. [3]	Retrospective	220 (5 years)	93	q4 h	6.0–8.0	Max–Min difference	48	100	CPC at 3 months	BGV during TH associated with poor outcome
Lee et al. [10]	Retrospective	147 (4 years)	82	q1 h	4.4–11.1	SD MAGC	48	100	CPC at 30 days	BGV during TH associated with poor outcome
Daviaud et al. [11]	Retrospective analysis of database	381 (5 years)	100	q3 h	5.1–7.7	Max–Min difference	48	82	CPC at hospital discharge	BGV was not associated with outcome

BGV Blood glucose variability, OHCA out-of-hospital cardiac arrest, MAGC mean absolute glucose change per patient per hour, CPC cerebral performance category, q4 h every 4 h, q3 h every 3 h, q1 h every hour, TH therapeutic hypothermia

BGV but did not significantly influence the results of the multivariate analysis. However, as only 14 % of patients suffered from diabetes, it is possible that such an analysis was largely underpowered.

Third, Daviaud et al. measured glucose levels using capillary glucometers; however, these devices have been shown to have a low accuracy in critically ill patients when compared to glucose measurements performed on venous/arterial blood. In particular, mean differences with the blood values may vary from 0.2 to 1.4 mmol/L (limits of agreement from 1.7 to 2.5 mmol/L), especially within the hypoglycaemic range [16]. Also, the use of vasopressors and the presence of oedema, both of which are common after CA, were important determinants of inaccuracy and might increase the risk of errors of capillary glucometers in this setting. Thus, capillary samples may not provide an adequate estimation of blood glucose levels and may have significantly influenced the assessment of BGV in this study.

Finally, there are still some missing clues between glucose management and outcome in CA patients. Although the potential importance of BGV to determine mortality/poor neurological recovery in such a population has to be recognized, there are as yet no data on the association of BGV with other outcomes, such as the development of acute renal or respiratory failure and the onset of sepsis. Also, a better understanding of all the clinical and therapeutic factors associated with high BGV

is needed; indeed, one may distinguish between the sources of glucose level variability induced by some interventions (i.e. corticosteroids in case of circulatory failure or early enteral nutrition), which are relatively controllable, and those due to changes in patient condition, such as the occurrence of infections or the need of high vasopressor dose. Moreover, high glucose concentrations and variability after CA might be an epiphenomenon, i.e. a marker of severe injury with limited pathogenic influence per se on brain damage, and future prospective studies that included several other variables would be necessary to answer this issue. Finally, a recent study has shown that loss of glucose complexity, as evaluated by fluctuation analysis of glucose levels over time, was also associated with higher mortality in critically ill patients: the lack of complexity may represent the failure of regulatory systems to maintain glucose homeostasis as a consequence of the underlying disease [17]. It might therefore be useful to adopt associated analyses of BGV and complexity in future studies on CA patients. The use of continuous glucose monitoring could be a reliable approach to better evaluate BGV in this setting.

Conflicts of interest P. Kalfon is a board member of LK2 (Saint-Avertin, France) and has shares in LK2. F.S. Taccone and K. Donadello have no conflict of interest to declare.

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