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### Glycaemic Control in the Critically Ill: What Have We Learned Since NICE-SUGAR?



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#### Introduction

Glycaemic control of the critically ill has been a topic of considerable interest in the critical care community since the publication of a single-centre randomised controlled trial (RCT) of intensive insulin therapy (IIT) targeting euglycaemia, blood glucose (BG) 80-110 mg/dL, in a population of mechanically ventilated surgical intensive care unit (ICU) patients, 63% of whom had undergone cardiovascular surgery (Van den Berghe et al. 2003). However, the dramatic reductions in mortality and morbidity demonstrated in this investigation were not reproduced in subsequent trials (Van den Berghe et al. 2006; Brunkhorst et al. 2008; Preiser et al. 2009; Arabi et al. 2008), two of which required premature termination due to high rates of hypoglycaemia in the interventional arms (Brunkhorst et al. 2008; Preiser et al. 2009). The NICE-SUGAR trial, conducted in 42 centres, and involving an heterogeneous cohort of 6,104 patients concluded that a moderate glycaemic target, 140-180 mg/dL, achieved with a very low rate of severe hypoglycaemia, was associated with modestly lower mortality than that achieved with 'tight' control, targeting 80-110 mg/dL (NICE-SUGAR Study Investigators 2009). This study prompted the promulgation of guidelines advocating loose glycaemic targets (Dellinger et al. 2008; Moghissi et al. 2010; Ichai and Preiser 2010; Qaseem et al. 2011), and many ICUs followed suit (Kaukonen et al. 2013); interest in tight control waned.

Nevertheless, a considerable amount of new literature has expanded our understanding of factors impacting glycaemic control in the critically ill. This concise review will describe investigations appearing after the publication of the NICE-SUGAR study and focus on several key themes: the independent association of three domains of glycaemic control – hyperglycaemia, hypoglycaemia, and glucose variability (GV) – on mortality; the possible emergence of a fourth domain, glucose complexity; the relationship of diabetic status to the domains of glycaemic control; and, finally, issues relating to monitoring frequency.

#### The Three Domains of Glycaemic Control: Hyperglycaemia, Hypoglycaemia and Glucose Variability

*Hyperglycaemia* is ubiquitous in acutely and critically ill patients, due to a combination of endogenous and iatrogenic factors (Duncan et al. 2009), and the treatment of hyperglycaemia has been the focus of the interventional trials of IIT. *Hypoglycaemia* has been the unifying complication of the interventional trials. The percentage of patients who sustained at least one episode of severe hypoglycaemia, most typically defined as a single blood glucose (BG) level of < 40 mg/dL, in the RCTs of IIT published before NICESUGAR ranged from 5.8% (Van den Berghe 2003) to 28.6% (Van den Berghe et al. 2008), in comparison to the 6.8% of patients in the interventional arm of NICESUGAR who had this complication (NICE-SUGAR Study Investigators 2009). Although the authors of the first Leuven study concluded that hypoglycaemia had no discernable deleterious impact (Van den Berghe et al. 2008), prospective RCT data as well as observational investigations have since determined that hypoglycaemia is independently associated with mortality. In 2010 the Leuven investigators published a post-hoc analysis of their two RCTs of IIT, and reported an odds ratio (95% CI) for mortality associated with a single episode of severe hypoglycaemia (BG < 40 mg/dL) of 3.23 (2.25-4.64) ( $p < 0.0001$ ) (Meyfroidt et al. 2010). Two years later this finding was confirmed by the NICE-SUGAR investigators (NICE-SUGAR Study Investigators 2012). The odds ratio (95% CI) of mortality associated with a single episode of severe hypoglycaemia was 2.10 (1.59-2.77) ( $p < 0.0001$ ). In addition, a single episode of moderate hypoglycaemia (BG 41-70 mg/dL) was also found to be independently associated with death, with odds ratio (95%CI) 1.41 (1.21-1.62) ( $p < 0.001$ ).

Observational data published after NICE-SUGAR corroborated the independent association of mild hypoglycaemia with mortality. In 2010 Egi et al. Clearly described increasing rates of death associated with mild hypoglycaemia – BG 54-63 mg/dL – in 4,946 patients admitted to two mixed medical-surgical ICUs in Australia (Egi et al. 2010). Similarly, an investigation including a mixed cohort of 6,240 patients from the Academic Medical Center in Amsterdam, Stamford Hospital (Stamford, CT, USA) and the GLUCONTROL RCT of IIT, reported that patients with minimum BG in the 80-110 mg/dL range had the lowest rate of death, with increasing rates of death associated with minimum BG 70-80, 55-70, 40-55 and < 40 mg/dL (Krinsley et al. 2011). For the entire cohort, a single episode of BG 40- 69 mg/dL was independently associated with increased risk of death ( $p = 0.0011$ ).

*Glucose variability (GV)*, the third domain of glycaemic control, was not contemplated in the design and reporting of the interventional trials of IIT. However, increased GV was reported to be independently associated with increased risk of death in observational studies published prior to NICE-SUGAR (Egi et al. 2006; Krinsley 2008), and this finding was subsequently corroborated by the Leuven investigators using data from their two interventional trials, published in 2010 (Meyfroidt et al. 2010). A robust literature has since evolved that describes the independent association of increased GV with risk of death in various settings: a mixed medicalsurgical population (Hermanides et al. 2010); in relation to nutritional support (Suhaimi et al. 2010); related to therapeutic hypothermia (Cueni-Villoz et al. 2011); in 37 Dutch ICUs (Meynaar et al. 2012); in acute pancreatitis (Zuo et al. 2012); in acute myocardial infarction (Su et al. 2013); and in association with administration of total parenteral nutrition (Farrokhi et al. 2014). Moreover, increased GV may herald the development of hypoglycaemia (Kauffmann et al. 2011).

Additional work suggests that derangements in these three domains of glycaemic control have a cumulative association with death in critically ill populations. Mackenzie and coinvestigators evaluated 3,422 patients admitted to four different specialty ICUs in Birmingham, UK, and found that the odds ratio (95% CI) for mortality in patients with hypoglycaemia was 2.5 (2.0-3.1) (Mackenzie et al. 2011). The odds ratio (95% CI) for mortality in patients with hypoglycaemia and hyperglycaemia was 4.8 (3.4-6.8). Among patients who had derangements in all three domains, the odds ratio (95% CI) for mortality was even higher – 6.0 (3.9-9.2). These findings were largely corroborated in an investigation that included 101,877 patients admitted to 344 US hospitals (Omar Badawi et al. 2012).

#### **Glucose Complexity: a Fourth Domain of Glycaemic Control in the Critically Ill?**

Complex biological systems are characterised by a highly complex output; critical illness can lead to 'decomplexification' (van Hooijdonk et al. 2012). Two examples include the loss of heart rate variability or temperature complexity in the setting of severe infection. Loss of complexity in the glycaemic profile has been demonstrated as humans progress from health through metabolic syndrome to type 2 diabetes (Churrua et al. 2008). Meyfroidt et al. Evaluated a measure of BG complexity, jackknifed approximate entropy, and reported that this parameter was significantly lower in non-survivors of the two Leuven investigations of IIT than in survivors ( $p = 0.0006$ ) (Meyfroidt et al. 2010). Two investigations using continuous glucose monitoring via subcutaneous sensors evaluated a different metric of glucose complexity – detrended fluctuation analysis – in small cohorts of critically ill patients, and corroborated the finding that glucose complexity was significantly lower in non-survivors than in survivors (Lundelin et al. 2010; Brunner et al. 2012). Curiously, in one of these studies high glucose complexity was also associated with increased mortality (Brunner 2012). Future research, in particular using monitoring technology employing higher degrees of analytic precision, will be needed to further clarify the relationship of glucose complexity to mortality, as well as to assess the effect of therapeutic interventions on this emerging domain of glycaemic control.

#### **What About Diabetic Status?**

A burgeoning literature has explored the independent association of diabetic status to mortality in the critically ill. An analysis of data from interventional trials of IIT suggested that IIT had more benefit to the non-diabetic patients in the trials (Krinsley et al. 2012). Multiple observational studies indicate that diabetes may, in fact, be independently associated with reduced risk of mortality in the critically ill. Graham and coworkers performed multivariable analysis on data from two large cohorts of patients – 36,414 patients from the Mayo Clinic system and 1.5 million patients from the University Health Consortium (Graham et al. 2010). The odds ratio (95% CI) for mortality associated with diabetes was 0.88 (0.79-0.98) ( $p = 0.022$ ) and 0.75 (0.74- 0.76) ( $p < 0.0001$ ) respectively. A meta-analysis of 141 studies, using unadjusted data only, demonstrated no overall association between diabetes and mortality in populations of medical, medical-surgical, general surgical and trauma patients (Siegelaar et al. 2011). Studies involving cardiac surgery patients were the only exception to this finding; in this patient group, patients with diabetes sustained higher mortality than did those without diabetes (Siegelaar et al. 2011).

Potential mechanisms to explain a protective effect of diabetes in the critically ill may include improved nutritional or caloric substrate in obese Type 2 DM patients and adaptation to previous oxidant stress. Hyperglycaemia is ubiquitous in the critical care unit, due to relative insulin resistance, counter-regulatory hormones and iatrogenic factors, such as nutritional therapy, intravenous fluid administration and corticosteroid use, but may be injurious primarily to non-diabetics. Tolerance to the deleterious effects of hyperglycaemia may in fact be the primary

mechanism protecting diabetics, and explain the 'diabetes paradox' (Krinsley and 2012). Preadmission glycaemic control in diabetics may have an important modulating effect on the relationship between glycaemic control during critical illness and mortality. Egi and colleagues evaluated the interaction of HgbA1c obtained prior to ICU admission and mean BG during ICU stay in a cohort of 415 diabetic patients admitted to two Australian ICUs (Egi et al. 2011). There was no difference in mean BG comparing survivors and non-survivors. However, patients with higher preadmission HgbA1c levels had higher mortality associated with lower mean BG levels, raising the intriguing possibility that aggressive correction of hyperglycaemia in patients with poor preadmission glycaemic control might contribute to adverse outcomes.

The relationship of diabetic status to the three domains of glycaemic control and mortality was explored in a recently published four-continent 9-centre observational study involving a heterogeneous population of 44,964 critically ill patients (Krinsley et al. 2013). Patients with diabetes had higher rates of mild and severe hypoglycaemia, higher GV and higher mean BG levels during ICU stay (all comparisons  $p < 0.001$ ). Nevertheless, for the entire cohort, diabetes was independently associated with decreased risk of mortality with odds ratio (95% CI) 0.92 (0.87-0.97)  $p = 0.003$ . Among patients with diabetes there was no relationship between mean BG during ICU stay and mortality, and mean BG 80-110 mg/dL was independently associated with increased risk of mortality. Among patients without diabetes, increments of mean BG above 80 mg/dL were associated with progressively higher rates of death and the BG ranges of 80-110 mg/dL and 110-140 mg/dL were independently associated with decreased risk of death. For all patients mild as well as severe hypoglycaemia were independently associated with increased risk of mortality. For all patients increasing GV was associated with increased mortality. However, among patients with diabetes GV was not independently associated with increased risk of mortality. In contrast, among non-diabetics, GV, as reflected by coefficient of variation (CV)  $> 20\%$ , was independently associated with increased risk of mortality. These findings were subsequently confirmed in a 10,320 patient study conducted in a single medical- surgical ICU (Sechterberger et al. 2013). Mean BG and high GV were independently associated with death in non-diabetics but not in diabetics, while hypoglycaemia was independently associated with death in the entire cohort.

### **The Importance of Measurement Frequency**

Blood glucose monitoring occurred every one to four hours in the major interventional trials of IIT. The frequency of BG monitoring ranged from 2.8 to 10.6 tests per 24 hours in the 9 centres included in the large observational study referenced earlier (Krinsley et al. 2013). It is logical to infer that intermittent BG monitoring should be associated with 'missed' episodes of hyperglycaemia and hypoglycaemia. This, in fact, was demonstrated in an evaluation utilising continuous subcutaneous monitoring (Holzinger et al. 2010). A recently published investigation using a Monte Carlo mathematical simulation of patients on glycaemic control protocols modelled the relationship between monitoring frequency and metrics of glycaemic control (Boyd and Burns 2014). The model measured BG with bias varying from  $-20\%$  to  $+20\%$  and imprecision varying from  $0\%$  to  $20\%$  CV, and the results were used to alter insulin infusion rates based on two published insulin treatment protocols. Boyd and Burns evaluated rates of hypoglycaemia, hyperglycaemia, GV and percentage of time in target BG ranges, comparing measurement frequencies of every five and 60 minutes. They found that the impact of doubling the analytic imprecision from  $5\%$  to  $10\%$  on these measures of glycaemic control was blunted, and even reversed, when the measurement frequency increased from every 60 minutes to every five minutes. These findings have important implications for the emerging technologies that are being developed to allow continuous or near-continuous BG measurement in the critically ill. In effect, increased monitoring frequency 'trumps' a degree of analytic inaccuracy.

### **Conclusions: A Look Ahead**

This brief review underscores the breadth of investigations that have informed our understanding of glycaemic control in the critically ill since publication of the NICE-SUGAR trial. It should be abundantly clear that current technologies, using intermittent monitoring, are not adequate to monitor and control the three domains of glycaemic control, a conclusion that was reached by a consensus group that met at the 2012 annual congress of the International Society of Intensive Care and Emergency Medicine (Finfer et al. 2013). Moreover, an era of a 'personalised' approach to glycaemic control, taking into account patient characteristics, including diabetes status and, perhaps for diabetics, preadmission glycaemic control, may determine glycaemic targets. Finally, future interventional trials should incorporate the findings of the glycaemic control studies published in the last several years in their design. We have passed the era where 'one size fits all' (Krinsley 2013).

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