**The future of glycaemic control in critically ill patients requires a close collaboration between bio-engineers and clinicians**

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Abstract: Glycaemic control has become a major issue in intensive care units (ICUs) in less than one decade. As the widespread use of tight glycaemic control is limited by several issues, including a moderate ability to keep blood glucose within a pre-defined range in spite of an increased workload. The use of systematic algorithms based on multiple-compartment models is considered as a major potential improvement, which cannot be designed and implemented without a close cooperation between bio-engineers and clinicians.

*Keywords:* *Glucose control, intensive insulin therapy, critically ill, intensive care unit, nursing workload, automated algorithms.*

1. INTRODUCTION

The recently emerging field of tight glucose control (TGC) in intensive care units (ICUs) is a typical example where collaborations between bio-engineers and bedside physicians and other healthcare professionals can be particularly welcome and fruitful. Indeed, the improvement in survival following the implementation of a tight glycaemic control policy by intensive insulin therapy reported from one centre in Belgium impressed the medical community (Van den Berghe et al., 2001). Several trials however failed to reproduce the same effects in single-centre and multiple-centre large-scale trials (Finfer and Delaney, 2008, Preiser et al., 2009). These overall results have also been reported in two different, recent meta-analysis studies (Marik and Preiser, Griesdale et al., 2009).

The reasons for such discrepancy are still a matter of intense debate (Preiser et al., 2010, Suhaimi et al., 2010). Among various possible factors, the inability to reproduce the same quality of glucose control than the pioneering centre, an increased workload not manageable by the nursing staff, and inaccuracies, poor design or non-compliance in the insulin algorithm, have all been advocated. All these aspects represent elements of protocol design that can be improved by a judicious cooperation between clinicians and bio-engineers to develop appropriate and meaningful automated therapeutic protocols.

Hence, this short paper discusses 4 main avenues of interaction where clinicians and bio-engineers can provide joint direction and leadership to improve patient outcomes. In particular it focuses upon those areas where engineering methods and systems, in combination with clinical expertise, overlap most and can have potentially the greatest impact.

2.Clinical-engineering interactions

*2.1 Mathematical modelling*

The physiological regulation of blood glucose involves several components, including cleavage and digestion of carbohydrates, the amount of glucose infused intravenously, the endogenous production of glucose from glycogen and from neoglucogenic substrates, the production of insulin and of counter-regulatory hormones, the resistance to insulin and the insulin-dependent uptake of glucose by peripheral tissues. The organs and systems involved in this complex process steps can be simulated in multi-compartment models. Specifically, the gastrointestinal tract, the liver, the pancreas, the muscle and the adipose tissue all contribute to the regulation of blood glucose. Once developed, based on actual data recorded in patients, a multi-compartment model will need a validation step, both *in silico* on virtual cohorts of patients and *in vivo*.

*2.2 Algorithm development*

After validation of a simulation model, algorithms for insulin delivery can then be calculated, to achieve a pre-defined target range for blood glucose. These algorithms will be designed to recommend an insulin infusion rate based on the actual patients’ condition, including the severity of illness severity, time from injury, and the other treatments administered. The performance of these algorithms can be evaluated in virtual cohorts as well.

Several indices of quality of glucose control are available and suitable for the comparison of performances of algorithms, including the time to reach the target, the rate of hypoglycaemia, the variability of blood glucose, the area under and above the per-defined limits (hypoglycaemic and hyperglycaemic indices), and many others (Eslami et al., 2008).

Once validated, the use of the systematic and reliable algorithms can be started in patients, where these are the safest and most efficient method to keep blood glucose within a pre-specified range. Using algorithms is also important to ensure the same level of care for every patient. Very importantly, in a typical ICU environment, several events can interfere with the application of protocol, including unplanned interruption of continuous feeding, rapid changes in insulin resistance in case of change in patients’ condition (Lin et al., 2008); fever, and administration of medications to name a few. Therefore, an ideal algorithm must be flexible and validated in a wide range of patients and clinical conditions.

*2.3. Application of new technologies*

Future developments of algorithms can be anticipated with a coupling of glucose monitoring devices. In particular, closed-loop systems for insulin administration could further improve the quality of glucose control and reduce clinical burden. However at the present stage, the instructions of closed-loop systems will still need a check by caregivers.

Indeed semi- and full-closed loop systems for neonatal intensive care units (NICU), ICU and type 1 diabetes are into development or use (Chase et al., 2008b, Harvey et al., 2010, LeCompte et al., 2009, Plank et al., 2006). A further and potentially important future development would be the transfer of data from point-of-care glucose meters to a centralised hospital data managing system, which in turn can provide output signal such as costs, maintenance issues and recommendations for insulin delivery.

*2.4. Ergonomic design and clinical burden*

The issue of nursing workload was felt as a major impediment for the large-scale implementation of tight glycaemic control policies. Indeed, as compared to the standard practice, the implementation of tight glycaemic control increased by 15-20% the time devoted to blood glucose checks, changes in the rate of insulin infusion, preparation of insulin solutions, careful monitoring of hypoglycaemic episodes. Model-based glycemic control algorithms, coupled with automated systems for blood glucose measurement and insulin delivery, have the potential to dramatically decrease the nursing workload if designed with their clinical use, ergonomic and environment in mind (Chase et al., 2008a). Hence, while improving patient care, such added and automated approaches could also reduce the associated costs.

3. SUMMARY

In conclusion, effective collaborations between bio-engineers and clinicians in the field of glycaemic control are likely to provide significant progress in clinical research, in the quality of care, and in cost-effectiveness.

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