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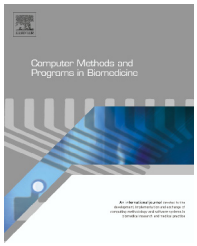

Brain mass estimation by head circumference and body mass methods in neonatal glycaemic modelling and control

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ABSTRACT

Introduction: Hyperglycaemia is a common complication of stress and prematurity in extremely low-birth-weight infants. Model-based insulin therapy protocols have the ability to safely improve glycaemic control for this group. Estimating non-insulin-mediated brain glucose uptake by the central nervous system in these models is typically done using population-based body weight models, which may not be ideal.

Method: A head circumference-based model that separately treats small-for-gestational-age (SGA) and appropriate-for-gestational-age (AGA) infants is compared to a body weight model in a retrospective analysis of 48 patients with a median birth weight of 750 g and median gestational age of 25 weeks. Estimated brain mass, model-based insulin sensitivity (S_I) profiles, and projected glycaemic control outcomes are investigated. SGA infants (5) are also analyzed as a separate cohort.

Results: Across the entire cohort, estimated brain mass deviated by a median 10% between models, with a per-patient median difference in S_I of 3.5%. For the SGA group, brain mass deviation was 42%, and per-patient S_I deviation 13.7%. In virtual trials, 87–93% of recommended insulin rates were equal or slightly reduced ($\Delta < 0.16$ mU/h) under the head circumference method, while glycaemic control outcomes showed little change.

Conclusion: The results suggest that body weight methods are not as accurate as head circumference methods. Head circumference-based estimates may offer improved modelling accuracy and a small reduction in insulin administration, particularly for SGA infants.

1. Introduction

Hyperglycaemia, the elevation of blood glucose (BG) concentration, is common in extremely preterm infants, typically of 27 weeks gestation or less and is closely correlated with morbidity and mortality [1–3]. Hyperglycaemia in neonates is frequently treated with insulin to lower BG concentrations [4]. However, reported insulin protocols have increased the risk of hypoglycaemia in this cohort [5,6], which is

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associated with neurological complications [7]. Hypoglycaemia is overrepresented in preterm infants, most severely in small-for-gestational-age (SGA) infants [8]. STAR (Stochastic TARgeted) is a model-based glycaemic control framework for critically ill patients [9,10]. In the neonatal intensive care unit (NICU) setting, STAR has delivered tight glycaemic control and reduced hypoglycaemia [11]. Its main attribute is a stochastic forecast of possible BG outcomes enabling a quantified level of risk of hypoglycaemia [12]. Hence, it directly mitigates the risk of inter- and intra-patient variability when using insulin.

STAR utilizes the NICING model [13] to simulate insulin therapy. The NICING model is a pharmacokinetic description of insulin–glucose dynamics in the preterm infant that uses the same fundamental dynamics as a clinically well-validated adult model of acute care hyperglcaemia [14–16]. This model is similar in fundamental dynamics to well-known type-1 diabetes models [17,18]. Patients are fit to this model to create treatment-independent insulin sensitivity profiles, which serve as the basis for describing patient condition. The glucose compartment of this model, with parameters given in Table 1, is defined:

$$\dot{G} = -p_G G(t) - S_I G(t)\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t) + EGP \times m_{body} - CNS \times m_{brain}}{V_{g,frac}(t) \times m_{body}} \quad (1)$$

Non-insulin-mediated glucose uptake by the central nervous system (CNS) is the rate at which glucose is removed from the blood for use in the brain. This rate is relatively constant [19], irrespective of the body's plasma insulin concentrations [20]. CNS uptake is a required parameter in the NICING model, as [13] notes that in contrast to the adult case, the brain represents a major source of glucose uptake in infants, due to their larger brain-to-body weight ratio. Hence, given significant variability between preterm infants and no clinically practical ability to measure it directly, this parameter should be modelled as accurately as feasibly possible.

In Eq. (1), CNS is weighted by a patient-specific brain mass m_{brain}. Currently, m_{brain} is calculated as 14% of body mass m_{body} [13]:

$$m_{brain} = 0.14 m_{body} \quad (2)$$

This calculation assumes that brain mass is directly proportional to body mass (m_{body}). Eq. (2) is clinically convenient, as it requires only m_{body} data, which is easily available. However, it may not be accurate. Dobbing and Sands [21] showed a trend between m_{body} and brain mass, but with notable variance. A more precise measure for estimating brain mass may be head circumference (HC) [22].

Improving the estimation of the patient-specific CNS term in the NICING model is projected to have three potential benefits for patients and clinicians:

(1) It may improve glycaemic control and outcomes of patients;
(2) It will improve the physiological accuracy of the model; and
(3) It will provide a method of brain mass estimation that is better justified by the existing literature.

Thus, this work serves as a feasibility study as to whether growth metrics, such as head circumference [22], which are also readily measured in infants, should be used in model-based glycaemic control methods to better account for and manage the inter-patient variability that can make control difficult for preterm infants [11,23]. Ultimately, improvements in glycaemic control that may come by this investigation could reduce the incidence of hyper- and hypo-glycaemia in this fragile cohort.

This work attempts to mitigate a limitation of STAR's model-based stochastic forecasting technique by improving physiological parameter estimation. Methods are not only limited by parameter estimation and modelling constraints, but also on the quality of the stochastic forecasting. A key component of improving stochastic models is understanding inter-patient variability [24]. Accounting for head circumference in the physiological model can reduce variability in stochastic modelling and forecasting.

2. Methods

2.1. Values for brain mass

Eq. (2) is estimated using data from Ho et al. [25]. This paper reports the mean and standard deviation body and brain mass for a range of preterm infants, divided into sub-cohorts by sex and ethnicity. Ethnicity was defined by 'black' or 'white', with no further detail provided.

The ratio of these group means was taken for black female and black male cohorts, which had the lowest mean gestational ages (mean GA = 27.3 weeks and 28.4 weeks, respectively), and then averaged to give $m_{brain} = 0.140 m_{body}$. White cohorts were neglected due to the larger mean body mass (1367 g for the white cohort versus 1058 g for the black cohort) and greater gestational age (30.0 weeks versus 27.9 weeks), which do not reflect the weight of infants who typically require glycaemic control [5,11]. If the same method was applied to the white cohort, it would give $m_{brain} = 0.131 m_{body}$, and if the entire cohort was used, then $m_{brain} = 0.136 m_{body}$. The calculated ratio for each cohort is summarized in Table 2.

While Eq. (2) captures a ratio that may be applicable to a patient around the median mass of 1055 g, it assumes a linear relationship with no offset between m_{brain} and m_{body}, which is not realistic far from this value. Because the cohort this method will be applied to is typically much smaller than 1055 g [11], the errors from this assumption will be amplified. Finally, the apparent choice of ethnic cohort may not best reflect the population of patients in New Zealand, where patients are predominantly of New Zealand European, Māori, Pacific Island, and Asian descent.

2.2. Head circumference and brain mass

A model relating HC to brain mass from Cooke et al. [22] is compared to the original NICING assumption that brain mass is 14% of m_{body}, based on Ho et al. [25] and in Eq. (2).