

What Makes Tight Glycemic Control Tight? The Impact of Variability and Nutrition in Two Clinical Studies

Fatanah Suhaimi, B.Eng.,¹ Aaron Le Compte, Ph.D.,¹ Jean-Charles Preiser, M.D., Ph.D.,²
Geoffrey M. Shaw, M.B.Ch.B.,³ Paul Massion, M.D., Ph.D.,² Regis Radermecker, M.D.,⁴
Christopher G. Pretty, M.E.,¹ Jessica Lin, Ph.D.,⁵ Thomas Desai, Ph.D.,⁶
and J. Geoffrey Chase, Ph.D.¹

Abstract

Introduction:

Tight glycemic control (TGC) remains controversial while successful, consistent, and effective protocols remain elusive. This research analyzes data from two TGC trials for root causes of the differences achieved in control and thus potentially in glycemic and other outcomes. The goal is to uncover aspects of successful TGC and delineate the impact of differences in cohorts.

Methods:

A retrospective analysis was conducted using records from a 211-patient subset of the GluControl trial taken in Liege, Belgium, and 393 patients from Specialized Relative Insulin Nutrition Titration (SPRINT) in New Zealand. Specialized Relative Insulin Nutrition Titration targeted 4.0–6.0 mmol/liter, similar to the GluControl A ($N = 142$) target of 4.4–6.1 mmol/liter. The GluControl B ($N = 69$) target was 7.8–10.0 mmol/liter. Cohorts were matched by Acute Physiology and Chronic Health Evaluation II score and percentage males ($p > .35$); however, the GluControl cohort was slightly older ($p = .011$). Overall cohort and per-patient comparisons (median, interquartile range) are shown for (a) glycemic levels achieved, (b) nutrition from carbohydrate (all sources), and (c) insulin dosing for this analysis. Intra- and interpatient variability were examined using clinically validated model-based insulin sensitivity metric and its hour-to-hour variation.

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Author Affiliations: ¹Department of Mechanical Engineering, Centre for Bio-Engineering, University of Canterbury, Christchurch, New Zealand; ²Department of Intensive Care, Centre Hospitalier Universitaire de Liege, Liege, Belgium; ³Department of Intensive Care, Christchurch Hospital, Christchurch School of Medicine, University of Otago, Christchurch, New Zealand; ⁴Department of Diabetology, Nutrition and Metabolic Disease, Centre Hospitalier Universitaire de Liege, Liege, Belgium; ⁵Department of Medicine, Christchurch School of Medicine, University of Otago, Christchurch, New Zealand; and ⁶Cardiovascular Research Centre, University of Liege, Liege, Belgium

Abbreviations: (ACCP) American College of Chest Physicians, (APACHE II) Acute Physiology and Chronic Health Evaluation II, (CDF) cumulative distribution function, (CHU) Centre Hospitalier Universitaire, (CI) confidence interval, (VISEP) Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis, (ICU) intensive care unit, (IQR) interquartile range, (NICE-SUGAR) Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation, (SPRINT) Specialized Relative Insulin Nutrition Titration, (T2DM) type 2 diabetes mellitus, (TGC) tight glycemic control

Keywords: critical care, GluControl, glycemic control, intensive care unit, intensive care, intensive insulin therapy, Specialized Relative Insulin Nutrition Titration, tight glycemic control, variability

Corresponding Author: J. Geoffrey Chase, Ph.D., Department of Mechanical Engineering, University of Canterbury, Private Bag 4800, Christchurch, New Zealand; email address geoff.chase@canterbury.ac.nz

Abstract cont.**Results:**

Cohort blood glucose were as follows: SPRINT, 5.7 (5.0–6.6) mmol/liter; GluControl A, 6.3 (5.3–7.6) mmol/liter; and GluControl B, 8.2 (6.9–9.4) mmol/liter. Insulin dosing was 3.0 (1.0–3.0), 1.5 (0.5–3), and 0.7 (0.0–1.7) U/h, respectively. Nutrition from carbohydrate (all sources) was 435.5 (259.2–539.1), 311.0 (0.0–933.1), and 622.1 (103.7–1036.8) kcal/day, respectively.

Median per-patient results for blood glucose were 5.8 (5.3–6.4), 6.4 (5.9–6.9), and 8.3 (7.6–8.8) mmol/liter. Insulin doses were 3.0 (2.0–3.0), 1.5 (0.8–2.0), and 0.5 (0.0–1.0) U/h. Carbohydrate administration was 383.6 (207.4–497.7), 103.7 (0.0–829.4), and 207.4 (0.0–725.8) kcal/day. Overall, SPRINT gave ~2x more insulin with a 3–4x narrower, but generally non-zero, range of nutritional input to achieve equally TGC with less hypoglycemia.

Specialized Relative Insulin Nutrition Titration had much less hypoglycemia (<2.2 mmol/liter), with 2% of patients, compared to GluControl A (7.7%) and GluControl B (2.9%), indicating much lower variability, with similar results for glucose levels <3.0 mmol/liter. Specialized Relative Insulin Nutrition Titration also had less hyperglycemia (>8.0 mmol/liter) than groups A and B.

GluControl patients (A+B) had a ~2x wider range of insulin sensitivity than SPRINT. Hour-to-hour variation was similar. Hence GluControl had greater interpatient variability but similar inpatient variability.

Conclusion:

Protocols that dose insulin blind to carbohydrate administration can suffer greater outcome glycemic variability, even if average cohort glycemic targets are met. While the cohorts varied significantly in model-assessed insulin resistance, their variability was similar. Such significant intra- and interpatient variability is a further significant cause and marker of glycemic variability in TGC. The results strongly recommended that TGC protocols be explicitly designed to account for significant intra- and interpatient variability in insulin resistance, as well as specifying or having knowledge of carbohydrate administration to minimize variability in glycemic outcomes across diverse cohorts and/or centers.

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