Endogenous insulin secretion and suppression during and after sepsis in critically ill patients: Implications for TGC protocols

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INTRODUCTION

OVERVIEW:
Insulin infusions over 2 U/hr have been shown to suppress endogenous insulin secretion in healthy subjects 30-45% [1]. Most tight glycemic control (TGC) protocols deliver insulin via infusion. This study examines the impact of bolus delivery of insulin in TGC on the endogenous insulin secretion of critically ill patients.

This study uses data collected prospectively from 16 patients enrolled in a clinical trial studying sepsis at the Christchurch Intensive Care Unit (ICU). C-peptide measurements taken during the study can be used to estimate endogenous insulin secretion following a bolus of insulin.

GOALS:
A better understanding of the body's response to exogenous insulin delivery during critical illness will help improve the performance and safety of TGC protocols. Bolus insulin may provide more effective TGC as unsuppressed endogenous insulin supplements the exogenous dose, possibly lowering the required doses and the risk of hypoglycemia

PATIENTS

16 patients from the Christchurch Hospital ICU enrolled in a prospective clinical trial studying sepsis each had two sets of blood samples assayed for insulin and C-peptide. Patients were included in the study if the met all of the following criteria:

- Age ≥ 16 years.
- Expected survival ≥ 72 hours.
- Expected ICU length of stay ≥ 48 hours.
- Entry to the SPRINT TGC protocol (2 sequential BG measurements ≥ 8 mmol/L).
- Suspected sepsis OR SIRS score ≥ 3.

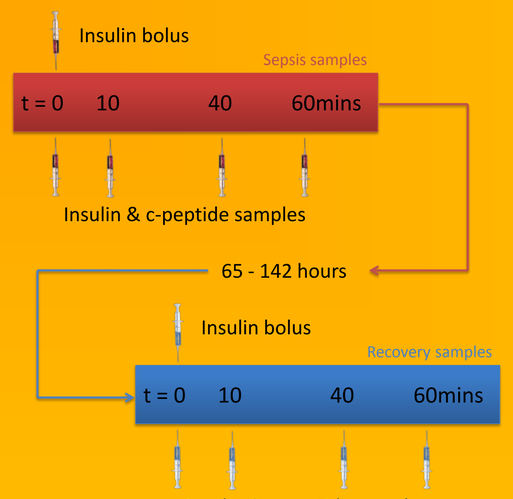
Where suspected sepsis indicates that they received treatment for sepsis with antibiotics. Patients with a known history of diabetes were subsequently excluded from this analysis.

The table below shows an outline of the patient characteristics.

N	16
Age	66 [56-74]
Gender (M/F)	7/9
APACHE II score	22 [16-26]
Confirmed sepsis	81%
ICU mortality	25%

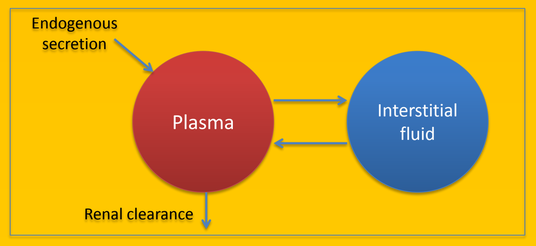
METHODS

Each patient had two sets of blood samples taken. The first set of samples were taken at the commencement of the SPRINT TGC protocol. The second set were taken when the SIRS score was consistently below 2. Bolus size was dictated by the SPRINT protocol, but was in the range 2-5 units.



ANALYSES

- Insulin secretion was estimated from c-peptide concentrations using a two-compartment pharmacokinetic model [2] and the iterative integral method for deconvolution [3].

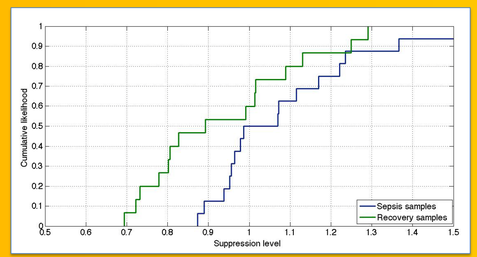


- The insulin and c-peptide secretion profile is modeled as a three phase, stepwise-constant secretion rate during each 60-minute sampling period.
- The start time and duration of phase-1 secretion was identified separately for each set of samples, providing a patient-specific fit to the data.
- The level of suppression was calculated as the ratio of the phase-1 (suppressed) secretion rate to the average of the phase-0 (basal) and phase-2 (return to basal) rates.

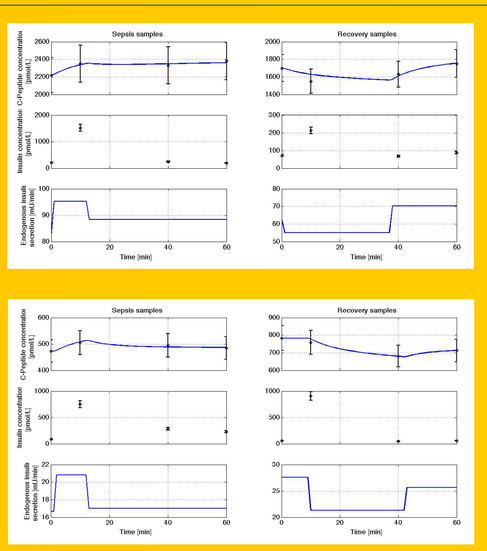
RESULTS

SUPPRESSION:
Median [IQR] level of suppression during the first sampling period (sepsis samples) was 1.03 [0.95-1.20], showing little or no suppression for most patients during suspected sepsis. Suppression during the post-sepsis, recovery samples was 0.89 [0.78-1.07], indicating limited suppression outside c-peptide assay error of 9%.

On an individual patient basis there is no definite tendency towards increased suppression with the recovery samples. Thus, these results reflect a shift in the overall cohort distribution.

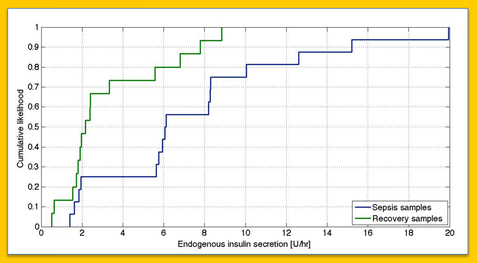


CDFs of calculated suppression levels for sepsis and recovery samples.



Examples of two patients showing the calculated plasma c-peptide concentration (top) and resulting endogenous secretion profiles (bottom).

SECRETION:
Median [IQR] endogenous insulin secretion during the sepsis and recovery sampling periods respectively was 6.1 [3.8-9.2] U/hr and 2.2 [1.7-5.0] U/hr, indicating a sizeable (but not quite statistically significant) drop in secretion, post-sepsis and later in stay ($p = 0.06$). However, this reduction in insulin secretion may be a result of the reduced blood glucose levels. BG levels over the two sampling periods were 8.4 [6.7-9.7] mmol/L and 5.9 [5.4-6.1] mmol/L ($p<0.05$) for the sepsis and recovery sets respectively.



CDFs of calculated endogenous insulin secretion levels for sepsis and recovery samples.

CONCLUSIONS

- Bolus delivery of insulin appears to cause limited suppression of endogenous insulin secretion, particularly during the early stages of critical illness with suspected sepsis.
- Bolus insulin may provide more effective TGC as unsuppressed endogenous insulin supplements the exogenous dose, possibly lowering the required doses and the risk of hypoglycemia.
- These results suggest a comparative study between bolus and infused insulin in TGC.

REFERENCES

[1] Argoud, G. et al.: Diabetes 1987; 36: 959-62 2.
[2] Van Cauter, E. et al.: Diabetes 1992; 41: 368-77.
[3] Docherty, P.D. et al.: The Open Medical Informatics Journal 2009; 3: 65-76.