Title: Observation of incretin effects during enteral feed transitions of critically ill patients

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List of Abbreviations:

- ICU = Intensive Care Unit
- SPRINT = Specialised Relative Insulin and Nutrition Titration
- TGC = Tight Glycaemic Control
- $SI$ = Insulin sensitivity metric (model-based)
- $\Delta SI\%$ = 3 hours median percentage changes in insulin sensitivity
- IQR = Interquartile range
- APACHE = Acute Physiology And Chronic Health Evaluation
- EN = Enteral nutrition
- PN = Parenteral nutrition
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Abstract

Background & Aim:

Critically ill patients are regularly feed via constant enteral (EN) nutrition infusions. However, the incretin effect or its impact on endogenous insulin concentration remains unclear. This study determines whether there is an EN-driven incretin effect in critically ill patients requiring glycaemic control.

Methods:

Clinically validated, model-based time-variant insulin sensitivity ($S_I$) profiles were identified for 52 non-diabetic patients on Specialized Relative Insulin Nutrition Titration (SPRINT) glycemic control during transitions off EN (ON/OFF), and back on to EN (OFF/ON). Incretin effects were observable via increased modelled $S_I$ after the OFF/ON transition or a decreased $S_I$ after the ON/OFF transition.

Results:

Patients exhibited a median -36% (IQR -82% to 24% p=0.001) reduction after the ON/OFF feed transition, and a median of +32% (IQR -5% to 53%, p=0.05) rise in measured $S_I$ after the OFF/ON transition. However, 32% of patients exhibited increased $S_I$ at the OFF/ON transition, and 37% exhibited reduced $S_I$ at the ON/OFF transition. The results are likely due to changes in patient condition over the 5-8 hours considered outweighing this effect. Blood glucose was the same during both transitions with median shifts of -2% and -3% after the ON/OFF, and OFF/ON transitions ($p>0.5$), respectively.

Conclusions:
Results imply a significant incretin effect is observed at a cohort level. The impact was stronger for the OFF/ON transition indicating that this effect may be blunted by long-term continuous EN infusions. These results provide the data to design conclusive studies, and to inform glycemic control protocol development and implementation.

**Keywords:** incretin effect, enteral nutrition, insulin sensitivity, Specialized Relative Insulin Nutrition Titration, tight glycemic control, enteral feed transition
1. Introduction

Critically ill patients exhibit increased gluconeogenesis, reduced insulin secretion and increased insulin resistance, resulting in hyperglycemia, increased complications and increased risk of death.\textsuperscript{1-2} Studies show that glycemic control can reverse these outcomes.\textsuperscript{2-3} However, intensive insulin therapy can also lead to increased hypoglycaemia and mortality.\textsuperscript{4-5} Variable patient-specific levels of endogenous insulin secretion may also play a role, particularly in early, acute phases of care.\textsuperscript{5} In addition, the route used for the provision of nutrition can also influence the effect of intensive insulin therapy on outcome. A recent meta-analysis\textsuperscript{6} demonstrated that intensive insulin therapy was not associated with an improved outcome when enteral nutrition was used as the predominant source of calories. This finding is consistent with the presence of an incretin effect, i.e. the stimulation of endogenous insulin by enteral feeding.

The incretin effect plays an important role in regulation of glucose metabolism in healthy subjects.\textsuperscript{7} Incretin enhances the postprandial appearance of insulin. The underlying mechanisms involve the release of the hormones glucose-dependent insulinoetric polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), which are released from the intestinal mucosa when glucose is ingested. As a result insulin secretion is enhanced in excess of what would have been released if the glucose were administered parenterally.\textsuperscript{8} Studies have shown that the incretin effect can enhance the insulin response to oral glucose by 50-70% in comparison to an equivalent IV dose.\textsuperscript{9-10}
Although many incretin effect studies have addressed the distinct physiology of diabetic and non-diabetic individuals, the incretin effect remains to be observed in a critically ill cohort. Critically ill patients are fed differently, typically relying on constant enteral (EN) infusions. Hence, it is possible that there is no incretin effect in these patients, who otherwise display significantly enhanced endogenous insulin secretion. Equally, their highly counter-regulated state and wide range of insulin secretion rate may result in a blunting of this responses as seen similarly in individuals with type 2 diabetes.

This study uses dense clinical data and a model-based analysis to observe the incretin effect via tracking the model-based insulin sensitivity ($S_I$) in a cohort of critically ill patients. Specifically, we hypothesized that model-based $S_I$ would fall during interruptions of EN and would rise when EN is re-started. These changes in $S_I$ would support the presence of an EN-related incretin effect in the population of non-diabetic critically ill patients studied.

2. Methods

2.1. Patient cohort

The data used in this paper was obtained from the Specialized Relative Insulin Nutrition Titration (SPRINT) study. Blood glucose concentration ($BG$) and enteral (EN) nutrition data from 371 critically ill patients on SPRINT study are used. These 371 patients were undergoing SPRINT tight glycaemic control (TGC), with 97% of patients had 50% or more
of their BG within a 4.0 to 7.0 (mmol·L$^{-1}$), where insulin and nutrition are given in balance based on estimated response to the prior insulin and nutrition intervention.$^{13}$ Hence, the protocol will prevent hyperglycaemia by matching the nutrition and exogenous insulin given to the body’s patient-specific ability to utilise them. Full details on this study can be obtained from Chase et al. (2008).$^{14}$ Specifically, the study inclusion required a minimum of 10 hours of EN feeding, followed by at least 7 hours with EN off, and then at least 5 hours of resumed feeding. Hence, only 52 of 371 SPRINT patients’ data were selected based on these criteria. Patients with diabetes (N=64) were also excluded due to irregularity of the incretin effect that is known to occur in diabetes.$^{9-10}$ This study omitted 255 further, non-diabetic patients as they did not have a period of zero EN input.

The clinical details of this cohort, including baseline variables, Acute Physiology and Chronic Health Evaluation (APACHE) II scores and APACHE III diagnosis codes are summarized in (Table 1). Data from the excluded non-diabetic patients (N=255) is added for comparison.

Table 1

The transition off EN (ON/OFF) is defined when EN nutrition given to the patient is stopped, while the (OFF/ON) transition when EN is started again. These times are known to within ±30 minutes from chart data. The glucose input from EN infusion varies from 0 to 1.65 (mmol·min$^{-1}$) where the range of patient-specific goal nutrition rates is 0.4 (mmol·min$^{-1}$) to
0.8 (mmol·min⁻¹). The compositions of EN were either from Glucerna® 1.2 CAL (Abbott) or RESOURCE® Diabetic (Novartis). The nutritional compositions are given in Table 2.

2.2. Identification of Model-Based $S_I$

Model-based $S_I$ is identified assuming constant endogenous insulin secretion as secretion cannot be directly measured at bedside. This assumption is required to measure the presence of an incretin effect with an increased modelled $S_I$ after the ON/OFF feed transitions. $S_I(t)$ is identified hourly using integral-based methods and clinical data.

The clinically validated Intensive Control Insulin-Nutrition-Glucose (ICING) model presented by Lin et al. is used to measure $S_I$ hourly from each patient’s clinical data:

$$
\dot{BG} = -p_G BG(t) - S_I(t) BG(t) \frac{Q(t)}{1 + \alpha_G Q(t)} + \frac{P(t) + EGP_b - CNS}{V_G} \tag{1}
$$

$$
\dot{Q} = n_I(l(t) - Q(t)) - n_C \frac{Q(t)}{1 + \alpha_G Q(t)} \tag{2}
$$

$$
\dot{l} = -n_{IL} l(t) - n_{II} l(t) - n_I(l(t) - Q(t)) + \frac{u_{ex}(t)}{V_I} + (I - x_I) \frac{u_{en}}{V_I} \tag{3}
$$

where: $BG$ (mmol·L⁻¹) denotes the glucose above an equilibrium level, $l$ and $Q$ are plasma and interstitial insulin, respectively (mU·L⁻¹), exogenous insulin is $u_{ex}(t)$ (mU·min⁻¹), $n_I$ (min⁻¹) defines the diffusion constant of insulin between compartments, and $n_C$ (min⁻¹) is the
cellular insulin clearance rate from interstitium. Patient endogenous glucose removal and insulin sensitivity are $p_G$ (min$^{-1}$) and $S_I$ (L·mU$^{-1}$·min$^{-1}$), respectively, glucose and insulin distribution volume are $V_G$ (L) and $V_I$ (L), Michaelis-Menten functions are used to portray saturations, with $\alpha_I$ (L·mU$^{-1}$) dictating the saturation of plasma insulin clearance, and $\alpha_G$ (L·mU$^{-1}$) for saturation of insulin-mediated glucose removal, $n_K$ (min$^{-1}$) and $n_L$ (min$^{-1}$) are the renal and hepatic insulin clearance rates, respectively, $x_L$ is the first pass hepatic clearance ratio$^{19}$, while $u_{en}$ is the endogenous insulin production (1000 mU·min$^{-1}$).

Enteral nutrition (EN), $P(t)$ is defined with Equations 4-6:

$$\dot{P}1 = -d_1 P1 + D(t) \tag{4}$$

$$\dot{P}2 = -\min(d_2 P2, P_{max}) + d_1 P_1 \tag{5}$$

$$P(t) = \min(d_2 P2, P_{max}) + PN(t) \tag{6}$$

where: $P1$ and $P2$ (mmol) represent the glucose in the stomach and gut, respectively, $P(t)$ is the glucose appearance in plasma (mmol·min$^{-1}$) from enteral nutrition. The parameters $d_1$ and $d_2$ are used to describe the rate of glucose transport through the enteral route into the bloodstream. These parameters are assumed constant across the cohort ($d_1 = 0.0347$ min$^{-1}$ and $d_2 = 0.0069$ min$^{-1}$)$^{18}$ whereas both parameters can vary significantly between individuals, potentially affecting description of transient changes in plasma glucose appearance after changes in EN feeding, and thus the modelling of $S_I$. The rate of transport from $P2$ is limited to the maximal gut glucose flux ($P_{max} = 6.11$ mmol·min$^{-1}$), and also $D(t)$ represents the glucose input from EN infusion (mmol·min$^{-1}$).
This model has been clinically validated with median prediction error less than 4-5%\(^{18}\) and is currently used in several clinical glycaemic control trials.\(^{20-21}\)

### 2.3. Data Analysis

A reduction in observed \(S_l\) after the ON/OFF transition implies an un-modelled decrease in the rate of endogenous insulin production due to incretin effects. In contrast, an increase in observed \(S_l\) implies an incretin effect at the OFF/ON transition. The \(S_l\) change (\(\Delta S_l\)) across the ON/OFF and OFF/ON transitions indicates an incretin effect for this cohort. \(\Delta S_l\) was calculated as:

\[
\Delta S_l = \frac{S_l(\text{after}) - S_l(\text{before})}{\text{mean}(S_l(\text{after}) - S_l(\text{before}))}
\]  \(\text{(7)}\)

The blood glucose changes, \(\Delta BG\) were also calculated similar to the \(\Delta S_l\).

The analysis uses a 3-hour moving average to reduce the effect of measurement error, noise, and the influence of transient effects caused by the cohort-constant assumption of these model terms. \(S_l\) profiles are derived over periods starting 3 hours before a transition until 5 hours after the transition. The 5-hour limit allows full gut emptying after ON/OFF transition or full resumes of the effect EN after the OFF/ON transition. Between these times, an incretin effect would show a steady biased shift in \(S_l\), if it exists. Results are illustrated via Bland–Altman plots, while Wilcoxon rank sum tests are used to compare distributions and the significance of any shift in \(S_l(t)\) over the cohort.
3. Results

Measured glucose data, EN model input data as well as ICING model fits of $BG$, $I$, $Q$, $S_I$ and $P$ are shown in (Fig. 1) for a typical case. The incretin effect is observed directly via insulin sensitivity changes ($\Delta S_I$) at ON/OFF and OFF/ON transitions.

Fig. 1.

(Table 3) summarises $\Delta S_I$ at the ON/OFF transition across the cohort. $S_I$ decreased after the ON/OFF transition until $t=+4$ hours, where it settled to a median reduction of -36%. The right-most column shows the number of confounders ($\Delta S_I > 0$). This implies that inter-patient or intra-patient variation obscures the observation or that the effect itself is not always observable. $\Delta S_I$ data after the OFF/ON transition are shown in (Table 4). Median $\Delta S_I$ increased by +32% (IQR -1 to 60%) at $t=+3$ hours after the OFF/ON feed transition. The number of confounders was slightly lower after the OFF/ON feed transition. In both cases, $BG$ remains effectively constant with only small changes. Hence, the impact of the incretion effect on glycaemia was quickly accounted for by the SPRINT glycaemic control protocol.

Table 3

Table 4
$S_I$ correlations over the ON/OFF ($r=0.49$, median=-36%, $p=0.0001$) and OFF/ON ($r=0.60$, median=+31%, $p=0.03$) transitions for $t=+4$ hours are shown in (Fig. 2). The changes in (Table 3–4) are evidenced by the bias about the equality line. (Fig. 2) shows the diversity of $\Delta S_I$ across both transitions.

**Fig. 2.**

Bland-Altman representations of the $\Delta S_I$ changes between $t=-2$ and $t=+4$ hours are shown in (Fig. 3). Only 3 patients clearly showed high $\Delta S_I$ measurements (>100%). These patients were diagnosed with either sepsis or pancreatitis. Both conditions significantly affect endogenous insulin secretion independently. Most changes show a clear shift with relatively consistent behaviours.

**Fig. 3.**

Bland-Altman representations the shifts in $BG$ after the ON/OFF and OFF/ON transitions between $t=-2$ and $t=+4$ hour’s are shown in (Fig. 4). The maximal median $BG$ shift across the cohort was -4% at the ON/OFF transition and +6% at the OFF/ON transition when $t=+3$ and $t=+4$ respectively. Median difference between these two transitions was approximately -1% at $t=-1$, +1, and +2 indicating tight consistent glucose levels across the cohort. The few
patients outside the 90% confidence interval (CI) were identified as having pancreatitis or similar diseases that significantly affect insulin secretion and thus, this analysis.

4. Discussion

This study showed the potential existence of an incretin effect after EN transitions (ON/OFF and OFF/ON) in a cohort with similar controlled BG levels. The incretin effect was observed via changes in model-based $S_I$ after transitions onto and off EN feed. This effect has been previously observed using different techniques in various, non-critically ill cohorts. In this study, a slightly stronger incretin effect is observed at OFF/ON EN feed transition.

The changes in plasma insulin via insulin secretion and activation by the liver were assumed to be observable through changes in measured $S_I$. The variability observed was outside the normal variation, which is centred around zero. Thus, the incretin effect was measured using the shift in $S_I$ after EN feed transitions as a surrogate rather than direct insulin measurement. Nauck et al. found that C-peptide responses after oral and intravenous glucose were less marked than between insulin responses. This implies that a considerable part of the different insulin responses to oral and intravenous glucose may be due to altered hepatic insulin extraction. Thus, it could be concluded that insulin sensitivity changes are more efficient indicator for post-hepatic endogenous insulin appearance, given the two possible outcome causes noted. A further study to confirm these findings could be verified with added insulin and/or C-peptide data.
ΔBG changes were insignificant over these transitions indicating there was no bias to this factor in the model-based analysis. Equally, this model and $S_I$ metric have been clinically validated on independent matched cohorts,\textsuperscript{13} in several clinical TGC studies,\textsuperscript{12} and against the gold-standard euglycaemic clamp.\textsuperscript{25}

The insulin response to EN glucose was noticeably enhanced after the OFF/ON transition, most likely as a result of the concomitant actions of incretins and neural responses to enteral nutrition. The predominant effect of incretin hormones is to enhance the endogenous insulin secretion that is triggered when the $\beta$-cells are exposed to rapid increases in glucose flux.\textsuperscript{24} At a cohort level, $\Delta S_I$ stabilised at $t=+4$ hours after EN transitions as the feed was designed for enhanced glycaemic stability via slow digestion.\textsuperscript{15-16} Hence, both transitions should have excited a change, but the OFF/ON transition may have observed better or more rapid change due to the essentially fasted patient state.

The Bland-Altman plots of $\Delta S_I$ (Fig. 3) show that the few larger outliers were diagnosed with chronic diseases that influence the pharmaco-dynamics of insulin and glucose. Patients with sepsis, trauma or pancreatitis can exhibit more drastic $S_I$ changes\textsuperscript{26} due to excessive counter-regulatory and acute immune response, as well as the direct affect on secretion with pancreatitis. Hence, the variability of results was reasonably expected, where the analysis without these 3-5 subjects did not change the overall results. Also, studies show that many metabolic abnormalities associated with stress, injury or infections were related to a loss of tissue sensitivity to insulin.\textsuperscript{26} Sepsis, trauma and other clinical states are characterized by a strong counter-regulatory hormone response. These hormone responses are believed to induce insulin resistance \textit{in vivo}, although some clinical studies failed to demonstrate
correlations between the counter-regulatory hormone response and defective insulin-mediated glucose disposal. However, the overall evidence is still inconclusive concerning the exact cellular and molecular mechanisms underlying insulin resistance in critical illness and their relationship to the observed metabolic abnormalities.

Specifically, this analysis consists of a group selected from a general ICU cohort (see Table 1 with a representative mixture of typical ICU diagnostic codes) who met the criteria that would enable the incretin effect to be observed in this study if the effect existed. It is not designed, as a trial to guarantee representation of any specific ICU cohort in particular. However, as seen in Table 1 the groups are similar in age and severity of illness compared to the remaining (non-diabetic) SPRINT cohort from which these 52 were extracted. The diagnostic groupings are less similar but still broadly represent a medical ICU cohort. Hence, the cohort analysed were not different from the overall SPRINT cohort or a typical medical ICU cohort, except in that they had nutritional stoppages for clinical reasons that enabled this study. Thus, these results justify a more direct clinical validation trial with measurement of insulin, C-peptide and incretin hormones during enteral and parenteral feed transitions. This may provide direct evidence of the incretin effect observed in this study and also provide enough data to allow generalisation of the result for broader cohorts. These results are sufficient to justify and define the needed cohort size to power such a validation trial.

It is generally accepted that intravenous parenteral nutrition (PN) prompts a lesser endogenous insulin secretion than EN nutrition, and thus may limit the incidence of hypoglycaemia due to un-modelled insulin secretion. Plasma insulin responses to glucose given by gastric or jejunal intubation were significantly greater than those seen after IV
infusion of the same glucose load in some studies. Likewise, Petrov et al. reported a higher prevalence of hyperglycemia during parenteral than enteral nutrition. Hence, if the risk of hypoglycaemia could be mitigated via advanced modelling methodology, the potential benefits of the incretin effect could aid patient recovery. In addition, enteral nutrition is also associated with a significantly lower incidence of infection, sepsis and bacterial translocation that may reduce the need for surgical interventions to control pancreatitis and a reduced length of hospital stay.

This study examined changes in $S_1$ about EN feeding transitions. Limited PN data (N<6) somewhat limited observation of the incretin effect with EN according to its most commonly used definition in comparison to PN. In this study, the SPRINT glycaemic control protocol also modulates enteral dextrose carbohydrate to aid control of hyperglycaemia, rather than the characterising the overall nutritional profile. Hence, a cross-over analysis with PN was not possible. A study conducted by Van den Berghe et al. found that a high glucose loading, via PN, with inadequate glycemic control is associated with increased morbidity and mortality rates. Thus, an ideal study design for the observation of incretin in critically ill patients that also used PN feeding in a cross-over format might have ethical limitations. In contrast, future studies could incorporate direct measurement of incretin hormones, such as GIP and GLP-1. This approach would also allow direct incorporation and identification of additional incretin hormone-related model parameters, as well as direct measurement of the effect without relying on PN analysis.

5. Conclusions
Overall, the findings of this study show the distinct existence of an incretin effect as an observable aspect of critically ill patient physiology. The findings were consistent with the presence of an EN-related incretin effect in a majority of critically ill patients. Clinically, the existence of this effect at EN nutrition transitions should also be considered in the management of glycaemia and could influence design of this therapy. Finally, while the results observed valid surrogates of the incretin effect, a prospective study with direct measurement and powered by these results may be required to confirm the outcomes directly.
Conflict of Interest:
The authors declare that they have no competing interests.
Statement of Authorship:

All authors have made substantial contributions and final approval of the conceptions, drafting, and final version of the manuscript.
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Figure legends

**Fig. 1.** A typical patient’s fitted profile. (A) Blood glucose, plasma insulin and interstitial insulin fitted profiles (B) EN rate (C) Time variant insulin sensitivity ($S_t$).

**Fig. 2.** The distributions of $S_t$ for two EN transitions of ON/OFF (A) and OFF/ON (B) EN transitions at the centred time averages of $t=-2$ and $t=+4$ hours (N=52). (Note the log-scale).

**Fig. 3.** The Bland-Altman of the averages of proportional change $S_t$ after the ON/OFF (A) and OFF/ON (B) EN transitions at the centred time averages of $t=-2$ and $t=+4$ hours (N=52).

**Fig. 4.** The Bland-Altman of the averages of proportional change $BG$ after ON/OFF (A) and OFF/ON (B) EN transitions at the centred time averages of $t=-2$ and $t=+4$ hours (N=52).
# Patient Data from SPRINT

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<th>Excluded, Non-Diabetic Cohort</th>
<th>Included Cohort</th>
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<tbody>
<tr>
<td>N</td>
<td>N=255</td>
<td>*N=52</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 [51-74]</td>
<td>65 [49-72]</td>
</tr>
<tr>
<td>% Male</td>
<td>70%</td>
<td>67%</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>18 [14-23]</td>
<td>19 [17-28]</td>
</tr>
</tbody>
</table>

* N=52 are the patient data used in this study. Note N=255 and N=52 exclude diabetic data.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of Patients (%)</th>
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<tbody>
<tr>
<td>Cardiovascular</td>
<td>38 (15%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>64 (25%)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>11 (4%)</td>
</tr>
<tr>
<td>Neurological</td>
<td>21 (8%)</td>
</tr>
<tr>
<td>Trauma</td>
<td>38 (15%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>71 (28%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(Renal, metabolic, orthopaedic)</th>
</tr>
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**Table 1** SPRINT Cohort baseline variables for included patients and non-diabetic excluded patients. Data are expressed as median [IQR]. (APACHE = Acute Physiology and Chronic Health Evaluation).
<table>
<thead>
<tr>
<th></th>
<th>Glucerna® 1.2 CAL (Abbott)</th>
<th>RESOURCE® Diabetic (Novartis)</th>
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</thead>
<tbody>
<tr>
<td>Carbohydrate</td>
<td>35 %</td>
<td>36 %</td>
</tr>
<tr>
<td>- Fiber</td>
<td>16 g/1000 mL</td>
<td>12 g/1000 mL</td>
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<tr>
<td>Protein</td>
<td>20 %</td>
<td>24 %</td>
</tr>
<tr>
<td>Fat</td>
<td>45 %</td>
<td>40 %</td>
</tr>
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</table>

Table 2 Enteral nutrition composition based on GLUCERNA® 1.2 CAL and RESOURCE® Diabetic (Novartis). 13-14
Table 3 Summary of proportional change of blood glucose ($\Delta BG$) and insulin sensitivity, ($\Delta S_I$) at ON/OFF feed transition (N=52). (*times are 3-hour averages centred at the time shown, and feed transition between t=-1 and 0. EN feed is stopped anytime between t=-1 and t=0).
## Table 4

Summary of proportional change of blood glucose ($\Delta BG$) and insulin sensitivity ($\Delta SI$) at OFF/ON feed transition (N=52). (*times are 3-hour averages centred at the time shown, and feed transition between $t=-1$ and $t=0$. EN feed is stopped anytime between $t=-1$ and $t=0$).
Figures

Fig. 1.
Fig. 3.
Fig. 4.