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Asymmetric changes in circulating insulin levels after an increase compared with a reduction in insulin pump basal rate in people with Type 1 diabetes

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What's new?

- After small insulin pump basal rate changes (typical of those programmed in clinical practice), there are substantial delays until changes in circulating insulin levels occur.
- For small basal rate changes of equal magnitude, it takes longer to achieve changes in circulating insulin after a rate reduction than after an increase.
- Clinical decisions regarding insulin pump basal rate changes should take account of the direction of rate change in addition to the magnitude.
- The time of day warrants consideration when anticipating the clinical effects of basal rate changes, as counter-regulatory hormone circadian variation may affect glycaemia when implementing minor changes at low basal rates.

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Abstract

Aims To investigate circulating insulin profiles after a clinically relevant insulin pump basal rate increase vs a reduction, and the associated glucose responses.

Methods A cohort of 12 adults with Type 1 diabetes undertook this two-stage university hospital study using Accu-Chek pumps (Roche Diagnostics, Mannheim, Germany) and insulin aspart. An insulin basal rate change of 0.2 unit/h (increase in first stage, reduction in second stage) was implemented at ~09:30 h, after a single overnight basal rate (without bolus insulin), while fasting participants rested. Frequent venous samples for the assessment of plasma free insulin, glucose and cortisol were collected from 60 min before until 300 min after rate change. The primary outcome was time to steady-state insulin.

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Results The 0.2-unit/h rate change represented a mean ± SD alteration of 23 ± 6%. After the rate increase, the median (interquartile range) times to 80% and 90% steady-state insulin were 170 (45) min and 197 (87) min, respectively. By contrast, after rate reduction, 80% steady-state insulin was not achieved. After the rate increase, mean ± SE insulin levels increased by 4.3 ± 3.1%, 12.0 ± 2.9% and 25.6 ± 2.6% at 60, 120 and 300 min, respectively (with no significant difference until 180 min). After the rate reduction, insulin decreased by 8.3 ± 3.0% at 300 min (with no significant difference until 300 min). After rate reduction, glucose levels paradoxically declined by 17.4 ± 3.7% after 300 min; cortisol levels also fell during observation (P=0.0003).

Conclusions The time to circulating insulin change after a 0.2-unit/h basal rate change was substantial, and was greater after a reduction than after an increase. Counter-regulatory hormone circadian variation may affect glycaemia when implementing minor changes at low basal rates. Both direction of basal rate change, and time of day, warrant consideration when anticipating the clinical effects of basal rate changes.

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Introduction

Subcutaneous delivery of rapid-acting analogue insulin via pump is increasingly being used by people with Type 1 diabetes [1–5]. Matching insulin dosing to individuals' varying insulin requirements is crucial to optimizing health and minimizing diabetes burden [6–8]. Insulin pumps provide the most flexible method of subcutaneous insulin delivery [9]. For adults, ~50% of insulin delivered via pump is basal insulin, therefore, decisions regarding basal rate adjustments may have a significant impact on metabolic control. The evidence on which basal dosing changes are based is a major factor in determining the effectiveness of these decisions, which, in turn, have an impact on physical and emotional well-being.

Detailed pharmacokinetic information is available regarding subcutaneous bolus delivery of rapid-acting insulin analogues [10,11]; however, scientific evidence for insulin pump basal rate changes is limited, predominantly pertaining to changes≥50% [12–15]. Yet, basal rate changes in clinical care are typically substantially less than 50%. With limited evidence to guide insulin pump basal rate adjustment in clinical practice, bolus

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pharmacokinetic data are often extrapolated. There are no data relating to insulin analogue basal rate reductions typical of basal profiles implemented clinically. Limited evidence regarding increases in basal insulin delivery indicates that, after large increases (e.g. 100%), it takes longer until changes in circulating insulin are observed than after bolus insulin delivery, and time to steady-state increases with the magnitude of basal increase [12,13]. In addition, although circadian changes in insulin sensitivity probably influence the impact of insulin on glycaemia, there is a lack of published information about this to guide clinical basal insulin dosing adjustment.

We hypothesized, first, that changes in circulating insulin after modest basal rate increases and reductions, typical of those used clinically, would not reflect profiles reported after large basal rate changes or with insulin bolus administration and, second, that circadian influences (including cortisol) that affect insulin sensitivity may influence basal insulin requirements. The primary aim of the present study was to investigate changes in circulating insulin after clinically relevant basal rate changes.

Methods

A prospective, two-stage study comparing insulin pump basal rate increase with basal rate reduction (ACTRN12612000449831) was conducted at St Vincent's Hospital Melbourne, Australia, after obtaining ethics committee approval and in accordance with the principles of the Declaration of Helsinki. All study visits were conducted by the same researchers (S.A.M. and J.C.H.). Volunteers were recruited from the hospital's diabetes clinics between April and November 2012; follow-up was completed in December 2012.

The insulin basal rate change selected for investigation, 0.2 units/h, was chosen after a review of insulin pump uploads from 69 adults with Type 1 diabetes attending St Vincent's Hospital Melbourne diabetes clinics. This review showed that the mean ± SD basal rate was 1.0±0.4 units/h, and the mean rate change magnitude was 0.21±0.04 units/h.

Participants

People aged >18 years with Type 1 diabetes, who had been using insulin pump therapy for ≥3 months, with established insulin delivery parameters, including overnight basal rates 0.60–1.40 units/h, were eligible. To enable implementation of a single basal rate from 02:00 h, individuals were excluded if their overnight rates varied by >0.20 units/h. Other exclusion criteria included diabetic ketoacidosis or severe hypoglycaemia within the preceding 3

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months, nephropathy (estimated GFR <40 ml/min/1.73 m^2), BMI <18 or >30 kg/m^2, and pregnancy.

Experimental protocol

There were two stages to the study: a basal rate increase stage followed by a basal rate reduction stage, with ~2 weeks between stages. Each stage was implemented as des cribed below.

Day 1

On day 1, participants attended the temperature-controlled trial centre at ~17:00 h and undertook an insulin delivery line change. Subcutaneous insulin aspart (NovoRapid; Novo Nordisk, Bagsvaerd, Denmark) was infused as per participants' established pump settings using standardized equipment: Accu-Chek Spirit Combo insulin pump (Roche Diagnostics, Mannheim, Germany); an 8-mm Teflon cannula, inserted 90° to anterior abdomen; and a 60-cm infusion line. A single overnight basal rate was achieved during the study by adjusting participants' usual basal delivery by up to 0.2 units/h.

Day 2

On day 2, participants undertook their usual activities.

Day 3

From midnight on day 3, participants fasted and received subcutaneous insulin delivered at a single basal rate without bolus insulin. Participants attended the trial centre at ~08:00 h. Bilateral intravenous 20-gauge cubital fossa cannulae were inserted for venous sampling and intravenous fluid, respectively. Starting at ~08:30 h, participants were observed whilst resting for 360 min. During observation, non-arterialized venous samples were collected at 15-min intervals for measurement of insulin, glucose and (hourly) cortisol. After a 60-min observation period, the basal rate was changed by 0.2 units/h (increased in the first stage, reduced in the second). After the 0.2- unit/h change, the rate was kept unmodified for 300 min. In the event of hypoglycaemia (<4.0 mmol/l), supplemental oral and intravenous glucose were administered. After stage completion, participants resumed their usual activities and diabetes care.

During both stages, intravenous 0.9% saline (154 mmol/l NaCl) was infused (100 ml/h) during venous sampling (6 h) to maintain euvolaemia. During the basal rate increase

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stage, when baseline blood glucose was ≤10 mmol/l, intravenous 5% dextrose was infused (100 ml/h, instead of saline) to minimize hypoglycaemia risk. In view of the differing dextrose protocols, glycaemia was not compared between stages.

Laboratory assays

All samples from each participant were measured in the same assay run. Plasma anti-insulin antibodies and free insulin concentrations were measured using a radioimmunoassay, and laboratory plasma glucose was quantified by a glucose oxidase method using a YSI Glucose Analyser (YSI, Yellow Springs, OH, USA), as previously described [14]. Plasma cortisol was quantified immunometrically by chemiluminescence (Abbott Laboratories, Abbott Park, IL, USA); inter-assay coefficient of variation 6.0% at 95 nmol/l and 3.4% at 449 nmol/l. Meter glucose was measured by Optium Xceed (Abbott Diabetes Care, Whitney, UK) using a glucose oxidase method with whole venous blood.

Statistical analysis

This was an exploratory study, with lack of available data regarding intra-individual variability of subcutaneous insulin analogue absorption when infused subcutaneously via pump to enable power calculations. Results are presented as mean ± SE unless otherwise specified. Two-tailed *P* values <0.05 were considered statistically significant. The primary outcome was time to steady-state insulin after basal rate change. Secondary outcomes related to the impact of rate change on circulating insulin and glucose profiles.

STATA version 13.0 and GRAPHPAD PRISM version 7.00 were used. Time to 80% and 90% steady-state insulin was calculated by fitting a three-variable logistic function to the individual data [16]. Changes over time and comparison of stages were evaluated using repeated-measures ANOVA with *post hoc* comparisons corrected using the Bonferroni method. Incremental plasma insulin area-under-the-curve calculations followed the Wolever method [17], with comparison using Wilcoxon's signed-rank test.

Fractional glucose disappearance was calculated after adjusting for the glucose infusion rate as described in the Pacberg euglycaemic clamp algorithm [18]. Relationships between fractional glucose disappearance with insulin and cortisol were assessed using multiple regression analysis. Correlation between cortisol and fractional glucose disappearance adjusted for insulin was calculated using a Spearman’s rank-order correlation test.

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Results

A total of 12 participants undertook the study; their clinical characteristics are summarized in Table 1. All had a fasting C-peptide concentration <0.1 nmol/l, and none was a shift worker. From a baseline mean ± SD basal rate of 0.91 ± 0.23 units/h, the 0.2 unit/h rate change implemented represented a mean ± SD 23 ± 6% alteration to the antecedent basal delivery.

All participants completed the rate increase stage. Two participants discontinued the rate reduction stage ~1 h post-reduction: one as a result of hyperglycaemia with ketosis, necessitating insulin bolus (a withdrawal criterion), and one because of a vasovagal episode. These participants' results were excluded from the rate reduction stage analysis. During the rate increase stage, seven participants had baseline day 3 blood glucose <10 mmol/l, therefore intravenous dextrose was administered (as per protocol). No hypoglycaemic event occurred during venous sampling during the rate increase stage. During the rate reduction stage, three participants required glucose supplementation to treat mild hypoglycaemia (plasma glucose nadir 3.4–3.7 mmol/l).

Insulin levels

Free insulin levels during the baseline hour did not differ between basal rate increase and basal rate reduction stages (65 ± 2 and 69±2 pmol/l, respectively; *P*=0.17; Fig. 1). After a basal rate increase, median (interquartile range) times to 80% and 90% steady-state insulin were 170 (45) min and 197 (87) min, respectively. By contrast, after rate reduction, 80% steady-state insulin was not reached by 300 min in any participant. During observation after rate change, there were asymmetrical free insulin changes when comparing rate increase with rate reduction stages: the incremental area under the curve above baseline after rate increase was greater than the incremental area under the curve below baseline after rate reduction (5286 [3435] vs 551 [696] pmol·min/l; *P*=0.047). After basal rate increase, free insulin increased from baseline by 4.3 ± 3.1%, 12.0 ± 2.9% and 25.6 ± 2.6% at 60, 120 and 300 min, respectively (with no significant difference from baseline to 180 min). After rate reduction, free insulin reduced from baseline by 2.4 ± 2.8%, 4.8 ± 2.9% and 8.3 ± 3.0% at 60, 120 and 300 min, respectively (with no significant difference from baseline to 300 min).

Glucose levels

Plasma glucose levels did not differ between rate increase and rate reduction stages during the baseline hour (9.3 ± 0.8 and 8.7 ± 1.1, respectively; *P*=0.86; Fig. 2A). After basal rate

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increase, plasma glucose fell from baseline by 3.9 ± 3.4%, 3.3 ± 3.5% and 25.7 ± 4.8% at 60, 120 and 300 min, respectively (with no significant difference from baseline to 225 min). After basal rate reduction, plasma glucose paradoxically fell from baseline by 4.8 ± 3.2%, 5.5 3.2% and 17.4 ± 3.7% at 60, 120 and 300 min, respectively (with no significant difference from baseline to 255 min).

Cortisol levels

Starting plasma cortisol levels at ~08:30 h did not differ between the stages (P=0.26), and were reduced similarly in both stages during observation (P=0.93 comparing stages; Fig. 2B). During the full 360-min observation, plasma cortisol levels declined by 119 ± 28 nmol/l during the basal rate increase stage (P=0.002), and declined by 116±20 nmol/l during the rate reduction stage (P=0.0003).

Fractional glucose disappearance

The calculated fractional glucose disappearance rate rose after a basal rate increase (reaching significance by 135 min). After rate reduction, the fractional glucose disappearance rate paradoxically trended upwards (although did not reach significance). Comparing changes in fractional glucose disappearance after rate increase vs reduction, the difference reached significance 180 min after a basal rate change; when adjusted for insulin levels, there was no significant difference between stages. Overall, fractional glucose disappearance correlated positively with plasma insulin and negatively with plasma cortisol (P=0.005). Contributions to this association differed by study stage. During the rate increase stage, after adjustment for plasma insulin, there was no association between the decrease in cortisol and fractional glucose disappearance (P=0.73). During the rate reduction stage, after adjustment for plasma insulin, a positive association was observed between the decrease in plasma cortisol level and fractional glucose disappearance (P=0.009).

Discussion

In the present study in adults with Type 1 diabetes we compared the effects of a clinically relevant insulin pump basal rate increase vs a reduction on plasma free insulin levels, and assessed associated glucose responses. The principal study findings were as follows: (1) asymmetric changes were observed in circulating insulin after basal rate increase vs reduction; (2) the time taken to affect circulating insulin levels was longer than predicted from data relating to bolus insulin delivery; and (3) cortisol circadian variation may

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significantly influence glycaemia, via changes in insulin sensitivity, when basal insulin delivery rates are low.

We observed that a 0.2-unit/h (~23%) change in insulin pump basal delivery resulted in delayed and gradual changes in circulating insulin levels. The Roche insulin pump used in the study delivers basal insulin subcutaneously via micro-boluses at 3-min intervals [19], therefore the study basal rate alterations were implemented within 3 min. No significant change in plasma free insulin level was observed until 3 h after a 0.2-unit/h rate increase, and until 5 h after a 0.2-unit/h reduction. In addition, steady-state plasma insulin was approached 3–4 h after rate increase, but had not occurred by 5 h after rate reduction. These findings of asymmetry and delay until the effect of a small basal rate change is apparent may reflect a buffering effect of the subcutaneous insulin reservoir between changes in subcutaneous insulin delivery and subsequent changes in the circulation [20].

Pharmacokinetic studies of rapid-acting insulin analogues report 50–60 min to maximum insulin concentration after a bolus [10,11]. Although bolus pharmacokinetics are often used to inform insulin pump basal profiles in clinical practice, our findings show bolus data have limited applicability to routine clinical pump adjustments. Effects of rapid-acting insulin analogue subcutaneous basal delivery changes ≥50% have been reported [12–15]; however, such rate changes are larger than those typically programmed within basal profiles in routine clinical care. After large basal rate increases, times to steady-state insulin have been reported of between 2.5 and 8 h, with larger increments taking longer to reach steady state [12,13,21]. The present finding of a 197-min delay until 90% steady-state insulin after a 0.2-unit/h rate increase is longer than the report of ~2 h after the 0.5-unit/h increase, and shorter than 4–8-h reported post-increases of 0.8–1.0 units/h [12,13]. To our knowledge, there are no published studies demonstrating time to steady-state insulin after small clinically relevant basal rate reductions. Our observation of a decrease of only ~8% in circulating insulin by 5 h after a 0.2-unit/h rate reduction is consistent with findings from pump studies which halved (19% fall by 3 h) [14] and ceased (70% fall by 3 h) [15] subcutaneous basal delivery. We suggest that the magnitude and direction of subcutaneous insulin basal rate changes not only determine the magnitude of the changes observed in circulating insulin, but also the time taken for these changes to be translated.

Physiological circadian variation of insulin secretion, insulin action and glucose tolerance is multi-factorial, with factors including tissue sensitivity to insulin and glucose

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counter-regulatory hormone levels implicated [22,23]. Increased insulin requirement around dawn has been demonstrated [24,25]. After study start at ~08:30 h in both stages, we observed a decline in plasma cortisol, consistent with physiological circadian episodic cortisol secretion [26,27]. Paradoxically, despite a 0.2-unit/h rate reduction, we observed an ~20% fall in glycaemia over 5 h, which paralleled declining cortisol (~40% over 6 h). Serial intravenous glycaemic clamp studies involving individuals with Type 1 diabetes show a circadian decrease in glucose utilization and glucose production, with an overall reduction in daytime glycaemia independent of insulinaemia [28]. Our findings are consistent with such circadian variation. We suggest that with circulating insulin near physiological basal levels, other hormonal influences are unmasked and effects of counter-regulatory hormones on insulin sensitivity and glycaemia become apparent. We hypothesize that the fall in glycaemia observed during both study stages was attributable at least partly to rising insulin sensitivity over the study morning, which in turn appears to be associated with declining cortisol. Calculating fractional glucose disappearance, and adjusting this for plasma insulin, tested this hypothesis. At near-basal insulin levels, as were present herein, insulin action from the minimal model represents fractional glucose disappearance [29]. After a rate increase, fractional glucose disappearance correlated more with insulin than cortisol levels; however, after rate reduction, the fractional glucose disappearance rate did not fall as expected, and glycaemia correlated with declining plasma cortisol. We propose that when insulin levels are low, the effect of circadian changes in counter-regulatory hormones on glycaemia may overshadow the effects of small reductions in basal insulin delivery.

A strength of the present study is that the basal rate change tested was congruent with typical clinical practice for adults with Type 1 diabetes, therefore, the findings have direct clinical applicability. The study design was robust, with standardized insulin, delivery equipment, cannula dwell, and equal magnitude rate changes in each direction while participants rested. By studying participants in fasting state, with a single basal rate overnight in the absence of bolus insulin, physiological basal circulating insulin levels were achieved at baseline.

The present study has some limitations. As we did not follow participants >5 h post-basal change, we cannot comment about late effects. Stage order may have led to bias; however, given there were no other changes in insulin delivery from participants' usual settings, major bias is unlikely. The study was primarily pharmacokinetic; although glucose levels are of greater clinical relevance than insulin levels, glycaemia is also affected by

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counter-regulatory hormones other than cortisol, which we did not measure or control for. Participants travelled to the hospital, therefore counter-regulatory hormones may have varied from their usual wakening levels. The fractional glucose disappearance calculations were exploratory, with the study not powered to detect changes in this metric. Finally, we studied only adults, and caution is recommended in extrapolating results to a paediatric population.

Study findings have implications for clinical decision-making regarding insulin pump therapy for adults with Type 1 diabetes. Based on our observations, it would be hard to justify more than four basal rates per day for most people. We suggest that, in order to achieve steady-state insulin after basal rate changes of conventional magnitude, rate changes within insulin pump basal delivery profiles are programmed at least 4–6 h apart (longer after a rate reduction than an increase). In addition, although insulin effects on glucose homeostasis primarily result from circulating free insulin, it is important to consider the role of varying circadian insulin sensitivity. When instituting small basal adjustments at low levels of insulin delivery, time of day (with associated counter-regulatory hormone levels and insulin sensitivity) should be considered. We propose that basal rate adjustments to influence insulin levels during late morning and early afternoon, at times of declining physiological cortisol secretion, would need less aggressive rate increases when seeking to lower glycaemia; conversely, if instituting a rate reduction intending to raise glucose levels, the change would need to be more aggressive. At times of physiological cortisol surges, such as early morning, the opposite would hold.

Our findings help address the evidence gap with regard to guiding optimum insulin pump basal delivery adjustment, and highlight the importance of considering the direction, as well as magnitude, of rate change. In addition, time of day may influence glucose counter-regulatory hormone circadian variation, overwhelming the impact of minor insulin delivery changes. Even with automated insulin delivery via a closed-loop system, basal rate optimization remains essential: programmed basal settings inform initial closed-loop delivery doses, and systems revert to manual basal delivery when closed-loop exits occur. Further research examining the pharmacokinetic and pharmacodynamic effects of continuous subcutaneous basal delivery of rapid-acting insulin analogues is warranted. Longer observation post-rate change, and assessing factors influencing intra-individual variability in insulin absorption and action after basal rate changes, are all relevant to future research optimizing insulin delivery via pump. The next generation of faster-acting insulins also require evaluation. In addition, for development of a personalized artificial pancreas, detailed

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understanding of the influence of counter-regulatory hormones and non-hormonal factors modulating glucose homeostasis will be beneficial to inform closed-loop insulin delivery algorithms.

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Competing interests

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Table 1 Clinical characteristics of study participants

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Characteristic	***N* = 12**
Age, years	36 ± 9
Women, *n* (%)	6 (50)
BMI, kg/m^2	27.1 ± 3.0
Diabetes duration, years	16 ± 9
Insulin pump therapy duration, years	4.6 ± 2.5
HbA_{1c}, mmol/mol	56 ± 8
HbA_1, %	7.3 ± 0.7
Estimated GFR, ml/min/1.73 m^2	102 ± 16
Microvascular diabetes complications, *n* (%)	2 (17)
Macrovascular diabetes complications, *n* (%)	0 (0)
Total daily insulin (units kg^{-1} day^{-1})	0.55 ± 0.12
Basal insulin proportion of total (%)	53.5 ± 12.9
Overnight basal insulin rate (units/h)	0.91 ± 0.23
Insulin antibody positive, *n* (%)	10 (83)

Data are mean ± SD, unless otherwise indicated.

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Fig. 1 Impact of 0.2-unit/h basal rate change at 0 min on circulating free insulin levels. Profiles by study stage. Values are mean ± SE. **P*<0.05 vs baseline.

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Fig. 2 Profiles of (a) plasma glucose and (b) plasma cortisol by study stage, with 0.2-unit/h basal rate change instituted at 0 min. Values are mean ± SE. *P<0.05 vs baseline.

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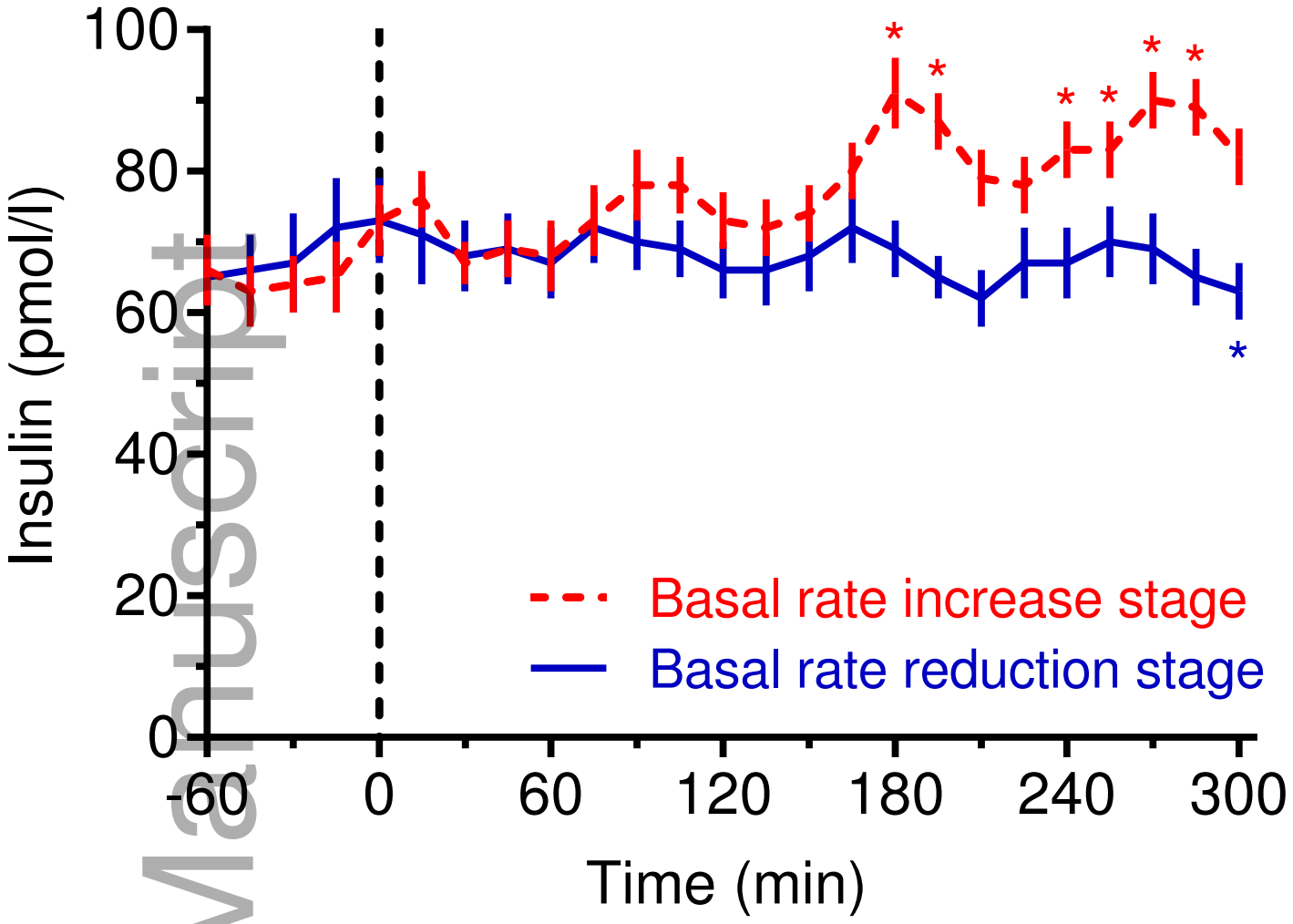

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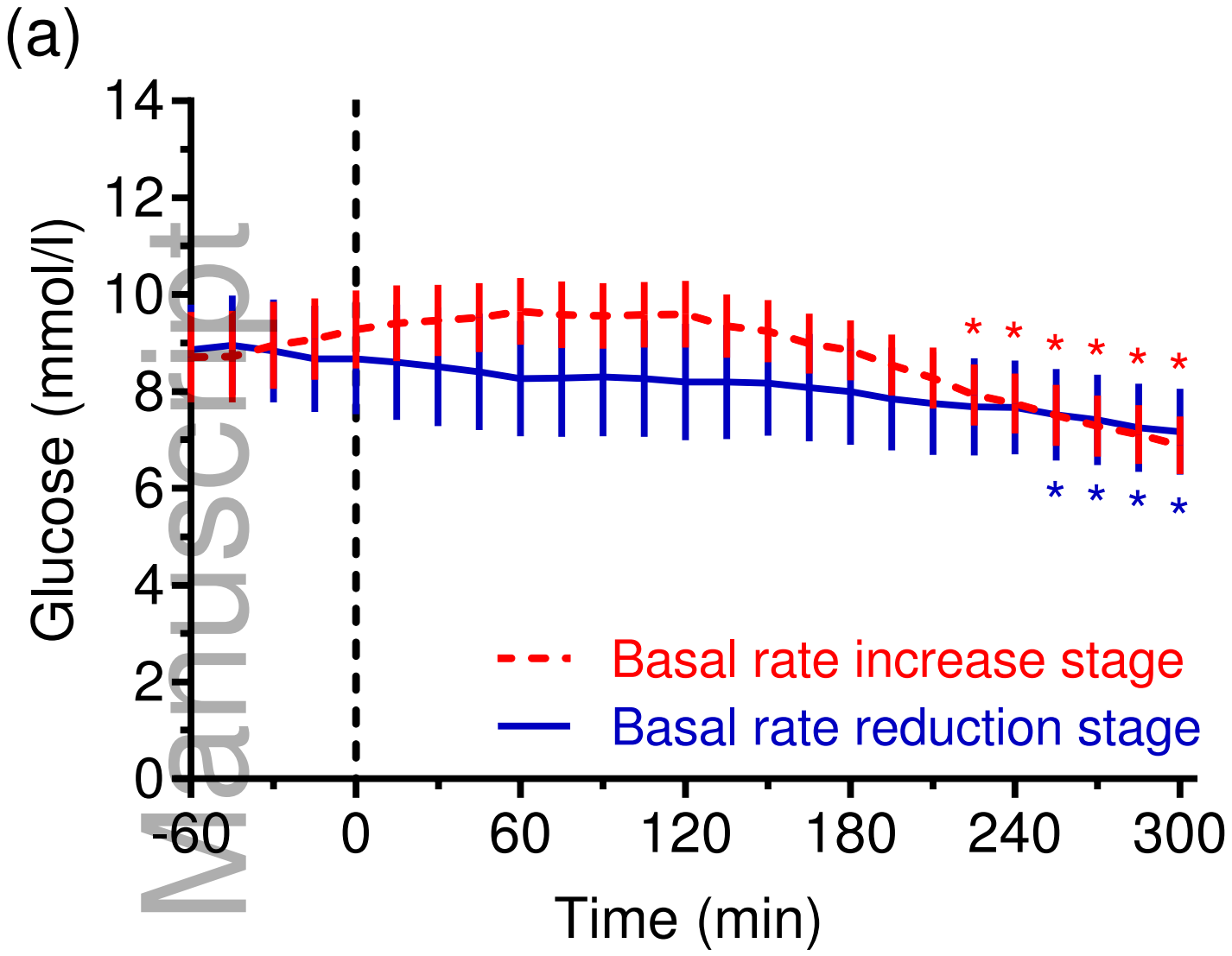

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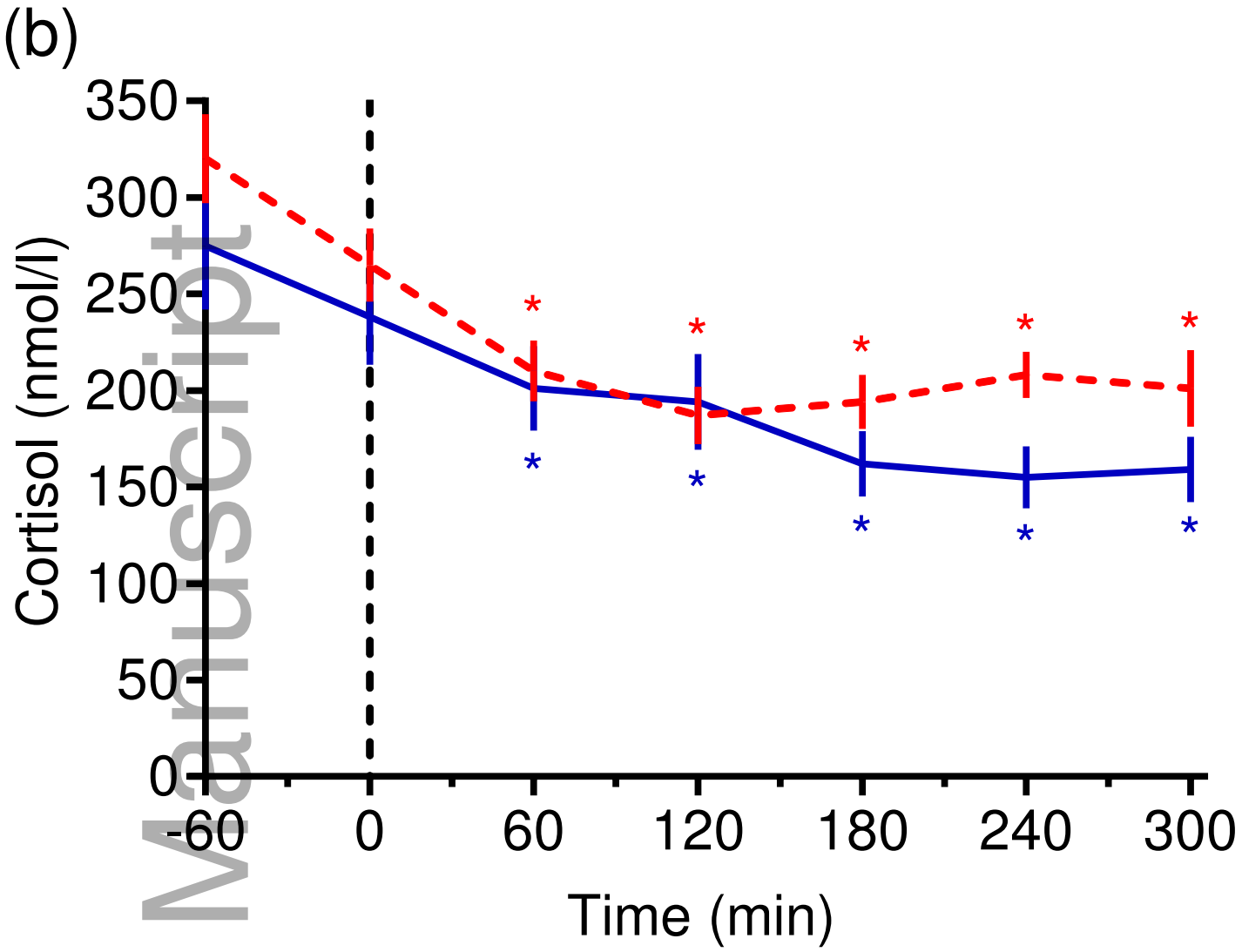

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