Impact of metoprolol on insulin sensitivity in the ICU

Christopher Pretty,* J. Geoffrey Chase,* Aaron Le Compte,* Jessica Lin, Geoffrey Shaw****

** University of Canterbury, Dept of Mechanical Engineering, Centre for Bioengineering, Christchurch, New Zealand (Tel: +64 3 364 2596; e-mail: Christopher.Pretty@pg.canterbury.ac.nz).*

***University of Otago, Dept of Medicine, Christchurch, New Zealand*

Abstract: Metoprolol (a cardio-selective β1-blocker) has been shown to reduce insulin sensitivity in 'healthy' individuals by 14-27%. It is regularly used in the Christchurch Hospital intensive care unit (ICU), but may unintentionally reduce insulin sensitivity and thus exacerbate stress-hyperglycaemia. This study used model-based methods to quantify the effect of metoprolol on insulin sensitivity in critically ill patients.

A model-based measure of insulin sensitivity was used to quantify changes between two matched retrospective cohorts of 17 ICU patients. All patients were admitted to the Christchurch hospital ICU between 2005 and 2007 and spent at least 24 hours on the SPRINT glycaemic control protocol.

A 9.7% reduction in whole-cohort median insulin sensitivity was seen between the control cohort and patients receiving metoprolol with a median dose of 100mg/d per patient. Comparing percentile patients as a surrogate for matched patients, reductions in median insulin sensitivity of less than 4% were observed for the 25th, 50th and 75th-percentile patients. These cohort and percentile patient reductions are less than the 14-27% reductions reported in 'healthy' subjects.

The limited reduction of insulin sensitivity in critically ill patients could be a result of moderation of the physiological impact of metoprolol due to already reduced levels of peripheral glucose uptake and insulin receptor sensitivity. This limited reduction is not expected to have any clinical impact on the level of tight glycaemic control achieved with the SPRINT protocol.

Keywords: Biomedical system modeling, simulation and visualization; Control of physiological and clinical variables; Cellular, metabolic, cardiovascular, neuro-systems

1. INTRODUCTION

Studies have shown that metoprolol reduces insulin sensitivity (S_I) when used to treat essential hypertension in otherwise healthy individuals (Jacob et al., 1996, Pollare et al., 1989). However, to the authors' knowledge there is no data about whether this effect extends to critically ill patients. The aim of this research was to determine to what extent this effect occurs in critically ill patients who are already relatively insulin resistant due to their condition.

Metoprolol is a commonly used beta-blocker in the Christchurch intensive care unit (ICU). It is a cardio-selective inhibitor of the β1-adrenergic receptor and is indicated for use in several diseases of the cardiovascular system. Use of metoprolol may unintentionally reduce insulin sensitivity and thus exacerbate stress-hyperglycaemia.

Critically ill patients exhibit marked insulin resistance compared to healthy people. Increased secretion of counter-regulatory hormones stimulate endogenous glucose production and reduces peripheral insulin sensitivity, resulting in hyperglycaemia (Black et al., 1982, McCowen et al., 2001, Mizock, 2001). Tight control of blood glucose to normal levels has been shown to reduce mortality and organ failure (Chase et al., 2010, Chase et al., 2008, Krinsley, 2003, Van den Berghe et al., 2006, Van den Berghe et al., 2001) Tight glycaemic control (TGC) is already difficult to achieve in critically ill patients due to their insulin resistant state, and may be made even more difficult by treatment with metoprolol.

Three studies have investigated the effects of metoprolol on insulin sensitivity using the gold-standard euglycaemic-hyperinsulinaemic clamp method (Falkner et al., 2008, Jacob et al., 1996, Pollare et al., 1989). Two of the studies (Jacob et al., 1996, Pollare et al., 1989) reported reductions in insulin sensitivity of 14-27% associated with metoprolol in non-diabetic individuals when used to treat hypertension. The study by Falkner (2008) showed a statistically non-significant 2% reduction in insulin sensitivity due to metoprolol in type-2 diabetics. This study uses model-based methods to quantify the effect of metoprolol on insulin sensitivity (1/insulin resistance) in critically ill patients.

2. SUBJECTS AND METHODS

2.1 Subjects

This study was conducted as a retrospective analysis of data from patients admitted to the Christchurch Hospital ICU between 2005 and 2007. Model-based methods were used to identify an insulin sensitivity profile for each patient. This insulin sensitivity data was then used to quantify differences between patients receiving metoprolol and a control cohort.

Two cohorts of patients were selected from the available records. 17 suitable patients were found for the metoprolol

cohort. These patients spent at least 24hrs on the SPRINT TGC protocol, did not receive any other beta-blockers besides metoprolol (oral or intravenous) and did not receive glucocorticoid or ACE-inhibitor treatment. The restrictions on other treatments significantly reduced the number of patients eligible for consideration, however these treatments are known to affect glucose metabolism (Henriksen et al., 2003, Lithell, 1992, Lithell, 1995, Pollare et al., 1989, Pretty et al., 2010) and hence may have confounded results.

Table 1. Comparison of the control and metoprolol cohorts. Data are shown as median [interquartile range] where appropriate.

	Control Cohort	Metoprolol Cohort	p-value
N	17	17	
Male/Female	12/5	13/4	1.00**
Op/Non-Op	4/13	4/13	1.00**
ICU Mortality	35%	24%	0.71**
Diabetic history	3/14	1/16	0.60**
Age (yrs)	63 [45-71]	57 [45-67]	0.69*
APACHE II score	19 [16-27]	20 [16-26]	0.70*
APACHE II ROD (%)	33.6 [19.7-53.3]	40.8 [12.9-61.3]	0.74*
Patient median BG (mmol/L)	5.7 [5.0-6.4]	5.8 [5.1-6.5]	0.11*
ICU Length of stay (hrs)	302 [139-512]	360 [178-655]	0.63*
Patient time on SPRINT (hrs)	141 [88-293]	178 [73-339]	0.45*
Total time on SPRINT (hrs)	3369	4126	
Daily dose of metoprolol (mg/d)	0	100 [50-200]	
Total time on metoprolol (hrs)	0	3079	

*p-values calculated with Mann-Whitney U-test. **p-values calculated with two-sided Fishers exact test.

Table 2. Diagnostic categories of the control and metoprolol cohorts.

Diagnostic category		Control cohort patients	Metoprolol cohort patients
Non-operative	Cardio	4	5
	Respiratory	2	2
	Gastro	2	1
	Sepsis	0	1
	Trauma	4	4
	Other (Renal etc)	1	0
Operative	Cardio	2	1
	Gastro	1	3
	Trauma	1	0

A control cohort of 17 patients was chosen to match the overall metoprolol cohort statistics such as age, gender, APACHE II score (Table 1) and diagnostic category (Table 2). In addition to not receiving any metoprolol, the control patients were also subject to the same limitations on other drug treatments and the SPRINT protocol as the metoprolol cohort.

In cases where patients did not receive treatment with metoprolol for the entire time they were on SPRINT, insulin sensitivity was considered to be affected by the drug for 12 hours following the last dose. Metabolism of metoprolol is extremely variable between patients (Chrysostomou et al., 2008), however a number of studies have shown that oral doses of 100-200 mg/day result in a duration of action for heart-rate and blood-pressure effects of 12-24 hours (Åblad et al., 1975, Freestone et al., 1982, Johansson et al., 1980, Johnsson et al., 1975, Reybrouck et al., 1978). Previous investigations have targeted the effects of chronic metoprolol dosing on insulin sensitivity, showing that a reduction in S_I is present even 20 hrs after the last dose (Jacob et al., 1996, Pollare et al., 1989). This variable and prolonged effect made comparison of the insulin sensitivity within the metoprolol cohort between periods on and off the treatment unfeasible as there are few hours of data that could confidently be considered unaffected by the drug.

The SPRINT protocol is a simple, lookup-table system derived from a model-based controller that modulates insulin and nutritional inputs. The protocol titrates insulin doses and nutrition rates to patient-specific insulin sensitivity for tight glycaemic control (Chase et al., 2008). SPRINT has been used in the Christchurch ICU since August 2005 on more than 1000 patients. The requirement for the patients in this study to be on the SPRINT protocol ensured that they had regular and accurate records of blood glucose levels, insulin administered and nutrition given. It also ensured the two cohorts had clinically very similar levels of glycaemic control.

The use of these patient records was permitted under existing ethics approval granted by the Upper South Regional Ethics Committee, New Zealand.

2.2 Model-based insulin sensitivity

This study used the glucose-insulin system model described by Pretty et al. (2010), with a minor change to the endogenous insulin secretion term (7) derived from data not yet published. The model-based insulin sensitivity has been shown to correlate well with the insulin sensitivity index (ISI) determined by the gold-standard euglycaemic-hyperinsulinaemic clamp ($r > 0.90$) (Lotz et al., 2008). Implementing this model in Matlab™ (Mathworks, Natick MA) with ICU patient data, an S_I value was identified every hour for every patient while on the SPRINT protocol. In this way, 3,369 and 4,126 S_I values were obtained for the control and metoprolol cohorts respectively.

The glucose-insulin system model is defined below in (1)-(7). The model parameters, rates and constants are as described in Pretty et al. (2010), except for n_I and V_I which have been adjusted to 0.03 min^{-1} and 4.0 L respectively. The values of

the parameters $k_{1\text{-}3}$ in (7) are 0.14 mU.L/mmol.min, 0.0147 L/mmol and 41 mU/min respectively.

$$\dot{G}(t) = -p_G G(t) - S_I(t)G(t)\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t)+EGP-CNS}{V_G} \quad (1)$$

$$\dot{Q}(t) = n_I\big(I(t) - Q(t)\big) - n_C\frac{Q(t)}{1+\alpha_G Q(t)} \quad (2)$$

$$\dot{I}(t) = -n_K I(t) - n_L\frac{I(t)}{1+\alpha_I I(t)} - n_I\big(I(t) - Q(t)\big) \ldots$$
$$\ldots + \frac{u_{ex}(t)}{V_I} + (1 - x_L)\frac{u_{en}(t)}{V_I} \quad (3)$$

$$P(t) = \min(d_2 P_2, P_{max}) + PN(t) \quad (4)$$

$$\dot{P}_2(t) = -\min(d_2 P_2(t), P_{max}) + d_1 P_1(t) \quad (5)$$

$$\dot{P}_1(t) = -d_1 P_1(t) + D(t) \quad (6)$$

$$u_{en}(t) = \max\left(0, \frac{k_1 G(t)}{1+k_2 G(t)} + k_3\right) \quad (7)$$

2.3 Analysis

Non-parametric statistics (median, interquartile range) were used to define the location and spread of insulin sensitivity and blood glucose as typical distributions are asymmetric and skewed, rendering Gaussian statistics unsuitable (Micceri, 1989). Cohort statistics were compared using the Mann-Whitney U-test for continuous data or two-sided Fisher's exact test for categorical data. Insulin sensitivity values were compared using cumulative distribution functions (CDFs) and the Mann-Whitney U-test for statistical significance. CDFs present the entire shape of the distribution, which was particularly useful for these skewed data sets (Hart, 2001). P–values of less than 0.05 were considered significant.

Overall cohort comparisons of insulin sensitivity were possible with the matched cohorts. However, as individual patients could not be explicitly matched, *percentile patients* were used as a surrogate for explicit per-patient analyses as described by Pretty et al. (2010). Comparisons were made between equivalent percentile patients from each cohort.

3. RESULTS

3.1 Overall cohort analysis

Insulin sensitivity in patients receiving metoprolol was typically lower than control patients in an overall cohort comparison. Median insulin sensitivity was reduced 9.7% from $4.04\text{x}10^{-4}$ to $3.65\text{x}10^{-4}$ L/mU.min ($p < 0.05$). Figure 1 shows the CDFs for both cohorts. There was a clear separation between the control cohort and the metoprolol cohort (while receiving metoprolol) distributions between the 10th and 90th percentile values. Outside this range, factors such as variable metabolism and dosing of metoprolol between patients as well as patient condition may be the cause of the insulin sensitivity distributions crossing over each other.

3.2 Percentile patient analysis

Analysis of the percentile patient data showed no statistically or clinically significant reduction in insulin sensitivity for patients receiving metoprolol. Figure 2 shows the CDFs for the 25th, 50th and 75th-percentile patients from both cohorts where the differences were 0.5-3.6%. The p-values for comparing equivalent curves were all greater than 0.2.

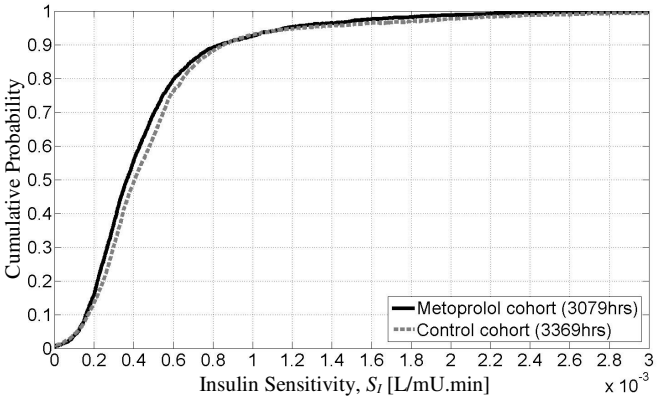

Figure 1. CDF's of insulin sensitivities for control and metoprolol cohorts. The metoprolol cohort had lower insulin sensitivity while receiving metoprolol between the 10th and 90th percentiles.

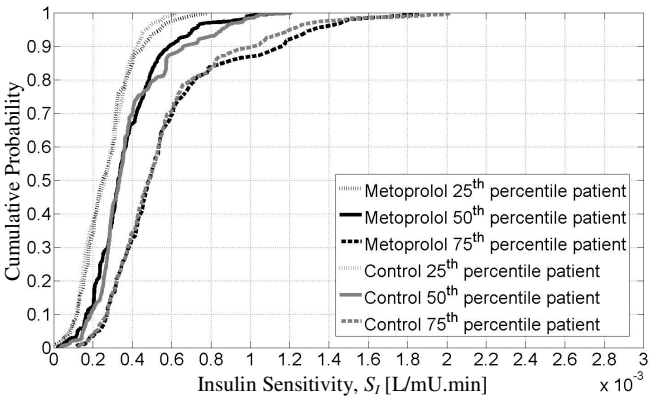

Figure 2. CDFs of insulin sensitivity for the 25th, 50th and 75th-percentile patients from the study cohorts.

The small size of the study cohorts meant that more extreme percentile patients were heavily influenced by individual outlying members of each cohort. As individual patients were not matched analysis of these more extreme examples produced no meaningful results.

4. DISCUSSION

Studies have shown that metoprolol can reduce insulin sensitivity 14-27% when used to treat essential hypertension in otherwise healthy individuals (Jacob et al., 1996, Pollare et al., 1989). A similar study in hypertensive subjects with non-insulin dependent diabetes mellitus (NIDDM) (Falkner et al., 2008) reported a statistically non-significant 2% reduction in insulin sensitivity associated with metoprolol. The aim of this study was to determine whether metoprolol had an effect on the insulin sensitivity of critically ill patients who are already relatively insulin resistant due to their condition.

The results presented in this study indicate that metoprolol may have a small effect on the insulin sensitivity of critically ill patients; however it is unlikely to be clinically significant.

A similar study investigating the effects of glucocorticoids on critically ill patients (Pretty et al., 2010) used virtual patient simulations to show that changes in S_I of 25% resulted in no clinically significant alterations to the level of glycaemic control under the SPRINT TGC protocol. Therefore a reduction in S_I of 0.5-10% as reported here may also be expected to have little clinical impact.

The dosage received by patients in this study varied between individuals and over the course of treatment. However, over the entire cohort the median daily dose of metoprolol was 100 mg/d (IQR: 50-200 mg/d).This dose is comparable to the doses of 200, 100 and 50-200 mg/d administered in the studies by Pollare et al. (1989), Jacob et al. (1996) and Falkner et al. (2008) respectively. Hence the reduction in impact of metoprolol on insulin sensitivity is likely not a result of the dosing.

The study by Falkner et al. (2008) added metoprolol to the participant's existing ACE-inhibitor or ARB hypertension treatment regime. Recent research has indicated that angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) lead to improved insulin sensitivity (Perkins et al., 2008, Lithell, 1992). It is therefore possible that reductions in insulin sensitivity associated with metoprolol are mitigated by increases in insulin sensitivity due to the concomitant use of ACE-inhibitors and ARBs, resulting in no significant change as reported by Falkner et al. (2008).

The mechanisms by which beta-adrenoceptor antagonist treatment (β-blockade) modifies insulin sensitivity are not yet understood. Both Pollare et al. (1989) and Jacob et al. (1996) suggest a possible haemodynamic explanation for the reduced insulin sensitivity. The reduced heart rate and contractility due to metoprolol result in reduced blood flow to the skeletal muscles. Thus there is lower glucose availability to these prime target tissues for glucose disposal at given insulin levels (Jacob et al., 1996, Pollare et al., 1989). And an apparent reduction in insulin sensitivity as defined by the rate of insulin mediated glucose uptake. Jacob et al. (1996) also suggest that β-blockade appears to reduce insulin clearance rates and the resulting hyperinsulinaemia may downregulate insulin receptors, directly lowering insulin sensitivity. The actual mechanism of action may be a combination of these factors or an as yet unidentified pathway.

The critical condition of the patients in this study may moderate the physiological impact of these proposed mechanisms of action. Critically ill patients already have significant peripheral insulin resistance (Black et al., 1982) and may therefore be less likely to show further large reductions caused by reduced blood flow or receptor downregulation compared to healthy subjects. This saturation of the physiological effect may explain the limited reduction of insulin sensitivity in critically ill patients compared with 'healthy' individuals seen in this study.

A major limitation of using model-based methods is that the parameter of interest (S_I) is not measured directly and may be influenced by modelling errors or un-modelled effects. The insulin sensitivity parameter in the model used for this research captures the relative net effect of altered endogenous glucose production, peripheral and hepatic insulin mediated glucose uptake and endogenous insulin secretion. Hence this model-based S_I represents more of a "whole-body" insulin sensitivity. While receptor downregulation is a direct modulation of peripheral insulin sensitivity, altered haemodynamics result in reduced "whole-body" insulin sensitivity rather than a specific reduction at the receptor site. Therefore, the suggested metoprolol mediated changes to glucose uptake, in addition to the direct effect on insulin sensitivity, cause a relative reduction in the model-based S_I. This model-based S_I correlates very well ($r>0.90$) with euglycaemic clamp derived insulin sensitivity, ISI (Lotz et al., 2008), providing support for this metric and overall analysis.

5. CONCLUSION

This research used model-based methods to show that metoprolol causes less of a reduction in the insulin sensitivity of critically ill patients than in healthy individuals. Both the percentile patient and cohort analyses point to reductions in insulin sensitivity associated with metoprolol treatment of 0.5-10%. These cohort and percentile patient reductions are less than the 14-27% reductions reported in 'healthy' subjects and similar to those reported for NIDDM subjects. This limited reduction of insulin sensitivity in critically ill patients could be a result of moderation of the physiological impact of metoprolol due to already reduced levels of peripheral glucose uptake and insulin receptor sensitivity. These reductions are not expected to have any clinical impact on the level of tight glycaemic control achieved with the SPRINT protocol.

REFERENCES

Åblad, B., Borg, K. O., Carlsson, E., Ek, L., Johnsson, G., et al. (1975). A survey of the pharmacological properties of metoprolol in animals and man. *Acta Pharmacologica Et Toxicologica,* 36**,** s5**,** 7-23.

Black, P. R., Brooks, D. C., Bessey, P. Q., Wolfe, R. R. & Wilmore, D. W. (1982). Mechanisms of insulin resistance following injury. *Annals of Surgery,* 196**,** 4**,** 420-35.

Chase, J. G., Pretty, C. G., Pfeifer, L., Shaw, G. M., Preiser, J.-C., et al. (2010). Organ failure and tight glycemic control in the SPRINT study. *Critical Care,* 14**,** 4**,** R154-R154.

Chase, J. G., Shaw, G., Le Compte, A., Lonergan, T., Willacy, M., et al. (2008). Implementation and evaluation of the SPRINT protocol for tight glycaemic control in critically ill patients: a clinical practice change. *Critical Care,* 12**,** 2**,** R49.

Chrysostomou, C. & Kazmerski, T. M. (2008). β-Blockers. In: Munoz, R., Schmitt, C. G., Roth, S. J. & Cruz, E. (eds.) *Handbook of Pediatric Cardiovascular Drugs.* 139-149. London, Springer.

Falkner, B. & Kushner, H. (2008). Treatment with metoprolol succinate, a selective beta adrenergic blocker, lowers blood pressure without altering insulin sensitivity in diabetic patients. *Journal of Clinical Hypertension,* 10**,** 1**,** 51-7.

Freestone, S., Silas, J. H., Lennard, M. S. & Ramsay, L. E. (1982). Comparison of two long-acting preparations of metoprolol with conventional metoprolol and atenolol in healthy men during chronic dosing. *British Journal of Clinical Pharmacology,* 14**,** 5**,** 713-8.

Hart, A. (2001). Mann-Whitney test is not just a test of medians: differences in spread can be important. *BMJ (Clinical research ed),* 323**,** 7309**,** 391-3.

Henriksen, E. J. & Jacob, S. (2003). Modulation of metabolic control by angiotensin converting enzyme (ACE) inhibition. *Journal of cellular physiology,* 196**,** 1**,** 171-9.

Jacob, S., Rett, K., Wicklmayr, M., Agrawal, B., Augustin, H., et al. (1996). Differential effect of chronic treatment with two beta-blocking agents on insulin sensitivity: the carvidilol-metoprolol study. *Journal of Hypertension,* 14**,** 4**,** 489-494.

Johansson, S. R., Mccall, M., Wilhelmsson, C. & Vedin, J. A. (1980). Duration of action of beta blockers. *Clinical Pharmacology & Therapeutics,* 27**,** 5**,** 593-601.

Johnsson, G., Regardh, C. G. & Solvell, L. (1975). Combined pharmacokinetic and pharmacodynamic studies in man of the adrenergic beta1-receptor antagonist metoprolol. *Life Sciences,* 36**,** s5**,** 31-44.

Krinsley, J. S. (2003). Decreased mortality of critically ill patients with the use of an intensive glycemic management protocol. *Critical Care Medicine,* 31**,** A19.

Lithell, H. (1992). Insulin resistance and cardiovascular drugs. *Clinical and Experimental Hypertension,* 14**,** 1**,** 151-162.

Lithell, H. (1995). The effect of ACE inhibitors and other antihypertensive agents on insulin resistance. *Nephrology, Dialysis, Transplantation,* 10**,** 5**,** 589-91.

Lotz, T. F., Chase, J. G., Mcauley, K. A., Shaw, G. M., Wong, X. W., et al. (2008). Monte Carlo analysis of a new model-based method for insulin sensitivity testing. *Computer Methods and Programs in Biomedicine,* 89**,** 3**,** 215-25.

Mccowen, K. C., Malhotra, A. & Bistrian, B. R. (2001). Stress-induced hyperglycemia. *Critical Care Clinincs,* 17**,** 1**,** 107-124.

Micceri, T. (1989). The Unicorn, The Normal Curve, and Other Improbable Creatures. *Psychological Bulletin,* 105**,** 1**,** 156-166.

Mizock, B. A. (2001). Alterations in fuel metabolism in critical illness: hyperglycaemia. *Best Pract Res Clin Endocrinol Metab,* 15**,** 4**,** 533-51.

Perkins, J. M. & Davis, S. N. (2008). The renin-angiotensin-aldosterone system: a pivotal role in insulin sensitivity and glycemic control. *Current Opinion in Endocrinology Diabetes & Obesity,* 15**,** 2**,** 147-52.

Pollare, T., Lithell, H., Selinus, I. & Berne, C. (1989). Sensitivity to insulin during treatment with atenolol and metoprolol: a randomised, double blind study of effects on carbohydrate and lipoprotein metabolism in hypertensive patients. *BMJ (Clinical research ed.),* 298**,** 6681**,** 1152-7.

Pretty, C., Chase, J. G., Lin, J., Shaw, G. M., Le Compte, A., et al. (2010). Impact of glucocorticoids on insulin resistance in the critically ill. *Computer Methods and Programs in Biomedicine***,** 2-10.

Reybrouck, T., Amery, A., Fagard, R., Jousten, P., Lijnen, P., et al. (1978). Beta-blockers: once or three times a day? *British Medical Journal,* 1**,** 6124**,** 1386-8.

Van Den Berghe, G., Wilmer, A., Hermans, G., Meersseman, W., Wouters, P. J., et al. (2006). Intensive insulin therapy in the medical ICU. *New England Journal of Medicine,* 354**,** 5**,** 449-61.

Van Den Berghe, G., Wouters, P., Weekers, F., Verwaest, C., Bruyninckx, F., et al. (2001). Intensive insulin therapy in the critically ill patients. *New England Journal of Medicine,* 345**,** 19**,** 1359-1367.