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Variability of Model based Insulin Sensitivity in Liver Transplanted Patients

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Abstract: During and after liver-transplantation (LT) it is very difficult to maintain normoglycema. Blood glucose (BG) metabolism suffers from this huge disturbance and the pathological state changes very quickly. In addition there is further stress from the state of the graft liver and the host body's ability to accept it. The number of physiological parameters, that can be observed is quite limited. Control can be implemented primarily by the administration of exogenous insulin and glucose. Thus, insulin sensitivity (SI) can be a key-parameter to observe physiological changes and develop patient and pathological state specific treatments. This study investigates the distribution of a validated, model-based SI over time and the main surgery phases in the LT.

1. INTRODUCTION

During liver-transplantation maintaining normoglycemia is very difficult. The human blood glucose metabolism system is very complex and involves many regulatory functions to maintain sufficient energy for the body's cells. Its main regulatory organ is the liver, as the nutrition rich blood coming from the gut reaches the liver first (Rehner and Daniel [2010]). It provides the large part of the endogenous secretion and uptake of blood glucose (BG) in the plasma and thus, dominates the glucose balance. These functions are glycogenesis, glycogenolysis, gluconeogenesis and glycolysis. In the absence of the liver, the system suffers a large disturbance. These system's changes also occur very fast, with some functions covered partially by other organs (Joseph et al. [2000]; Battezzati et al. [2004]; Tsinari et al. [2004]; Ichimiya et al. [1995]; Cano [2002]). A typical significant increase of BG after the anhepatic status has been reported frequently (Ichimiya et al. [1995]; Atchison et al. [1989]; Homlok et al. [2013a]). The changes of these intrinsic processes can be measured continuously (Ichimiya et al. [1995]; Kiuchi et al. [1995]; Lauritsen et al. [2002]) even though in clinical practice restricted measurements limit the ability to see all these changes. Interventions are limited to exogenous dextrose and insulin. The utilization of the insulin is defined by insulin sensitivity, which defines the balance between insulin concentration and glucose disposal (Pretty et al. [2012]). Insulin sensitivity can be defined by specialised clinical tests or by model-based methods. However, clinical tests require steady state of glucose metabolism, which is not feasible during LT. Thus, the model-based option was chosen.

1.1 Aim

Our goal is to develop a model-based method, that can be used clinically to describe the physiological changes during and just after LT. From this information a patient specific therapy can be defined to maintain normoglycemia. There's evidence on the decreased morbidity and mortality of the ICU patients due to safe, effective glycemic control (Bagshaw et al. [2009]; Egi et al. [2006]; Krinsley [2008]; Chase et al. [2010.]) However, it is an open question in LT with no specific clinical evidence (Ammori et al. [2007]).

This paper describes a model-based analysis of SI variability during and after the surgery to better understand and then control BG in LT.

2. METHODS

2.1 Patient data

Patient data was recorded at the Budapest Transplantation Clinic for 19 LT patients. BG level was measured frequently (30 minutes to 2 hours) during and after surgery. The patients got dextrose in parenteral form (goal-feed 4 g/hr) and insulin infusions. A total of 58 hours of pre-anhepatic and 24 hours of Anhepatic status (78 ± 23.89 [min] for individual patients) were monitored. We selected a 10 hours critical timespan after reperfusion at each patient, where the metabolic state was most unstable (Homlok et al. [2013b]), for this analysis. According to the surgery steps and previous studies, the LT process can be divided into four surgery phases: the pre-anhepatic; the anhepatic; the post-anhepatic I; and the post anhepatic II (stabilized status). In the stabilized status after reperfusion data of 55 ± 15 [hour] for individual patients. The administered Insulin amounted 20.55 ± 30.22 [mU/min]

for pre anhepatic 32.25 ± 32.71 [mU/min] for anhepatic 71.27 ± 49.58 [mU/min] in the post-anhepatic 78.99 ± 57.77 [mU/min] in the "stabilized" status. The entered nutrition according to the surgery phases was 0.20 ± 0.20 [mmol/L/min] during the pre anhepatic 0.30 ± 0.18 [mmol/L/min] in the anhepatic 0.33 ± 0.19 [mmol/L/min] in the post anhepatic and 0.42 ± 0.21 [mmol/L/min] in the "stabilized" phase.

2.2 Insulin sensitivity

Insulin sensitivity (SI) maintains a balance between the insulin concentration and the disposal of the glucose in the interstitial space. By studying the time variability of insulin sensitivity, we obtain information about the patients' current metabolic status (Pretty et al. [2012]). Based on the SI value, proper exogenous insulin based therapy can be developed to maintain the normoglycemic state (Fisk et al. [2012]). Based on the treatment history (BG measurements, insulin intake, and glucose intake), the SI value is calculated by using a physiological model describing the metabolic precesses of the human body. The ICING model (Lin et al. [2011]) is able to calculate the SI values, using an integral-based identification method and data (Hann et al. [2005]). However the SI value represents not only the whole body insulin resistance (Pretty et al. [2012]), as well as any unknown variability of endogenous glucose production and endogenous insulin secretion. It has a correlation ratio of 0.9 with the "gold standard" hyperinsulinemic clamp (Lotz et al. [2008]), which is significant in considering other methods. Considering its usability and the clinical constraints, the ICING model-based SI estimation is an adequate and applicable method.

2.3 Evaluating insulin sensitivity values

SI values were evaluated as median (IQR). The dataset was clustered according the surgery phases, and distributions, of SI values in different surgery phases were compared. The distribution of differencies in two consecutive SI values was determined to investigate the variability of SI changes in different surgery phases. The distributions of the phases (Fig.2) were compared using the Wilcoxon rank sum test, as the SI values do not follow a normal distribution. $P < 0.05$ is consideredstatistically significant.

3. RESULTS & DISCUSSION

Pre-anhepatic status's SI values are related to cirrhotic pathological state including intra-operative stress induced variability. Thus, the distribution in Fig. 2-4 shows large variation. We are not able to see the impaired insulin resistance state unequivocally, which was also shawn by Kruszynska et al. [1991]. There's a trend clearly observable in Fig. 1 that insulin resistance falls until the $12th$ hour after anhepatic status and $10th$ hour after reperfusion as the $25th\%$ and $75th\%$ IQR ranges show no significant changes until the $12th$ hour. However, after reperfusion the minimum limit is hit frequently indicating no insulin mediated glucose disposal, which raises the question of how these specific LT patients may deviate from better known ICU metabolic function.

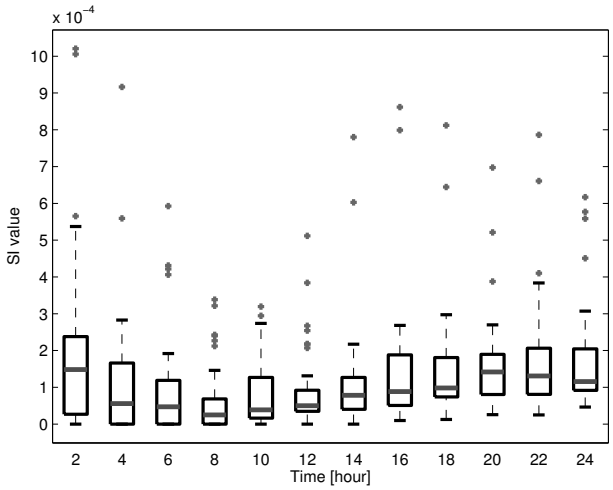

Fig. 1. SI distribution over the time. The dataset starts at the hepatectomy. The anhepatic status lasts 80.2 ± 30 mins, (Homlok et al. [2013a]). Each box-plot represent SI values of 2 hours. On the figure we can see a tendency of decreasing SI value till the 8-10 hours after the hepatectomy.

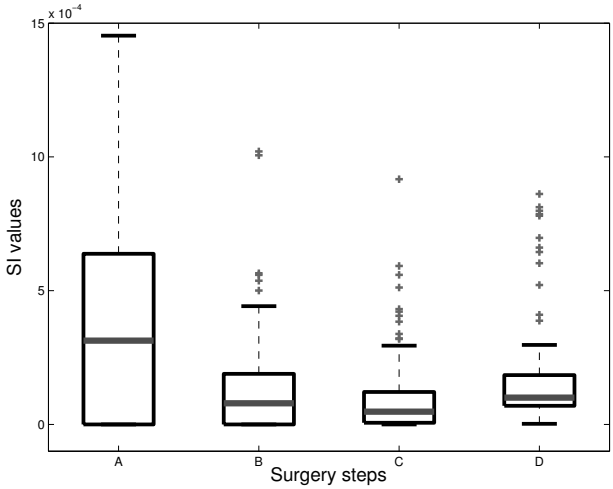

Fig. 2. The SI value statistics of the surgery phases: A (pre-anhepatic status), B (anhepatic status), C (post anhepatic status I.), D (post-anhepatic status II.). The high variability of the pre-anhepatic (A) status is the result of the rare measurements and - supposedly - the cirrhosis of the original liver of the patients. The B, C phases show decrease in SI, due to the frequently occurring minimal value of the SI. This minimal value is limited manually in the model.

Table 1. Wilcoxon sum rank test for comparing the distributions from different phases on median values

	preAH (A)	AH (B)	post-AH I. (C)
pre-AH (A)	•	•	•
AH (B)	$P = 0.026$	•	•
post-AH I. (C)	$P < 0.0001$	$P = 0.002$	•
post-AH II. (D)	$P < 0.0001$	$P = 0.560$	$P < 0.0001$

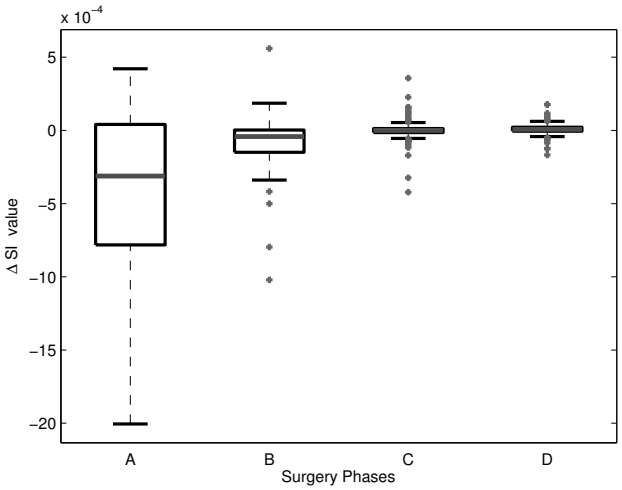

Fig. 3. The distribution of the differences of the successive SI values (delta SI values). The variation of the distributions decreases by the advancing surgery steps, the difference between the C and the D phases is not significant, however the number of the SI lower limit occur numerous time in C, where the D phase does have a stable physiological SI levels.

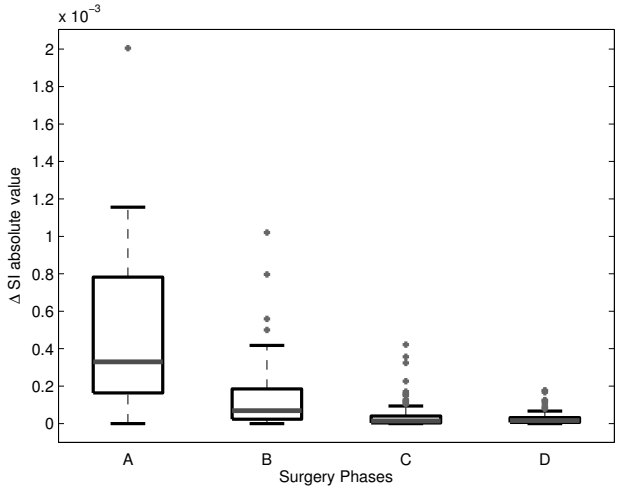

Fig. 4. Distribution of the absolute delta SI values in the main surgery phases. We can see significantly smaller changes of the SI in the C and D phases than in the pases A and B. This is the result of the normalized metabolic state of the patients in these phases. However, in the C phase the absolute SI value is still frequently close to the minimum SI as it can be seen on Fig. 2.

The Wilcoxon sum rank test (Table 1) shows the most of the differences between the phases are statistically significant, except between AH phase and post-AH II. phase.

In this study, the function of the grafted liver should have been clustered based on the outcome (Kiuchi et al. [1995]). However, the positive effect on the outcomes of maintaining normoglycemic status in the intra- and post-operative phases hasn't been proven clearly yet (Ammori et al. [2007]).
As we have shown in previous studies, due to the quick pathological changes during LT, this model cannot capture accurately all the BG changes (Homlok et al. [2013a]). Therefore, the SI values decrease significantly, in numerous cases to 0 or any set physiologically realistic minimum limit. This behavior indicates that the physiological parameters of the model have to be set specifically for these pathological changes. In the ICING model, the minimum value of SI is set to a very small but nonzero value. The SI identification methods does not allow SI below this SI_{MIN} value. In the patient history those phases when $SI = SI_{MIN}$ are likely associated with physiological changes where the ICING model was unable to reflect the dynamics of the BG change. Hence, there is an indicator from the model that thise time periods require LT cohort specific values.

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