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Impact of haemodialysis on insulin sensitivity of acute renal failure (ARF) patients with sepsis in critical care

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Abstract— **Critically ill patients often develop renal failure in addition to their primary diagnosis. However, the effect and impact of haemodialysis (HD) on insulin sensitivity n critically ill patients remains unclear. Specifically, this study investigates insulin sensitivity of acute renal failure (ARF) patients with sepsis who underwent HD and glycaemic control. Model-based insulin sensitivity (S_I) profiles were identified for 20 critically ill ARF patients on Specialized Relative Insulin Nutrition Titration (SPRINT) glycaemic control during intervals onto HD (OFF/ON), and after HD (ON/OFF). Patients exhibited a median -18% (IQR -36% to -5% p<0.05) reduction in measured S_I after the OFF/ON dialysis transition, and a median 9% (IQR -5% to 37%, p<0.05) rise after the ON/OFF transition. Almost 80% of patients exhibited decreased S_I at the OFF/ON interval, and 60% exhibited increased S_I at the ON/OFF transition. Results indicate that HD commencement has significant effect on insulin pharmacokinetics at a cohort and per-patient level. These results provide the data to design conclusive studies of HD effects on S_I, and to inform glycaemic control protocol development and implementation for this specific group of critically ill patients with ARF-sepsis.**

I. Introduction

Acute renal failure (ARF) is a common complication among critically ill patients especially for elderly patients with diabetes [1]. Approximately 36% of critically ill patients are diagnosed with ARF [2, 3] with a significant proportion progressing to chronic renal failure requiring weekly haemodialysis (HD) [4]. Several epidemiological studies have shown an increase in morbidity and mortality following the development of ARF [3, 5, 6].

The increasing incidence of critically ill patients with ARF associated with insulin resistance may be explained by several factors, including a rising incidence of sepsis [7, 8], major surgery (especially cardiothoracic), nephrotoxic medications, and chronic medical conditions [6]. With both uraemia and HD treatment, glycaemic control (GC) can be complicated [5] as GC affects insulin secretion, insulin clearance, gluconeogenesis [9], and peripheral tissue sensitivity of insulin [10]. Many studies claimed that HD treatment improved patient condition by removing waste and toxin. However, other clinical studies showed that HD treatment cleared plasma insulin through increased absorption [11-13]. Overall, the effect of renal failure on metabolic kinetics in critically ill patients is unknown. These unknown effects have the potential to complicate metabolic management and the treatment itself.

This study uses dense clinical data and a model-based analysis to investigate changes in a clinically validated model-based S_I metric at HD transitions in a cohort of critically ill patients with sepsis. These changes in model-based S_I would thus offer a unique observation on insulin sensitivity and kinetics in this population of critically ill patients with ARF-sepsis that would better inform metabolic care.

II. Methods

A. Patient Cohort

Retrospective blood glucose (G) measurements, nutrition administration rates (P), and insulin delivery (u_{ex}) data used in this study were obtained from the Specialized Relative Insulin Nutrition Titration (SPRINT) pilot study of 371 critically ill patients that required glycaemic control [14]. 51 of 371 patients had acute renal failure (ARF) treated with HD. However, only 39% (20/51) ARF patients were diagnosed with sepsis. The exogenous insulin and nutrition given to these patients were optimized to maximise blood glucose time in the range between 4.0 to 7.0 mmol.L^{-1}, minimising hyperglycaemia, via patient-specific nutrition and insulin administration [13].

The 51 ARF patients were treated with haemodialysis (HD) with polysulfone (PS) dialyzer membrane (APS-15SA: Asahi Medical Co.,Ltd, Tokyo. This PS dialyzer membrane is reported to affect plasma insulin clearance during HD treatment [15]. Patients were haemodialysed three times weekly (in fasting state) for a minimum of 4 hours of in the Christchurch Hospital Intensive Care Unit (ICU).

Study inclusion from ARF sub-cohort of 20 sepsis patients required a minimum of 5 hours of patient data before dialysis, followed by at least 6 hours of dialysis, and then at least 5 hours after dialysis. The baseline details of this sub-cohort are summarized in Table I. Full details on SPRINT can be obtained from Chase et al. (2008)[14].

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TABLE I. SPRINT COHORT BASELINE VARIABLES (N=20). DATA ARE EXPRESSED AS MEDIAN [IQR]. (APACHE=ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION)

	Median	[IQR]
Age(years)	65	[46-73]
% Male	76%	
APACHE II score	24	[19-30]

B. Identification of Model-Based S_I

Model-based S_I is identified hourly by fitting G measurements with estimated endogenous insulin secretion using the ICING (Intensive Control Insulin-Nutrition-Glucose) model [16]. An integral-based method [17] and clinical data are used to identify patient-specific stepwise S_I profile with 1-hour resolution. The model nomenclature is in Table II and it is mathematically defined:

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

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

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

$$\dot{P}_1 = d_1 P_1 + D \quad (4)$$

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

$$P = \min(d_2 P_2, P_{max}) + PN \quad (6)$$

$$u_{en}(G) = \begin{cases} u_{min}, u_{min} > k_1 G + k_2 \\ k_1 G + k_2, u_{min} \le k_1 G + k_2 \le u_{max} \\ u_{max}, u_{max} < k_1 G + k_2 \end{cases} \quad (7)$$

Model estimation of endogenous insulin secretion ($u_{en}(G)$) is in the range between 16.7mU.min^{-1} and 266.7mU.min^{-1} as a function of glycaemic level (G) [18]. This overall metabolic model has been clinically validated with median prediction error less than 4-5% [19]. The model has been used in several clinical glycaemic control trials and insulin sensitivity tests [20]. A prior parameters identification of ICING was validated based on clinical data of SPRINT using integral-based method [17].

C. Calculations and Statistical Analysis

Numerical calculations and parameter identification were performed using MATLAB (The MathWorks Inc., Natick, MA). The proportional difference in S_I (ΔS_I) was calculated as:

$$\Delta S_I = 2\frac{S_{I(after)} - S_{I(before)}}{\left(S_{I(before)} + S_{I(after)}\right)} \quad (8)$$

Blood glucose changes, ΔG were calculated in a similar manner to ΔS_I to assess any changes in glycaemia that could affect results.

This analysis uses a 2-hour moving average to reduce the effect of measurement error, and the influence of transient effects. S_I profiles are identified over periods starting 3 hours before dialysis commencement until 4 hours after dialysis ends. This range ensures full settling of patient responses after transitions.

TABLE II. NOMENCLATURES OF THE ICING MODEL

Parameters	Description			Unit
G	Blood glucose level			(mmol.L^{-1})
Q	Interstitial insulin level			(mU.L^{-1})
I	Plasma insulin level			(mU.L^{-1})
P_1	Stomach glucose content			(mmol)
P_2	Gut glucose content			(mmol)
P	Rate of glucose appearance in plasma			(mmol.min^{-1})
$u_{en}(G)$	Endogenous insulin secretion			(mU.min^{-1})
Parameters and kinetic values of ICING model based on diabetic status				
EGP	Endogenous glucose production		1.16	(mmol.min^{-1})
CNS	Central nervous system glucose uptake		0.3	(mmol.min^{-1})
p_G	Patient endogenous glucose removal		0.006	(min^{1})
S_I	Insulin sensitivity			(L.mU^{-1}.min^{-1})
α_G	Saturation parameter of insulin-mediated glucose removal		0.0154	(L.mU^{-1})
V_G	Plasma glucose distribution volume		13.3	(L)
n_I	Plasma-interstitium insulin diffusion rate		0.006	(min^{-1})
n_C	Receptor-bound insulin degradation		0.006	(min^{-1})
n_K	Renal insulin clearance		0.0542	(min^{-1})
n_L	Hepatic insulin clearance		0.1578	(min^{-1})
α_I	Saturation parameter for hepatic insulin clearance		0.0017	(L.mU^{-1})
V_I	Insulin distribution volume		4.0	(L)
x_L	First pass hepatic clearance		0.67	
d_1	Rate of glucose transport		0.0347	(min^{-1})
d_2	through the enteral route into the bloodstream		0.0069	(min^{-1})
P_{max}	Maximal gut glucose flux		6.11	(mmol.min^{-1})
u_{min}	Minimum pancreatic secretion rate		16.7	(mU.min^{-1})
u_{max}	Maximum pancreatic secretion rate		266.7	(mU.min^{-1})
k_1	Pancreatic insulin secretion glucose-sensitivity	*NGT: *T2DM: *T1DM	14.9 4.9 0.0	(mU.L.mmol^{-1}.min^{-1})
k_2	Pancreatic insulin secretion offset	*NGT: *T2DM: *T1DM:	-49.9 -27.4 16.7	(mU.min^{-1})
Exogenous input variables of ICING-2 model				
u_{ex}	Intravenous insulin input rate			(mU.min^{-1})
D	Oral glucose input rate from enteral nutrition			(mmol.min^{-1})
PN	Intravenous glucose input rate from parenteral nutrition			(mmol.min^{-1})

*Note: NGT=Normal Glucose Tolerance, T1DM=Type 1 Diabetes Mellitus, T2DM=Type 2 Diabetes Mellitus

III. RESULTS

Fig. 1 shows ΔS_I over 6 hours at the OFF/ON and ON/OFF dialysis transitions for ARF patients with sepsis.

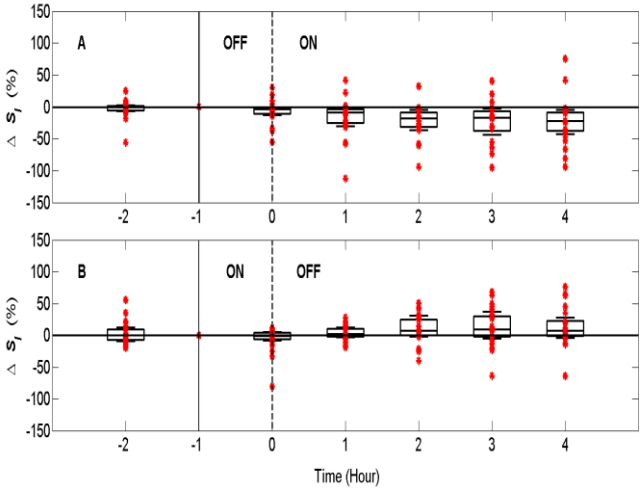

Fig. 1. Dialysis period of 6 hours at OFF/ON (A) and ON/OFF (B) dialysis transition t=-2 to t=4 hours (N=20).

S_I decreased after the OFF/ON dialysis transition until t=2 hours, where it settled with median ΔS_I=-18% (IQR: [-36, -5] %; p<0.05). There were a comparatively low number of confounders (1/20) that shows contrary ΔS_I (i.e. ΔS_I>0) outside the IQR indicating a strong effect of HD on insulin kinetics is observable. Median ΔS_I increased by 9% for the ON/OFF transition (Fig.1B), (IQR: [-5, 37] %; p<0.05) at t=3 hours after the ON/OFF transition. The number of confounders (8/20) is significantly higher for the ON/OFF indicates that the HD effect cannot be confirmed at this transition although p <0.05. *G* remains effectively constant at both transitions. However, changes in S_I outcomes were not significant (p>0.05) even 4 hours after the ON/OFF transition.

An investigation of extended dialysis interval (>10 hours) of ΔS_I for both OFF/ON and ON/OFF dialysis transition across the N=26 from 51 ARF subjects (varied metabolic dysfunctions) with sufficient data is also implemented. S_I decreased during the OFF/ON dialysis interval until t=8 hours, where it settled to a median reduction of -25% (IQR: [-10, -51] %; p=0.04). There were only 2 confounders (ΔS_I->*0*) from 26 patients at t=8 hours. However, while the ON/OFF transition results improved relative to the hypothesized effect, the results were still insignificant (p>0.07).

IV. Discussion

This study investigated the effect of dialysis on insulin kinetics through a clinically validated model-based ΔS_I metric at both OFF/ON and ON/OFF dialysis transitions. Significant insulin sensitivity changes occurred within 2 hours after the OFF/ON dialysis transition (p<0.05). This analysis indicates that model-based S_I decreased over the initial 4-hours after HD started and the changes occurred as rapidly as 2 hours. This result suspected that dialysis significantly affected plasma insulin levels via changes in renal insulin clearance and/or endogenous insulin secretion, compared to baseline model assumptions as mentioned earlier in identification of model-based S_I.

The model-based ΔS_I at the ON/OFF dialysis transition in this study was insignificant (p>0.05). It is impossible to delineate the effects that contribute to changes in S_I in this study, due to model identifiability issues [21] and the side effects of other diagnosed critical illnesses apart from ARF [22]. However, a prior study with acute intravenous administration of 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) given to ARF patients during HD may increase insulin secretion and reverse glucose intolerance [23]. An improvement in glucose intolerance has been observed with lower mean glucose during dialysis and more rapid disappearance rate of glucose in the immediate post-dialysis period [24]. In general, glucose metabolism and renal function are expected to increase gradually after post-dialysis when toxic substances that are suspected of hindering renal function have been extracted. Also, long-term (4.9 weeks) HD treatment has been shown to normalize insulin sensitivity and result in a marked improvement in glucose metabolism [12], but this might not completely normalize glucose utilization [25].Thus, over longer intervals, inter-patient or intra-patient variation may further obscure the observation of the effect itself [20].

Thus, a substantial change in S_I at the OFF/ON dialysis transition indicates a strong and fast process of cleaning and clearing toxic substances from blood leading to improve effective S_I due to either decreased u_{en} or increased n_K clearance. However, at the ON/OFF dialysis transition, the recovery process to regulate and normalize blood is a lot slower physiologically. Hence, the model-based S_I, after dialysis in this study may be expected to remain unchanged, as observed here, even for extended periods after HD treatment.

The model-based S_I is an indication of overall glucose metabolism of critically ill patients and does not necessarily reflect the precise cellular physiology of peripheral insulin sensitivity. The model-based ΔS_I at a cohort level used in this study are unlikely to be caused in this case by actual variance in true peripheral S_I at a cellular level. In particular, there is no apparent stimulus induced by HD to directly affect S_I. However, the implication of ΔS_I during HD transitions will assist clinicians in finding the best treatment for the critically ill patients with ARF-sepsis that minimize HD effects on the insulin clearance during dialysis.

Thus, ΔS_I reflects changes in renal clearance or/and endogenous insulin secretion, which in turn result in changes in the model-based S_I calculated based on fixed assumptions for these values.

V. Conclusion

The distinct change in model-based insulin sensitivity during HD treatment was a significant and observable aspect of critically ill patient physiology. The findings were consistent with the presence of effects of HD treatment in a

majority of ARF patients from other studies [2-8]. Clinically, the effect of the main contributors (n_K and u_{en}) of effective insulin sensitivity changes during HD from a baseline model or clinical assumptions suitable for other critically illnesses with ARF cohort should also be considered in glycaemic control. However, the precise pharmaco-kinetics/dynamics driving this change remain ambiguous.

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