

Jennifer A. Sim  
M. Horowitz  
M. J. Summers  
L. G. Trahair  
R. S. Goud  
A. V. Zaknic  
T. Hausken  
J. D. Fraser  
M. J. Chapman  
K. L. Jones  
A. M. Deane

## Mesenteric blood flow, glucose absorption and blood pressure responses to small intestinal glucose in critically ill patients older than 65 years

Received: 12 March 2012  
Accepted: 13 September 2012  
Published online: 25 October 2012  
© Springer-Verlag Berlin Heidelberg and ESICM 2012

J. A. Sim (✉) · M. J. Chapman ·  
A. M. Deane  
Discipline of Acute Care Medicine,  
University of Adelaide, North Terrace,  
Adelaide, SA, Australia  
e-mail: jennifer.sim@student.  
adelaide.edu.au  
Tel.: +61-8-82224000  
Fax: +61-8-8222367

M. Horowitz · L. G. Trahair · K. L. Jones  
Discipline of Medicine, University  
of Adelaide, Royal Adelaide Hospital,  
Level 6 Eleanor Harrauld Building,  
North Terrace, Adelaide, SA, Australia

M. J. Summers · R. S. Goud ·  
A. V. Zaknic · J. D. Fraser ·  
M. J. Chapman · A. M. Deane  
Intensive Care Unit, Level 4, North  
Building, Royal Adelaide Hospital, North  
Terrace, Adelaide, SA 5000, Australia

T. Hausken  
Medical Department, Institute of Medicine,  
University of Bergen, Haukeland University  
Hospital, Bergen, Norway

**Abstract Purpose:** To compare nutrient-stimulated changes in superior mesenteric artery (SMA) blood flow, glucose absorption and glycaemia in individuals older than 65 years with, and without, critical illness. **Methods:** Following a 1-h ‘observation’ period ( $t_0$ – $t_{60}$ ), 0.9 % saline and glucose (1 kcal/ml) were infused directly into the small intestine at 2 ml/min between  $t_{60}$ – $t_{120}$ , and  $t_{120}$ – $t_{180}$ , respectively. SMA blood flow was measured using Doppler ultrasonography at  $t_{60}$  (fasting),  $t_{90}$  and  $t_{150}$  and is presented as raw values and nutrient-stimulated increment from baseline ( $\Delta$ ). Glucose absorption was evaluated using serum 3-*O*-methylglucose (3-OMG) concentrations during, and for 1 h after, the glucose infusion (i.e.  $t_{120}$ – $t_{180}$  and  $t_{120}$ – $t_{240}$ ). Mean arterial pressure was recorded between  $t_{60}$ – $t_{240}$ . Data are presented as median (25th, 75th percentile). **Results:** Eleven mechanically ventilated critically ill patients [age 75 (69, 79) years] and nine healthy volunteers [70 (68, 77) years] were studied. The magnitude of the nutrient-stimulated increase in SMA flow was markedly less in the critically ill when compared with healthy subjects [ $\Delta t_{150}$ : patients 115 (–138, 367) versus health 836 (618, 1,054) ml/min;  $P = 0.001$ ]. In patients, glucose absorption was reduced during, and for 1 h after, the

glucose infusion when compared with health [AUC<sub>120–180</sub>: 4.571 (2.591, 6.551) versus 11.307 (8.447, 14.167) mmol/l min;  $P < 0.001$  and AUC<sub>120–240</sub>: 26.5 (17.7, 35.3) versus 40.6 (31.7, 49.4) mmol/l min;  $P = 0.031$ ]. A close relationship between the nutrient-stimulated increment in SMA flow and glucose absorption was evident (3-OMG AUC<sub>120–180</sub> and  $\Delta$ SMA flow at  $t_{150}$ :  $r^2 = 0.29$ ;  $P < 0.05$ ). **Conclusions:** In critically ill patients aged >65 years, stimulation of SMA flow by small intestinal glucose infusion may be attenuated, which could account for the reduction in glucose absorption.

**Keywords** Critical illness · Superior mesenteric artery · Glucose absorption · Nutrition · Postprandial hypotension · Splanchnic blood flow

### Abbreviations

3-OMG	3- <i>O</i> -Methylglucose
ATP	Adenosine triphosphate
GLUT-2	Glucose transporter-2
SGLT-1	Sodium glucose luminal transporter-1
SMA	Superior mesenteric artery
MAP	Mean arterial blood pressure

## Introduction

Mechanically ventilated patients are fed artificially, either parenterally or enterally [1]. The provision of nutrient via a nasogastric tube is standard of care [1, 2], as it is easier to administer, cheaper [1] and associated with fewer complications than parenteral nutrition [1, 2]. However, enteral nutrition may be associated with 'inadequate' nutrient delivery [3, 4] which, in the critically ill, may result in increased morbidity, particularly infections [4], and loss of lean body mass, which in itself may contribute to ventilator dependency, and prolonged length of stay [5]. Thus, there is a need to improve the methods used to administer enteral nutrition.

Abnormally delayed gastric emptying is a major cause of inadequate nasogastric nutrient delivery in the critically ill [6]. Delayed gastric emptying can be treated with either prokinetic drugs [1] or postpyloric delivery of nutrient [5, 7]. While postpyloric nutrition may increase caloric delivery [8–11], absorption of glucose [as assessed by the non-metabolised analogue, 3-*O*-methylglucose (3-OMG)], is markedly reduced in the critically ill [12], which is likely to also apply to other nutrients [13]. Because of the complications associated with inadequate nutrition, it is important to define potential mechanisms underlying disordered glucose absorption in the critically ill.

Glucose is absorbed predominantly in the proximal small intestine via a sodium-glucose co-transporter (SGLT-1) at the luminal membrane and glucose transporter-2 (GLUT-2)-facilitated diffusion at the basolateral membrane [14]. Decreased small intestinal perfusion may logically reduce glucose absorption via effects on the transporters [15]. The luminal SGLT-1 is driven by the electrochemical gradient generated by a basolateral sodium-potassium adenosine triphosphate (ATP)ase [16]. Reduced perfusion would diminish both the oxygen available for ATPase activity and the glucose concentration gradient across the basolateral membrane that drives GLUT-2-mediated facilitated diffusion. While glucose malabsorption has been demonstrated in the critically ill [12, 17, 18], the underlying mechanisms are unknown, and nutrient-mediated splanchnic blood flow has not been adequately investigated in this group.

In health, small intestinal nutrient markedly increases superior mesenteric artery (SMA) blood flow [19], and in persons >65 years this increase in SMA flow is associated with a reduction in systemic blood pressure [19, 20]. Moreover, the reduction in blood pressure induced by glucose is load dependent, such that small intestinal infusion rates of glucose at 2–3 kcal/min, but not 1 kcal/min, reduced blood pressure [21]. However blood pressure was evaluated using an oscillometric technique, which is inferior to invasive arterial measurements [22]. Because any reduction in systemic blood pressure is potentially hazardous to the critically ill [23], it is surprising that the relationship between small intestinal glucose infusion and

blood pressure in this group has not been investigated. However, if small intestinal nutrient is associated with either increased SMA flow, or a fall in systemic blood pressure, it is most likely to be seen in patients >65 years, given that small intestinal glucose is known to reduce blood pressure in healthy individuals >65 years [24], but has little effect in younger subjects [21].

The primary aim of this study is to evaluate the effect of critical illness on SMA blood flow both in the fasted state and in response to small intestinal infusion of glucose at 2 kcal/min in subjects older than 65 years. We hypothesised that the nutrient-stimulated increase in SMA flow would be less in critically ill patients aged >65 years than in age-matched healthy subjects. Secondary aims are to measure the effect of critical illness on glucose absorption, systemic mean arterial pressure (MAP) and glycaemia in response to small intestinal glucose infusion, and relate these effects to those observed on SMA flow.

## Methods

### Subjects

#### *Patients*

Mechanically ventilated patients >65 years who were receiving, or suitable to receive, enteral nutrition via a postpyloric feeding catheter were recruited from the Intensive Care Unit at the Royal Adelaide Hospital. Written, informed consent was obtained from patients' next of kin. Exclusion criteria included previous surgery on the oesophagus, stomach or duodenum, any gastrointestinal surgery during their current hospital admission, patients in whom MAP was required to be >80 mmHg (e.g. patients with intracerebral arterial vasospasm), patients receiving exogenous catecholamine infusion (noradrenaline and/or adrenaline) >30 µg/min, known diabetes mellitus, patients receiving antihypertensive medications [i.e. prescribed in the previous 24 h (IV or enteral)], and body mass index (BMI) >32 kg/m<sup>2</sup>. While administration of prokinetic drugs was not a formal exclusion criterion, none of the subjects received these agents in the 12 h prior to the commencement of the study.

#### *Controls*

Tube-tolerant healthy volunteers >65 years, recruited from an existing database, were studied. Exclusion criteria comprised contraindication to either naso-duodenal feeding or radial artery catheter placement, previous gastrointestinal surgery or disease, use of antihypertensive medications or medications known to affect gastrointestinal motility, BMI >32 kg/m<sup>2</sup>, known diabetes mellitus,

smoking >10 cigarettes/day, alcohol consumption >20 g/day.

The protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital, performed according to Australian National Health and Medical Research Centre guidelines for the conduct of research on unconscious patients, and registered with the Australian New Zealand Clinical Trials Registry (<http://www.anzctr.org.au>, ID 336577).

## Protocol

### Patients

Patients were studied after a fast of  $\geq 8$  h. If insulin was being administered, infusions were ceased at least 2 h prior to study commencement. Postpyloric feeding tubes were inserted using a non-invasive technique described previously [25], and correct placement confirmed on abdominal radiography.

### Controls

Healthy subjects were instructed to drink 250 ml Ensure (Abbott laboratories BV, Zwolle, Holland), a 1 kcal/ml mixed nutrient liquid, at 2200 hours before fasting overnight. This was undertaken in an attempt to replicate the enteral feeding that occurs in the critically ill. Subjects then arrived at the Royal Adelaide Hospital at 0830 hours. Following subcutaneous injection of local anaesthetic, a catheter was inserted into the radial artery. A postpyloric tube was then inserted via an anaesthetised nostril, using the same technique as in the critically ill [25].

As insertion of catheters may cause 'stress', particularly in volunteers, once all catheters were in place a 60-min 'observation' period was undertaken. At  $t_{60}$ , 0.9 % saline was infused into the duodenum at 2 ml/min until  $t_{120}$ . Between  $t_{120}$  and  $t_{180}$ , an infusion of nutrient [30 g D-(+)-glucose monohydrate + 3 g 3-OMG (Sigma-Aldrich, Castle Hill, NSW, Australia) dissolved in water to a total of 120 ml] was infused into the duodenum at a rate of 2 kcal/min. A 60-min 'postprandial observation' period was undertaken from  $t_{180}$  to  $t_{240}$ . Insulin was not administered during the study period.

## Measurements

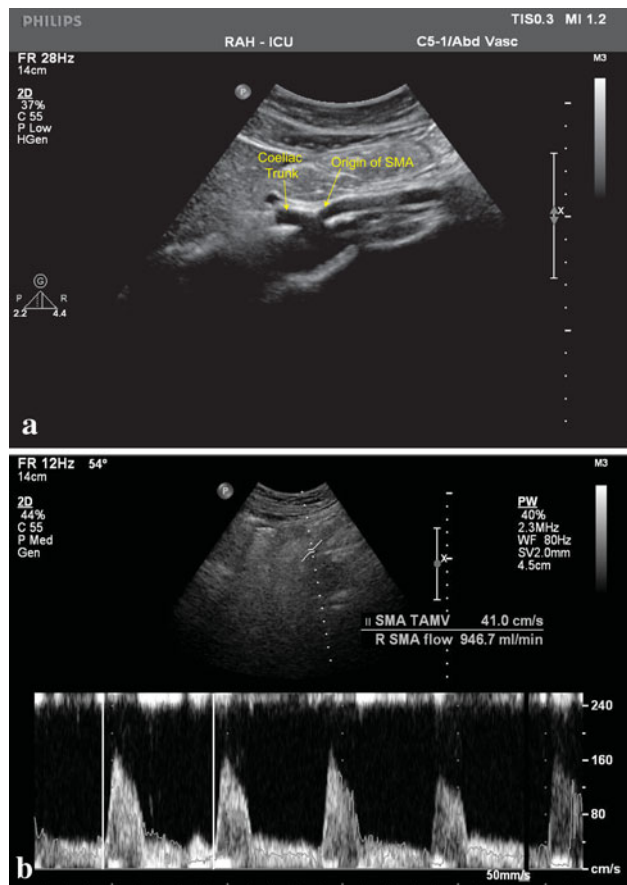
### Superior mesenteric artery blood flow

Superior mesenteric artery (SMA) blood flow velocity was measured by duplex ultrasonography (Philips iE33 xMATRIX, Bothell, WA, USA) [26]. In brief, the investigator measured the diameter of the SMA during

systole from magnified B-mode longitudinal images of the SMA (Fig. 1a). The investigator and ultrasound machine were kept constant. A 3.5C broad-spectrum 2.5–4-MHz convex transducer was used to scan subjects at each time point [ $t_{60}$  (baseline),  $t_{90}$  (during small intestinal saline infusion),  $t_{120}$  (at end of small intestinal saline infusion),  $t_{150}$  (during small intestinal glucose infusion),  $t_{180}$  (at end of small intestinal glucose infusion) and  $t_{240}$  (at the end of the study)]. Blood flow (ml/min) measurements were calculated immediately, using the formula:  $\pi \times r^2 \times \text{TAMV} \times 60$ , where  $r$  is the radius of the superior mesenteric artery and TAMV is the time-averaged mean velocity [26]. The angle between the Doppler and the mesenteric artery was always  $<60^\circ$  (Fig. 1b).

### Serum 3-O-methylglucose, glycaemia and glycated haemoglobin

Arterial samples were taken every half hour from  $t_{60}$  to  $t_{120}$ , at  $t_{125}$ ,  $t_{135}$ , then every 15 min from  $t_{120}$  to  $t_{240}$ .



**Fig. 1** a Ultrasound screen during superior mesenteric artery diameter measurement. b Ultrasound screen during superior mesenteric artery velocity blood flow measurement

Serum was separated by centrifugation (3,200 rpm for 15 min at 4 °C) and stored at -70 °C for subsequent analysis. Serum 3-OMG was measured using liquid chromatography/mass spectroscopy, with an assay sensitivity of 0.0103 mmol/l [12]. Blood glucose concentrations were determined using a portable glucose meter (MediSense Precision; Abbott Laboratories, MediSense Products, Bedford, MA, USA). Glycated haemoglobin (HbA<sub>1c</sub>) concentration was determined from fasting arterial blood samples and measured using high-performance liquid chromatography (Variant II Turbo; Bio-Rad Laboratories, CA, USA).

### Mean arterial pressure

Mean arterial pressures (MAP) were recorded from the arterial catheter every 2 min and reported as the mean over 10 min.

### Statistical analysis

All analyses were conducted using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). As some data were skewed, they are presented as median (25th, 75th percentile). Specific time points were chosen a priori. These were baseline ( $t_{60}$ ), during saline infusion ( $t_{90}$ ), during nutrient infusion ( $t_{150}$ ), at the end of the nutrient infusion ( $t_{180}$ ) and at the end of the study ( $t_{240}$ ). As the SMA, glycaemia and MAP data were significantly different at baseline between patients and healthy subjects, these data are also presented as change from baseline. 3-OMG area under the curve (AUC) was calculated using the trapezoidal rule. Time to peak (TTP) was used to

determine total and rate of glucose absorption respectively. All comparative data (patient versus healthy subject) were analysed using Mann-Whitney  $U$  test. Comparisons between SMA flow values as change from baseline during saline ( $\Delta t_{90}$ ) and change from baseline during nutrient ( $\Delta t_{150}$ ) were calculated using Wilcoxon signed-rank test.  $P$  value  $\leq 0.05$  was considered significant.

## Results

The studies were well tolerated, and there were no adverse events evident. Eleven critically ill patients and nine healthy subjects were studied (Table 1). Satisfactory ultrasound assessment of SMA blood flow was obtained from all patients enrolled into the study.

### SMA flow

Fasting SMA flow was increased in patients when compared with health, but flow was reduced in patients during small intestinal glucose infusion (Fig. 2a, b).

A similar magnitude of change in SMA flow was observed in each group during saline [ $\Delta t_{90}$ : patients 55 (-149, 260) versus health 99 (-35, 232) ml/min;  $P = 0.545$ ], at the end of the glucose infusion [ $\Delta t_{180}$ : 170 (-204, 544) versus 711 (366, 1056) ml/min;  $P = 0.056$ ] and at the study end [ $\Delta t_{240}$ : 42 (-118, 202) versus 114 (-91, 319) ml/min;  $P = 0.72$ ]. However, the increase in SMA flow during small intestinal glucose was markedly attenuated in patients when compared with controls (Fig. 2a, b).

**Table 1** Demographics of study participants

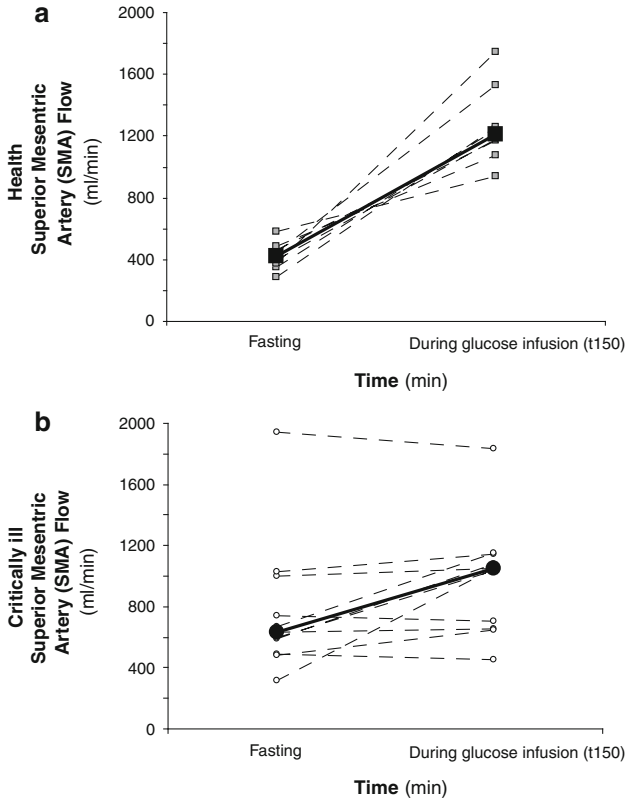
	Critically ill patients ( $n = 11$ )	Healthy subjects ( $n = 9$ )
Age (years)	75 (69, 79)	70 (68, 77)
Sex (M:F)	8:3	7:2
BMI (kg/m <sup>2</sup> )	25 (19, 31)	26 (25, 28)
HbA <sub>1c</sub> (%)	6.0 (5.7, 6.3)	5.9 (5.5, 6.2)
APACHE II score (study day)	21 (12, 21)	N/A
Diagnosis	Neurological (4), infective (3), cardiac (2) and trauma (2) <sup>a</sup>	N/A
Length in ICU at study day (days)	3 (2, 4)	N/A
Serum creatinine >120 mmol/l on day of study ( $n$ )	3	N/A
Received catecholamines ( $n$ )	1	N/A

Data are median (25th, 75th percentile)

ICU intensive care unit, M male, F female, BMI body mass index, HbA<sub>1c</sub> glycated haemoglobin, APACHE Acute Physiology and Chronic Health Evaluation

<sup>a</sup> Neurological (4), subarachnoid haemorrhage (1), ischaemic stroke (1), subdural hematoma (1), status epilepticus (1). Infective

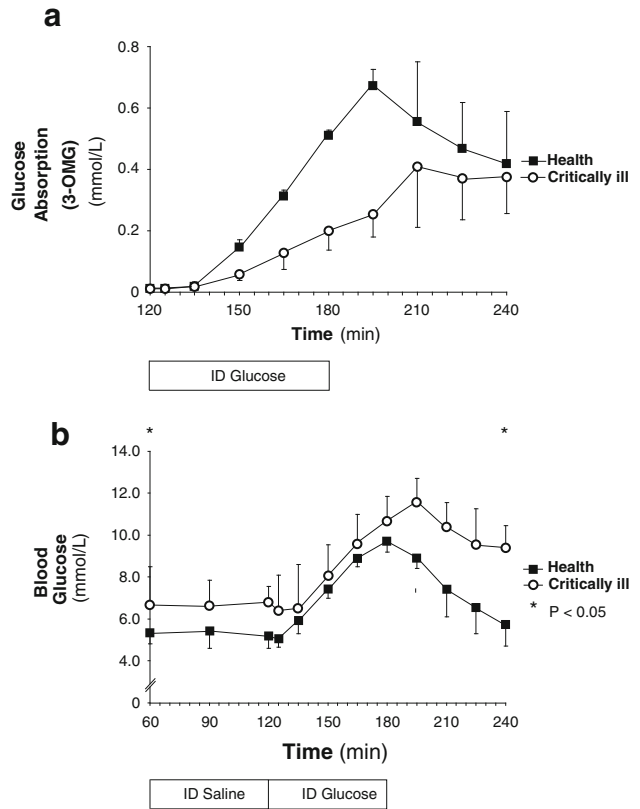
(3): community-acquired pneumonia (2) and hospital-acquired pneumonia (1). Cardiac (2): cardiac failure (1) and postcardiac surgery (1). Trauma (2): blunt chest/pelvis trauma (1) and burn injury (1)



**Fig. 2** Superior mesenteric artery blood flow in **a** healthy subjects (filled squares) and **b** critically ill patients (open circles). Fasting SMA flow was greater in patients [ $t_{60}$ : patients 636 (379–894) versus health 402 (325–480) ml/min;  $P = 0.001$ ]. However, during glucose infusion, SMA flow was reduced in patients [ $t_{150}$ : 1,050 (808, 1,292) versus 1,212 (1,030, 1,393) ml/min;  $P = 0.026$ ]. Accordingly, the magnitude of the nutrient-stimulated increase in SMA flow was markedly less in the critically ill when compared with healthy subjects [ $\Delta t_{150}$ : 115 (–138, 367) versus 836 (618, 1,054) ml/min;  $P = 0.001$ ]. Data in the figure represent median of the cohort at time points (fasting and  $t_{150}$ ) in bold with individual subjects represented by dotted lines. Analysis is reported as median and interquartile ranges of the difference within subject

### 3-O-Methylglucose concentrations (glucose absorption), glycaemia and glycated haemoglobin

In both groups serum 3-OMG rose during the small intestinal glucose infusion ( $t_{120}$ – $t_{180}$ ) and had not returned to baseline at  $t_{240}$ . In patients glucose absorption (3-OMG AUC) was reduced during glucose infusion (Fig. 3a). This difference continued until the study end (Fig. 3a). When analysing individual time points 3-OMG concentrations were lower in patients compared with controls during [ $t_{150}$ : 0.06 (0.03, 0.09) versus 0.15 (0.11, 0.19) mmol/l;  $P = 0.01$ ] and at the end of glucose infusion [ $t_{180}$ : 0.20 (0.14, 0.27) versus 0.51 (0.47, 0.56) mmol/l;  $P = 0.001$ ]. In addition, peak 3-OMG concentrations were reduced in patients compared with control [Peak<sub>3-OMG</sub>: 0.47 (0.30, 0.63) versus 0.71 (0.52, 0.88) mmol/l;  $P = 0.01$ ]. The



**Fig. 3** **a** Serum 3-OMG concentrations. In the critically ill glucose absorption was reduced during the glucose infusion [AUC<sub>120–180</sub>: patients 4.6 (2.6, 6.6) versus health 11.3 (8.4, 14.2) mmol/l min;  $P < 0.001$ ], which was sustained until study end [AUC<sub>120–240</sub> 26.5 (17.7, 35.3) versus 40.6 (31.7, 49.4) mmol/l min;  $P = 0.031$ ]. **b** Blood glucose concentrations. Glucose concentrations were greater at the start and end of the study [ $t_{60}$ : 6.7 (5.1, 8.3) versus 5.2 (4.8, 5.6) mmol/l;  $P = 0.006$  and  $t_{240}$ : 9.4 (8.4, 10.5) versus 5.7 (4.8, 6.6) mmol/l;  $P < 0.001$ ]. Overall glycaemic response to nutrient was greater in the critically ill [AUC<sub>GLYCAEMIA</sub>: 1,453 (1,162, 1,743) versus 1,190 (1,097, 1,283) mmol/l min;  $P = 0.007$ ]. Critically ill patients (open circles,  $n = 11$ ) and healthy subjects (filled squares,  $n = 9$ ). Data are median and interquartile ranges

time to peak concentration was comparable between the two groups [TTP<sub>3-OMG</sub>: 210 (210, 240) versus 195 (195, 210) min;  $P = 0.23$ ].

Blood glucose was higher in patients at baseline and at the end of the study (Fig. 3b). While glycaemia was comparable between groups during [ $t_{150}$ : 8.1 (6.6, 9.7) versus 7.4 (6.6, 8.2) mmol/l;  $P = 0.37$ ] and at the end of the glucose infusion [ $t_{180}$ : 10.7 (9.0, 12.5) versus 9.7 (9.3, 10.2) mmol/l;  $P = 0.37$ ], overall glycaemic response was greater in the critically ill (Fig. 3b).

The change in glycaemia from baseline was less in patients during the glucose infusion [ $\Delta t_{150}$ : 1 (0.3, 1.8) versus 2.1 (1.5, 2.7) mmol/l;  $P = 0.02$ ], but greater at the end of the study [ $\Delta t_{240}$ : 2.4 (1.3, 3.5) versus 0.0 (–0.6, 0.6) mmol/l;  $P = 0.001$ ]. Change in glucose concentration

was similar at the end of the glucose infusion [ $\Delta t_{180}$ : 3.3 (2.0, 4.6) versus 4.4 (4.0, 4.8) mmol/l;  $P = 0.23$ ].

Peak glycaemia was comparable [Peak<sub>GLYCAEMIA</sub>: 11.6 (10.3, 13.0) versus 9.9 (8.9, 10.9) mmol/l;  $P = 0.112$ ], but the time taken for the glycaemia to peak was later in patients compared with healthy subjects [TTP<sub>GLYCAEMIA</sub>: 195 (195, 195) versus 180 (169, 192) min;  $P = 0.003$ ].

Glycated haemoglobin concentrations were <6.5 % in all subjects (Table 1).

#### Mean arterial pressure

Mean arterial pressure (MAP) was lower in patients at baseline [ $t_{60}$ : 83.3 (72.0, 95.0) versus 107.5 (95.1, 119.9) mmHg;  $P = 0.01$ ] and at the end of the study [ $t_{240}$ : 90.9 (81.6, 100.2) versus 107.0 (95.5, 118.5) mmHg;  $P = 0.043$ ], but comparable at all other time points [ $t_{90}$ : 91.5 (84.5, 98.5) versus 106.5 (95.5, 117.5) mmHg;  $P = 0.62$ ;  $t_{150}$ : 92.1 (82.2, 101.9) versus 100.4 (89.9, 111.9) mmHg;  $P = 0.152$ ;  $t_{180}$ : 85.4 (73.4, 97.3) versus 98.9 (89.7, 108.1) mmHg;  $P = 0.156$ ].

In healthy subjects there was a significant reduction in MAP at the end of glucose infusion, but in the critically ill MAP was stable during the glucose infusion (Fig. 4).

#### Relationships of SMA flow with glucose absorption and MAP

There was a strong association between SMA flow and total glucose absorption in all subjects (Fig. 5). However, there was no significant relationship between the change in SMA flow and the change in MAP during glucose infusion.

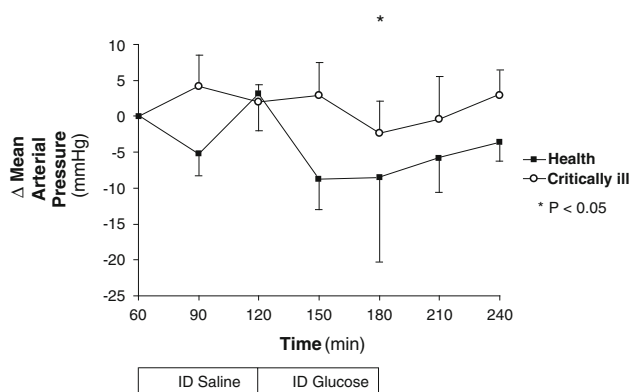
## Discussion

This study suggests that in critically ill patients >65 years fasting SMA flow is greater than in healthy subjects, but the glucose-stimulated increment in SMA blood flow is markedly attenuated. The latter finding may account for the absence of any effect of small intestinal glucose on MAP in this group. The study also reaffirms that small intestinal glucose absorption is diminished in the critically ill despite elevated glycaemia, and supports the hypothesis that this may be attributable to an attenuation of glucose-stimulated increases in SMA flow.

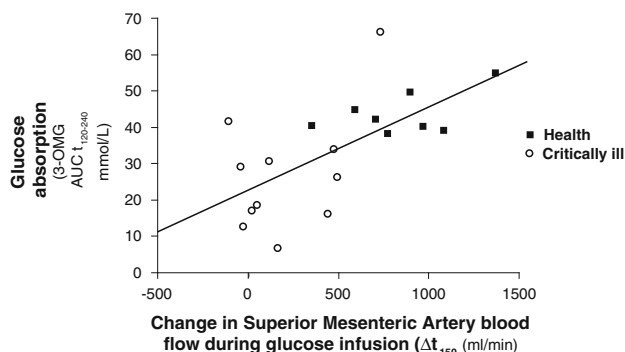
Small intestinal nutrient stimulates an increase in hepatosplanchnic blood flow in both septic [27] and postcardiac surgery [28] patients. In a study by Rokyta

et al. [27] no change in MAP was observed in septic patients, which contrasts with the effect in healthy persons >65 years [20]. In these previous studies, however, glucose absorption was not measured [27]. Moreover, the investigators delivered a mixed nutrient (carbohydrate, fat, protein) liquid [27, 28] at a load (0.75 kcal/min) [27] not known to stimulate changes in SMA flow in health and less than recommended standard feeding regimens. Both studies also measured SMA flow using indocyanine green clearance. Rokyta et al. measured hepatosplanchnic blood flow by the Fick principle using continuous primed indocyanine green infusion with hepatic vein catheterization, while Revelly et al. used the less accurate method of systemic clearance of indocyanine green as a surrogate for hepatosplanchnic blood flow. The accuracy of indocyanine green clearance to measure hepatosplanchnic blood flow relies on adequate hepatic perfusion and function, which is frequently disordered in the critically ill. Using ultrasound, Gatt and colleagues [29] observed increased SMA flow in hospitalized patients following enteral nutrition. However, only three mechanically ventilated patients were studied, and, accordingly, the results cannot be considered as representative of the critically ill. Furthermore, intragastric nutrient was administered, and, as gastric emptying is highly variable in this group [6], the nutrient stimulus was poorly controlled, in contrast to small intestinal nutrient infusion, which has the capacity to deliver a predictable load. For these reasons mesenteric blood flow during enteral feeding had, hitherto, been inadequately quantified in the critically ill. Despite the lack of studies in this area, it is widely considered by many authorities that mesenteric blood flow is markedly reduced in this group [30].

In patients, the fasting (baseline) SMA flow was increased, which is contrary to the previously held belief that gastrointestinal blood flow is reduced in critical illness. There are a number of possible mechanisms. In some critically ill patients, transit of chyme through the small intestine may be impaired [12], such that an 8-h fast is insufficient to allow complete clearance of chyme, resulting in nutrient stimulation during the 'fasting' period in the critically ill. A hyperdynamic circulation, which may be due to increased cardiac output and/or hypervolaemia, also may contribute to the increased mesenteric artery blood flow (while receiving a similar percentage of cardiac output). It is possible that the reduced increment in blood flow in the critically ill in response to nutrient may have been due to the elevated blood flow at baseline. However this is unlikely given that blood flows as substantial as 2,500 ml/min have been recorded in response to nutrient exposure in health [31], suggesting that the 800–1,200 ml/min recorded in these patients is submaximal.



**Fig. 4** Change in MAP. In patients MAP was unaffected by small intestinal glucose infusion, but, in health, a substantial reduction in MAP was observed at the end of the glucose infusion [ $\Delta t_{180}$ :  $-1.7$  ( $-5.6, 2.2$ ) versus  $-7.2$  ( $-19.5, 5.1$ ) mmHg;  $P = 0.035$ ]. Critically ill patients (*open circles*,  $n = 11$ ) and healthy subjects (*filled squares*,  $n = 9$ ). Data are median and interquartile ranges



**Fig. 5** Relationship between the change in SMA flow and glucose absorption [3-OMG AUC<sub>120–180</sub> and SMA flow at  $t_{150}$  ( $n = 20$ ):  $r^2 = 0.29$ ;  $P < 0.05$ ]. Critically ill patients (*open circles*) and healthy subjects (*filled squares*)

The amount of glucose absorbed, as indicated by the 3-OMG AUC, was substantially less in patients compared with healthy subjects both during small intestinal glucose infusion and throughout the study. These data are consistent with our previous study in an unselected group of critically ill patients [12]. It is unlikely that fasting hyperglycaemia per se explains the reduction in glucose absorption that was observed in the critically ill—as hyperglycaemia in the physiological range has been shown to increase, rather than reduce, glucose absorption [24]. In addition, because 3-OMG was administered directly into the small intestine, the effect is not attributable to a difference in gastric emptying, highlighting that abnormalities within the small intestine must contribute to this phenomenon. An association between nutrient-stimulated SMA flow and glucose absorption was apparent, suggesting that disordered

SMA flow may contribute to reduced absorption in the critically ill. Despite attenuation of glucose absorption in the critically ill, the glycaemic response was similar, likely reflecting disordered glucose handling in critically ill patients [12].

There are limitations to this study. Both groups comprised small numbers with clinical heterogeneity. However, despite this limitation there was significant difference in baseline and incremented SMA flow between our patient group and healthy subjects. We used 3-OMG to estimate glucose absorption, but the serum concentrations had not returned to zero at the study end. However, 3-OMG is cleared unchanged by the kidneys, and renal function is commonly impaired in the critically ill even when markers, such as serum creatinine, are within ‘normal’ limits [32], which would have favoured a false-negative result. We did not measure cardiac output and, therefore, are unable to quantify the percentage of blood flow that was directed to the SMA. It should be noted, however, that our hypothesis was that flow would be reduced, rather than increased, when compared with health. It should also be recognised that only SMA blood flow was measured, and micro-circulation at the mucosal surface may not reflect circulatory changes in the SMA [33]. Furthermore, even in health the use of ultrasound to measure SMA flow is technically demanding [26], and while ultrasound as a modality to measure mesenteric blood flow in the critically ill is appealing, it is not yet established. Finally, only three of the patients were admitted because of sepsis, and only one was receiving catecholamine infusion. For this reason our data should be extrapolated cautiously to critically ill patients with shock.

In summary, this study suggests that fasting SMA flow is increased whereas glucose-stimulated increases in SMA flow are markedly attenuated in critically ill patients >65 years when compared with health. In healthy subjects >65 years glucose-stimulated increases in SMA flow were associated with a reduction in MAP and greater glucose absorption. In comparison, the patients >65 years absorbed less glucose and no effect on MAP was observed during small intestinal glucose infusion. Thus, reduced glucose absorption in critically ill relatively haemodynamically stable patients older than 65 years may reflect, at least in part, diminished nutrient-stimulated perfusion of the absorptive surface of the small intestine.

**Acknowledgments** The study was supported by a NHMRC project grant (1025648). Ms. Jennifer Sim was supported by a Florey Honours Bachelor of Medical Sciences 2011 Scholarship, and Dr. Adam Deane was supported by a Sylvia and Charles Viertel Charitable Foundation Clinical Investigatorship. We acknowledge the guidance of Ms. Kylie Lange regarding appropriate statistical testing.

## References

- Heyland DK, Dhaliwal R, Day A, Jain M, Drover J (2004) Validation of the Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients: results of a prospective observational study. *Crit Care Med* 32:2260–2266
- Martindale RG, McClave SA, Vanek VW, McCarthy M, Roberts P, Taylor B, Ochoa JB, Napolitano L, Cresci G (2009) Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition: executive summary. *Crit Care Med* 37:1757–1761
- Berger MM, Chioloro RL, Pannatier A, Cayeux MC, Tappy L (1997) A 10-year survey of nutritional support in a surgical ICU: 1986–1995. *Nutrition* 13:870–877
- Villet S, Chioloro RL, Bollmann MD, Revelly JP, Cayeux RNM, Delarue J, Berger MM (2005) Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. *Clin Nutr* 24:502–509
- Deane A, Chapman MJ, Fraser RJ, Bryant LK, Burgstad C, Nguyen NQ (2007) Mechanisms underlying feed intolerance in the critically ill: implications for treatment. *World J Gastroenterol* 13:3909–3917
- Heyland DK, Tougas G, King D, Cook DJ (1996) Impaired gastric emptying in mechanically ventilated, critically ill patients. *Intensive Care Med* 22:1339–1344
- Davies AR, Froomes PR, French CJ, Bellomo R, Gutteridge GA, Nyulasi I, Walker R, Sewell RB (2002) Randomized comparison of nasojejunal and nasogastric feeding in critically ill patients. *Crit Care Med* 30:586–590
- Montecalvo MA, Steger KA, Farber HW, Smith BF, Dennis RC, Fitzpatrick GF, Pollack SD, Korsberg TZ, Birkett DH, Hirsch EF et al (1992) Nutritional outcome and pneumonia in critical care patients randomized to gastric versus jejunal tube feedings. The Critical Care Research Team. *Crit Care Med* 20:1377–1387
- Hsu CW, Sun SF, Lin SL, Kang SP, Chu KA, Lin CH, Huang HH (2009) Duodenal versus gastric feeding in medical intensive care unit patients: a prospective, randomized, clinical study. *Crit Care Med* 37:1866–1872
- Kearns PJ, Chin D, Mueller L, Wallace K, Jensen WA, Kirsch CM (2000) The incidence of ventilator-associated pneumonia and success in nutrient delivery with gastric versus small intestinal feeding: a randomized clinical trial. *Crit Care Med* 28:1742–1746
- Meert KL, Daphtary KM, Metheny NA (2004) Gastric vs small-bowel feeding in critically ill children receiving mechanical ventilation: a randomized controlled trial. *Chest* 126:872–878
- Deane AM, Summers MJ, Zaknic AV, Chapman MJ, Di Bartolomeo AE, Bellon M, Maddox A, Russo A, Horowitz M, Fraser RJ (2011) Glucose absorption and small intestinal transit in critical illness. *Crit Care Med* 39:1282–1288
- van Schijndel RJMS, Wierdsma NJ, van Heijningen EMB, Weijs PJM, de Groot SDW, Girbes ARJ (2006) Fecal energy losses in enterally fed intensive care patients: an explorative study using bomb calorimetry. *Clin Nutr* 25:758–764
- Levin RJ (1994) Digestion and absorption of carbohydrates—from molecules and membranes to humans. *Am J Clin Nutr* 59:690S–698S
- Boucher BA, Wood GC, Swanson JM (2006) Pharmacokinetic changes in critical illness. *Crit Care Clin* 22:255–271
- Wright EM, Hirayama BA, Loo DF (2007) Active sugar transport in health and disease. *J Intern Med* 261:32–43
- Johnston JD, Harvey CJ, Menzies IS, Treacher DF (1996) Gastrointestinal permeability and absorptive capacity in sepsis. *Crit Care Med* 24:1144–1149
- Chapman MJ, Fraser RJ, Matthews G, Russo A, Bellon M, Besanko LK, Jones KL, Butler R, Chatterton B, Horowitz M (2009) Glucose absorption and gastric emptying in critical illness. *Crit Care* 13:R140
- Gentilcore D, Hausken T, Meyer JH, Chapman IM, Horowitz M, Jones KL (2008) Effects of intraduodenal glucose, fat, and protein on blood pressure, heart rate, and splanchnic blood flow in healthy older subjects. *Am J Clin Nutr* 87:156–161
- Vanis L, Gentilcore D, Rayner CK, Wishart JM, Horowitz M, Feinle-Bisset C, Jones KL (2011) Effects of small intestinal glucose load on blood pressure, splanchnic blood flow, glycemia, and GLP-1 release in healthy older subjects. *Am J Physiol Regul Integr Comp Physiol* 300:R1524–R1531
- Trahair LG, Vanis L, Gentilcore D, Lange K, Rayner CK, Horowitz M, Jones KL (2012) Effects of variations in duodenal glucose load on blood pressure, heart rate, superior mesenteric artery blood flow and plasma noradrenaline in healthy young and older subjects. *Clin Sci (Lond)* 122:271–279
- Araghi A, Bander JJ, Guzman JA (2006) Arterial blood pressure monitoring in overweight critically ill patients: invasive or noninvasive? *Crit Care* 10:R64
- Thibault R, Pichard C, Wernerman J, Bendjelid K (2011) Cardiogenic shock and nutrition: safe? *Intensive Care Med* 37:35–45
- Kuo P, Wishart JM, Bellon M, Smout AJ, Holloway RH, Fraser RJ, Horowitz M, Jones KL, Rayner CK (2010) Effects of physiological hyperglycemia on duodenal motility and flow events, glucose absorption, and incretin secretion in healthy humans. *J Clin Endocrinol Metab* 95:3893–3900
- Deane AM, Fraser RJ, Young RJ, Foreman B, O’Conner SN, Chapman MJ (2009) Evaluation of a bedside technique for postpyloric placement of feeding catheters. *Crit Care Resusc* 11:180–183
- Perko MJ (2001) Duplex ultrasound for assessment of superior mesenteric artery blood flow. *Eur J Vasc Endovasc Surg* 21:106–117
- Rokyta R Jr, Matejovic M, Krouzicky A, Senft V, Trefil L, Novak I (2004) Post-pyloric enteral nutrition in septic patients: effects on hepato-splanchnic hemodynamics and energy status. *Intensive Care Med* 30:714–717
- Revelly JP, Tappy L, Berger MM, Gersbach P, Cayeux C, Chioloro R (2001) Early metabolic and splanchnic responses to enteral nutrition in postoperative cardiac surgery patients with circulatory compromise. *Intensive Care Med* 27:540–547
- Gatt M, MacFie J, Anderson AD, Howell G, Reddy BS, Suppiah A, Renwick I, Mitchell CJ (2009) Changes in superior mesenteric artery blood flow after oral, enteral, and parenteral feeding in humans. *Crit Care Med* 37:171–176
- Kolkman JJ, Mensink PB (2003) Non-occlusive mesenteric ischaemia: a common disorder in gastroenterology and intensive care. *Best Pract Res Clin Gastroenterol* 17:457–473



31. Vanis L, Gentilcore D, Hausken T, Pilichiewicz AN, Lange K, Rayner CK, Feinle-Bisset C, Meyer JH, Horowitz M, Jones KL (2010) Effects of gastric distension on blood pressure and superior mesenteric artery blood flow responses to intraduodenal glucose in healthy older subjects. *Am J Physiol Regul Integr Comp Physiol* 299:R960–R967
32. Hoste EA, Damen J, Vanholder RC, Lameire NH, Delanghe JR, Van den Hauwe K, Colardyn FA (2005) Assessment of renal function in recently admitted critically ill patients with normal serum creatinine. *Nephrol Dial Transplant* 20:747–753
33. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL (2002) Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med* 166:98–104