Autonomic function, postprandial hypotension and falls in older adults at one year after critical illness

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Critical illness is frequently associated with acute cardiovascular autonomic dysfunction and delayed gastric emptying.[1-3] The latter is often markedly delayed, sufficient to compromise delivery of nutrition,[4] and it may be a marker of autonomic dysfunction affecting the gastrointestinal tract. However, few longitudinal data exist regarding whether these problems persist in survivors following the resolution of critical illness.

Both autonomic dysfunction and gastric dysmotility may result in a clinically relevant postprandial fall in blood pressure known as postprandial hypotension.[5] Postprandial hypotension is recognised to be an independent risk factor for falls, coronary events, stroke and all-cause mortality,[6,7] irrespective of whether it is symptomatic.[8] Older patients may be at particular risk of postprandial hypotension after critical illness because age-related physiological changes already attenuate compensatory mechanisms.[9]

Given that increasing numbers of older patients are admitted to intensive care units (ICUs) worldwide[10] and that older survivors of critical illness experience substantial morbidity, mortality and health care use following ICU discharge,[11,12] interventions to improve outcomes in this cohort are needed. We have previously reported in an older cohort of patients at 3 months after ICU discharge that postprandial hypotension occurs frequently (in 29% of patients), is more common than orthostatic hypotension, and is often asymptomatic.[13]

This longitudinal study was designed to assess whether postprandial hypotension and its clinical predictors, gastric dysmotility and cardiovascular autonomic dysfunction, persist or resolve as older survivors of critical illness recover. The primary aim of this study was to estimate the prevalence of postprandial hypotension in a cohort of older survivors at 12 months after ICU discharge. Secondary aims were: to compare the prevalence of postprandial hypotension, orthostatic hypotension and cardiovascular autonomic dysfunction at 3 and 12 months after ICU discharge; to determine whether there is a change in gastric emptying over this period; and to evaluate the effect of postprandial hypotension at 3 months on quality of life and the risk of falls, hospitalisation and mortality in the year after ICU discharge.

ABSTRACT

Objective: Postprandial hypotension occurs frequently in older survivors of critical illness at 3 months after discharge. We aimed to determine whether postprandial hypotension and its predictors — gastric dysmotility and cardiovascular autonomic dysfunction — persist or resolve as older survivors of critical illness recover, and whether postprandial hypotension after intensive care unit (ICU) discharge is associated with adverse outcomes at 12 months.

Design: Prospective observational study.

Setting: Tertiary medical–surgical ICU.

Participants: Older adults (aged ≥ 65 years) who had been studied 3 months after ICU discharge and who returned for a follow-up study at 12 months after discharge.

Main outcome measures: On both occasions after fasting overnight, participants consumed a 300 mL drink containing 75 g glucose, radiolabelled with 20 MBq ^{99m}Tcphytate. Blood pressure, heart rate, blood glucose concentration and gastric emptying rate were measured concurrently before and after ingestion of the drink. Falls, quality of life, hospitalisation and mortality rates were also quantified.

Results: Out of 35 older adults studied at 3 months, 22 returned for the follow-up study at 12 months. Postprandial hypotension was evident in 29% of participants (95% CI, 14–44%) at 3 months and 10% of participants (95% CI, 1–30%) at 12 months. Postprandial hypotension at 3 months was associated with a more than threefold increase in the risk of falls in the year after ICU discharge (relative risk, 3.7 [95% CI, 1.6–8.8]; P = 0.003). At 12 months, gastric emptying was normal (mean time taken for 50% of gastric contents to empty, 101.6 [SD, 33.3] min) and cardiovascular autonomic dysfunction prevalence was low (9% [95% CI, 1–29%]).

Conclusions: In older adults who were evaluated 3 and 12 months after ICU discharge, postprandial hypotension at 3 months was associated with an increased risk of subsequent falls, but the prevalence of postprandial hypotension decreased with time.

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Methods

Study design and participants

This was a prospective observational study. The methods have been described in detail previously.[13] In brief, patients were eligible if they were aged 65 years or over and received at least 48 hours of care in the ICU of a tertiary teaching hospital in South Australia. Participants had been admitted to the ICU between November 2015 and June 2016. Exclusion criteria included inability to provide informed consent, residence more than 50 km from the hospital, death during hospitalisation, or anticipated death within 3 months of ICU discharge. The 35 participants who completed the study at 3 months after ICU discharge were contacted by telephone to take part in the follow-up study at a minimum of 12 months after ICU discharge.

Study protocol

The protocol was prospectively registered (ACTRN12616000303448) and approved by the Royal Adelaide Hospital Research Ethics Committee. All participants provided written informed consent. Demographic and health data were extracted from the participants' medical records.

On the day of the study, each participant had fasted from solids and liquids for 12 hours, but had taken their usual medications with a sip of water.[14] Anthropometric data, autonomic nerve function scores, and blood pressure (BP) were recorded at baseline. Each participant then sat with their back against a gamma camera and rested for 30 minutes. Following the rest period, participants ingested a 300 mL drink containing 75 g glucose, radiolabelled with 20 MBq ^{99m}Tcphytate (Radpharm Scientific, Canberra, Australia) within a 2-minute period. The end of ingestion of the drink was designated t = 0 min.

Blood pressure and heart rate

Seated systolic BP (SBP), diastolic BP (DBP) and heart rate (HR) were measured using an automated oscillometric monitor (DINAMAP ProCare 1000, GE Medical Systems, Waukesha, WI, USA) at 3-minute intervals from t = –9 minutes until t = 240 minutes. Baseline seated BP and HR values were calculated as the mean of three consecutive measurements during the rest period (t = –9, –6 and –3 min).[13,15] Postprandial hypotension was defined as a fall in SBP of 20 mmHg or greater for 30 minutes or longer within 120 minutes following ingestion of the glucose drink.[5]

Orthostatic hypotension and autonomic nerve function

All participants underwent standardised cardiovascular autonomic reflex tests using ANX 3.0 Autonomic Nervous System monitoring technology (ANSAR Group, Philadelphia, PA, USA) as previously described.[13,15] Each test result was scored according to predefined age-adjusted criteria,[16] and autonomic dysfunction was defined as a total score 3 or more (online Appendix 1, available at cicm.org.au/Resources/Publications/Journal). Orthostatic hypotension was defined according to predefined age-adjusted criteria.[16]

Gastric emptying

Gastric emptying was measured by scintigraphy (e.cam gamma camera, Siemens, Knoxville, TN, USA).[17] Radioisotopic data were acquired in dynamic mode for 240 min after ingestion of the glucose drink, using 1-minute frames for t = 0–60 minutes and 3-minute frames thereafter. Data were corrected for radionuclide decay, subject movement and gamma ray attenuation using established techniques.[17] The time preceding activity being seen in the proximal small intestine (lag phase) and the time taken for 50% of gastric contents to empty (T_{50}) were calculated.[17]

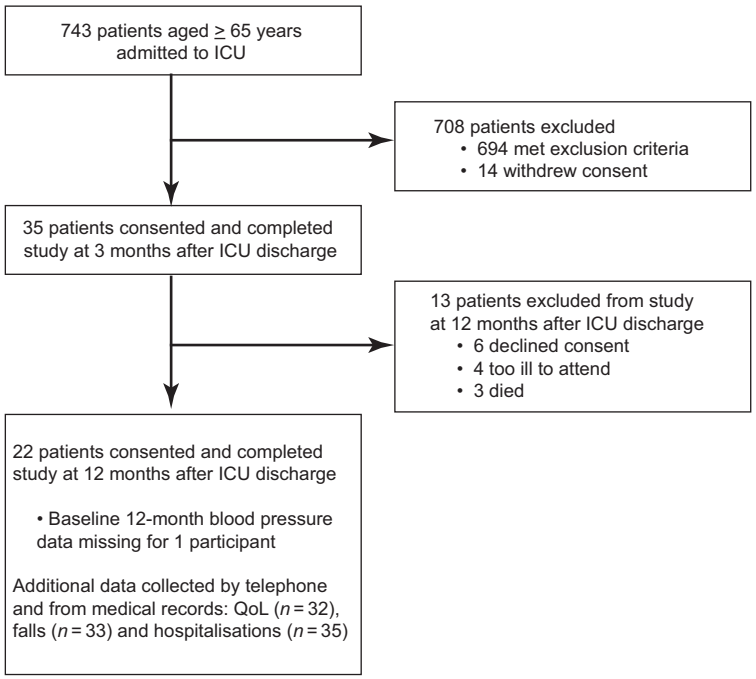
Blood glucose

Blood glucose concentration was measured at 15-minute intervals, commencing immediately before ingestion of the glucose drink, using a portable glucometer (MediSense Optium, Abbott, Abbott Park, IL, USA).

Postprandial hypotension symptoms, frailty, functional status, quality of life and health care resource use

In the absence of a validated questionnaire to define symptoms associated with postprandial hypotension (eg, dizziness, fainting, falls), a series of specific questions were developed (online Appendix 2).[13] Frailty was measured using the Clinical Frailty Scale score.[18] Independent activities of daily living were quantified using the Katz Index of Independence in Activities of Daily Living and the Lawton Instrumental Activities of Daily Living Scale.[19,20] Health-related quality of life was measured using the EuroQol (EQ-5D-5L) instrument, which is comprised of a descriptive system and a visual analogue scale (VAS).[21] The descriptive system assesses five dimensions of health (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression), each with five response levels ranging from no problems (Level 1) to extreme problems (Level 5). The VAS provides a single global rating of self-perceived health ranging from 0 to 100, with greater scores indicating better self-perceived health. Health care resource use data were collected prospectively using monthly patient diaries and corroborated with hospital inpatient and outpatient clinical records and self-reports at the study visit.[22] Patients who were unable to attend the study visit at 12 months were contacted by telephone and their medical records were reviewed for assessment of quality of life, falls and health care resource use.

Figure 1. Flow diagram detailing participant selection



ICU = intensive care unit. QOL = quality of life.

Statistical analysis

Data are presented as mean (standard deviation), if normally distributed, or median (interquartile range), if skewed. Prevalence data are presented as percentage (95% confidence interval [CI]). BP and HR were analysed as changes from baseline (mean of three fasting measurements), while gastric emptying data and blood glucose concentrations were analysed as absolute levels. The incremental area under the curve (iAUC) (area above baseline) was calculated for HR, and the inverse iAUC (area below baseline) was calculated for SBP and DBP for t = 0–60 minutes and t = 0–120 minutes. EQ-5D-5L scores were dichotomised and expressed as counts and percentages for when a score other than Level 1 (no problems) was reported by participants for each of the five dimensions. The EQ-5D-5L VAS data are presented as median (IQR).

Differences in baseline SBP, maximum fall in SBP, maximum rise in HR, autonomic dysfunction score, peak blood glucose concentration, gastric emptying T_{50} and iAUCs for BP and HR between 3 and 12 months were analysed with paired *t* tests. Prevalence values for postprandial hypotension, orthostatic hypotension and autonomic dysfunction were compared between 3 and 12 months after ICU discharge with the McNemar exact test. The relationships between postprandial hypotension at 3 months and quality of life, falls, hospitalisation and mortality in the year after ICU discharge were assessed with logistic regression; these results are presented as relative risks (RRs) and 95% CIs. The difference in EQ-5D-5L VAS scores was assessed with the Mann–Whitney test and presented as the Hodges–Lehmann median difference and 95% CI. All analyses were performed using SPSS 24.0 (IBM Corporation, Armonk, NY USA). A *P* value < 0.05 was considered statistically significant. All physiological data are presented only for the participants attending the study visit at 12 months with no imputation for missing data. Data regarding quality of life, falls, and health care resource use are presented for the whole longitudinal study cohort of 35 patients.

Results

Of the original cohort of 35 patients, 13 (37%) participants did not attend the 12-month follow-up (Figure 1). All participants who were alive but could not return in person at 12 months were willing to complete questionnaires by telephone. Characteristics of the 22 participants who were studied at 12 months are provided in Table 1. Characteristics of the whole cohort of 35 participants are provided in the online Appendix 3 (Table S1). The participants' physiological data at 3 months after ICU discharge have previously been published[13] and these results are not repeated in this article other than in comparison with the data obtained at 12 months (Table 2).

Baseline seated BP measurements were unavailable for one participant. As this participant completed all other aspects of the study, their data were included for analysis of gastric emptying and autonomic dysfunction, but not for assessment of postprandial hypotension. This participant did not have postprandial hypotension at 3 months after ICU discharge.

Primary outcome

Postprandial hypotension

Changes in SBP, DBP and HR during the 4 hours after ingestion of the glucose drink are presented (Figure 2 and online Appendix 3, Table S2). Two of the 21 participants studied (10%; 95% CI, 1–30%) had postprandial hypotension at 12 months, neither of whom reported symptoms in the 12 months since ICU discharge. Neither of these participants had a history of diabetes or elevated blood glucose concentrations during the study days that would indicate diabetes. One of these participants also had

Table 1. Characteristics of the participants who completed the study at 12 months after discharge from ICU

Characteristic	Participants followed up 12 months after ICU discharge (*n* = 22)
Age on 12-month study day (years), mean (SD)	74 ± 4.5
Sex (male)	19 (86%)
Body mass index on 12-month study day (kg/m^2), mean (SD)	28.7 ± 9.8
ICU diagnostic group	
Cardiac	6 (27%)
Infective	4 (18%)
Neurological	4 (18%)
Trauma	3 (14%)
Surgical	2 (9%)
Vascular	2 (9%)
Endocrine (other than diabetes)	1 (5%)
APACHE II score during ICU admission, mean (SD)	15.9 ± 5.0
Duration of ICU admission (days), median (IQR)	3.5 (2.3–6.0)
Duration of hospital admission (days), median (IQR)	13.5 (10.0–21.5)
Mechanically ventilated during ICU admission	10 (45%)
Duration of mechanical ventilation (hours), median (IQR)	34 (15–78)
Vasoconstrictor or inotrope during ICU admission	11 (50%)
Renal replacement therapy during ICU admission	0
Tube enteral feeding during ICU admission	6 (27%)
Diagnosed with hypertension at 12 months	11 (50%)
Receiving antihypertensives and diuretics at 3 months	
β-Blocker	10 (45%)
Angiotensin-converting enzyme inhibitor	5 (23%)
Spironolactone	2 (9%)
Frusemide	4 (18%)
Angiotensin II receptor blocker	4 (18%)
Calcium channel blocker	2 (9%)
Receiving antihypertensives and diuretics at 12 months	
β-Blocker	9 (41%)
Angiotensin-converting enzyme inhibitor	4 (18%)
Spironolactone	3 (14%)
Frusemide	2 (9%)
Angiotensin II receptor blocker	7 (32%)
Calcium channel blocker	1 (5%)
Receiving insulin at 3 months	2 (9%)
Receiving insulin at 12 months	2 (9%)
Patients with known type 2 diabetes at 12 months	8 (36%)

APACHE = acute physiology and chronic health evaluation; ICU = intensive care unit; IQR = interquartile range; SD = standard deviation.

postprandial hypotension at 3 months and was taking stable doses of medications for hypertension (angiotensin-converting enzyme inhibitor and β-blocker).

Of the ten participants diagnosed with postprandial hypotension at 3 months after ICU discharge, four were lost to follow-up — one had died and three were unable to attend due to ongoing illness. Five of the six remaining participants who attended both study days had postprandial hypotension at 3 months but not at 12 months. Only one of these participants had a reduction in prescribed antihypertensives or diuretics between 3 and 12 months (cessation of angiotensin-converting enzyme inhibitor). Furthermore, the sustained SBP fall observed in the 2 hours following ingestion of the glucose drink in the cohort at 3 months was not evident at 12 months (inverse iAUC 0–60 min, 461 [420] *v* 259 [297] mmHg.min, respectively [*P* = 0.049]; inverse iAUC 0–120 min, 1064 [898] *v* 508 [620] mmHg.min, respectively [*P* = 0.01]) (Figure 2, panel A). The maximum fall in SBP following ingestion of the drink was also greater at 3 months than at 12 months following ICU discharge (–28 [16] *v* –20 [12] mmHg; *P* = 0.02).

Secondary outcomes

Autonomic nerve function and orthostatic hypotension

Two participants (9%; 95% CI, 1–29%) had cardiovascular autonomic dysfunction at 12 months, and both also had orthostatic, but not postprandial, hypotension.

Table 2. Comparison of postprandial hypotension, autonomic function and gastric emptying in the 22 participants who were studied at 3 and 12 months after discharge from ICU

Variable	3 months after ICU discharge (*n* = 22)	12 months after ICU discharge (*n* = 22)	*P*
Baseline seated systolic blood pressure (mmHg), mean (SD)*	126 ± 25	122 ± 17	0.25
Maximum fall in systolic blood pressure (mmHg), mean (SD)*	−28 ± 16	−20 ± 12	0.02
Maximum rise in heart rate (beats/min), mean (SD)*	+14 ± 11	+14 ± 8	0.85
Postprandial hypotension, *n* (% [95% CI])*	6 (28% [11–52%])	2 (10% [1–30%])†	0.22
Orthostatic hypotension, *n* (% [95% CI])	1 (5% [0–23%])	2 (9% [1–29%])‡	> 0.99
Cardiovascular autonomic dysfunction score,§ mean (SD)	1.36 ± 0.6	1.23 ± 0.6	0.45
Cardiovascular autonomic dysfunction, *n* (% [95% CI])	1 (5% [0–23%])	2 (9% [1–29%])‡	> 0.99
Peak blood glucose concentration (mmol/L), mean (SD)	14.0 ± 4.1	13.7 ± 3.9	0.65
Gastric emptying T_{50} (min), mean (SD)	103.4 ± 28.3*	101.6 ± 33.3	0.77

ICU = intensive care unit; SD = standard deviation; T_{50} = time taken for 50% of gastric contents to empty. * Only 21 patients included in analysis. † Includes one patient who was also diagnosed with postprandial hypotension at 3 months after ICU discharge and one patient who was diagnosed with postprandial hypotension at 12 months but not at 3 months after discharge. ‡ Both new cases (diagnosed at 12 months but not at 3 months). § Maximum cardiovascular autonomic dysfunction score is 6.

Neither of these participants had cardiovascular autonomic dysfunction at 3 months. The mean maximal orthostatic falls in SBP and DBP for the whole cohort were –8 (21) mmHg and –6 (9) mmHg, respectively. There were no significant differences in the prevalence of orthostatic hypotension, prevalence of cardiovascular autonomic dysfunction or cardiovascular autonomic dysfunction scores between 3 and 12 months (Table 2).

Gastric emptying

Gastric emptying of the glucose drink approximated a linear pattern after a brief lag phase of 1.3 (1.5) minutes (Figure 3). The mean gastric emptying T_{50} was 101.6 (33.3) minutes at 12 months, which was not different to that at 3 months (T_{50}, 103.4 [28.3] min) (*P* = 0.77).

Blood glucose

Mean blood glucose concentration increased from 6.8 (1.8) mmol/L and peaked at 13.7 (3.9) mmol/L (Figure 4) after ingestion of the glucose drink. In nine participants (41% [95% CI, 21–64%]), the blood glucose concentration was greater than 11.0 mmol/L at t = 120 minutes, consistent with a diagnosis of diabetes.[23] Three of these participants (14% [95% CI, 3–35%]) were not previously known to have diabetes. Peak blood glucose concentration after ingestion of the drink was similar at 3 and 12 months (14.0 [4.1] mmol/L *v* 13.7 [3.9] mmol/L; *P* = 0.65).

Functional status and frailty

All 22 participants who returned for the study at 12 months were residing at home. Scores on the Katz Index of Independence in Activities of Daily Living, Lawton Instrumental Activities of Daily Living Scale and Clinical Frailty Scale were 5 (1.3), 8 (0.5) and 3 (1.1) respectively. One participant was classified as moderately frail but still independent, six participants as vulnerable but independent, and all other participants as independent and not frail.

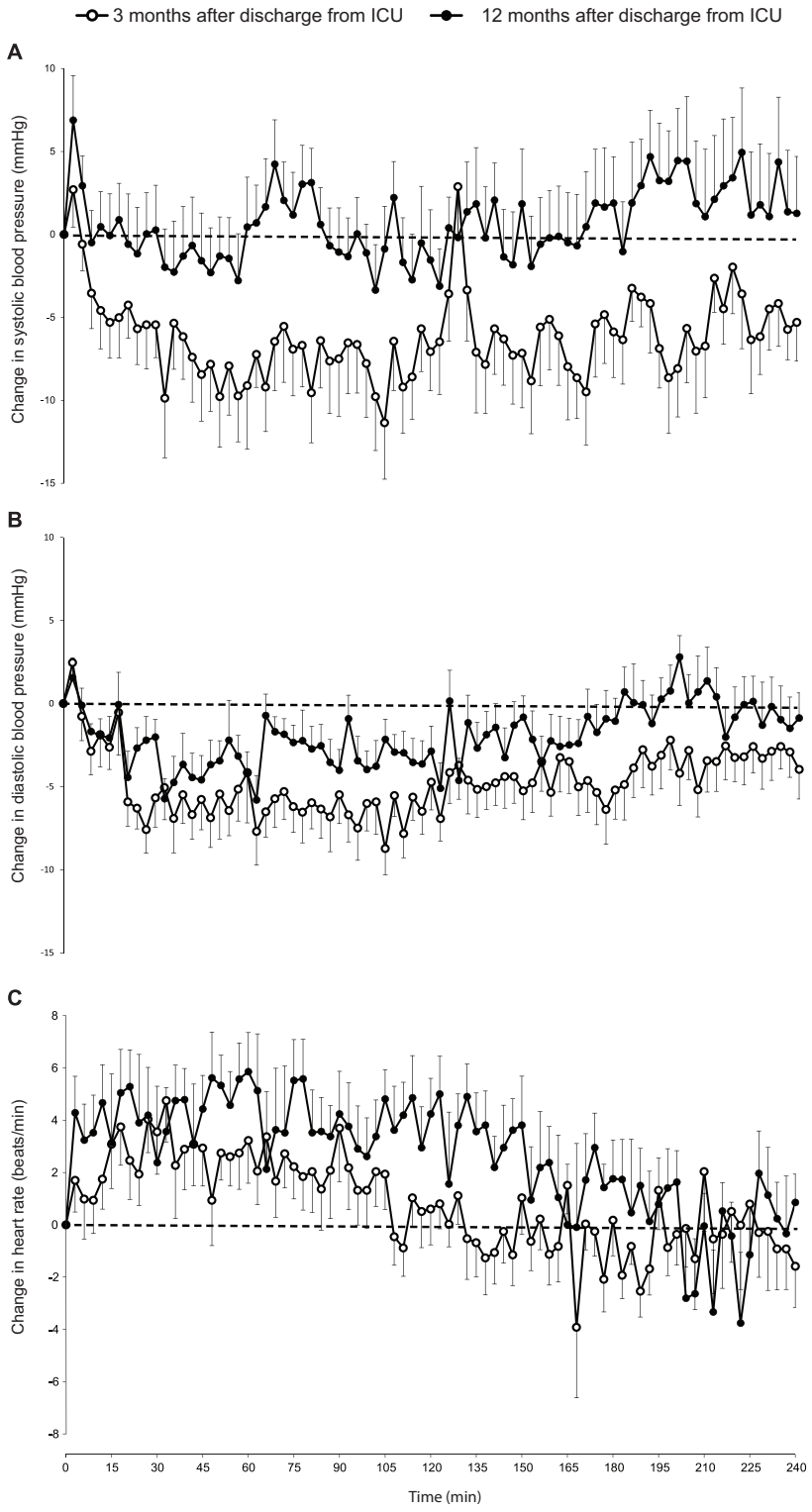
Postprandial hypotension as a predictor of falls, quality of life, hospitalisation and mortality in the year after ICU discharge

Twelve (36%) participants reported at least one fall in the 12 months since ICU discharge. The reported number of falls ranged from one to four over this period and one participant had been admitted to hospital due to a fall. Postprandial hypotension at 3 months after ICU discharge was associated with a more than threefold increase in risk of falls in the year after ICU discharge (7/9 [78%] *v* 5/24 [21%]; RR, 3.7 [95% CI, 1.6–8.8]; *P* = 0.003).

Quality-of-life scores at 12 months are shown in the online Appendix 3 (Table S3). Postprandial hypotension at 3 months did not predict an abnormal score in any of the five dimensions of the EQ-5D-5L instrument at 12 months. Similarly, there was no difference in EQ-5D-5L VAS scores between participants without and those with postprandial hypotension at 3 months (Hodges–Lehmann median difference, –10 [95% CI, –20 to 5]; *P* = 0.185).

Seventeen (49%) participants had been readmitted at least once to an acute care hospital in the year after ICU discharge. Twenty participants (57%) had presented to an emergency department. Eighteen participants (51%) had accessed inpatient or outpatient rehabilitation services in the year after ICU discharge. One participant who had postprandial hypotension at 3 months (10%) and two

Figure 2. Changes in systolic blood pressure (A), diastolic blood pressure (B) and heart rate (C) over 240 minutes after ingesting the glucose-containing drink, at 3 (open circles) and 12 (closed circles) months after discharge from ICU*



ICU = intensive care unit. * Data are mean ± standard error of mean.

who did not have postprandial hypotension at 3 months (8%) had died in the year after ICU discharge. Postprandial hypotension at 3 months did not predict readmission to an acute care hospital (6/10 [60%] *v* 11/25 [44%]; RR, 1.36 [95% CI, 0.7–2.7]; $P = 0.37$) or mortality (1/10 [10%] *v* 2/25 [8%]; RR, 1.25 [95% CI, 0.13–12.3]; $P = 0.85$) in the 12 months after ICU discharge.

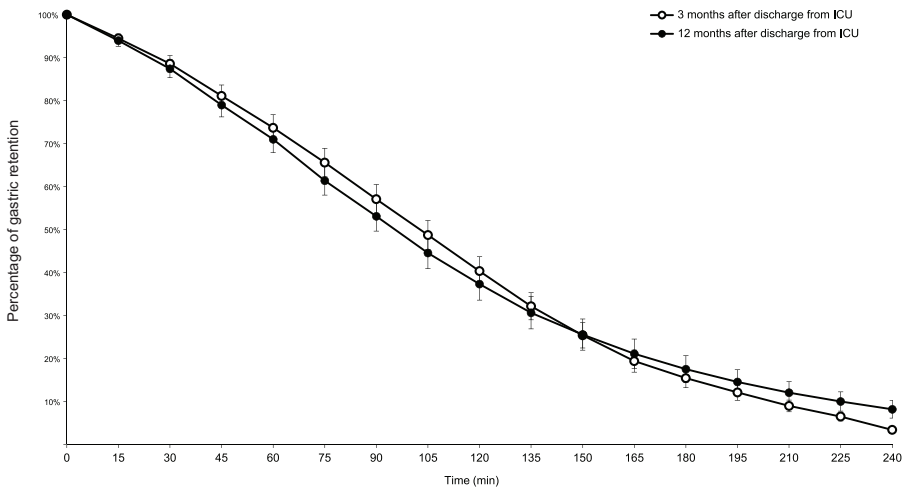
Discussion

Key findings

The findings of this study indicate that postprandial hypotension, which affected almost a third of this older cohort at 3 months after ICU discharge and was shown to be a predictor of falls, resolves in the year following critical illness. Furthermore, gastric emptying was normal at 3 months after ICU discharge and remained unchanged at 12 months. Cardiovascular autonomic neuropathy was also unexpectedly infrequent in this cohort. To our knowledge, this is the first time that autonomic function and gastric emptying have been measured at 1 year after critical illness.

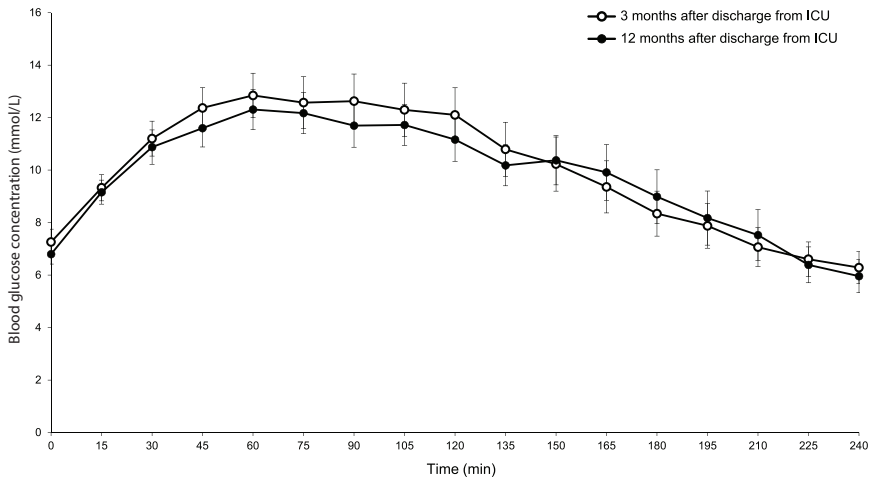
Despite enrolling a cohort of older ICU survivors who were "relatively well" (ie, alive 3 months after ICU discharge, willing to return to be studied at 12 months, < 50% ventilated during their original ICU admission, and short duration of ICU admission), approximately 20% could not return for the study at 12 months because of illness or death. Also, among those who did return, readmission to hospital had occurred frequently. Nonetheless, all 22 participants who returned for the 12-month study were living independently.

Figure 3. Gastric emptying over 240 minutes after ingesting the glucose-containing drink, at 3 and 12 months after discharge from ICU, displayed as percentage gastric retention over time*



ICU = intensive care unit. * Data are mean ± standard error of mean.

Figure 4. Blood glucose concentration over 240 minutes after ingesting the glucose-containing drink, at 3 and 12 months after discharge from ICU*



ICU = intensive care unit. * Data are mean ± standard error of mean.

Clinical implications

The clinical implications of this study include that a third of the older survivors who were studied reported at least one fall in the year following ICU discharge and that postprandial hypotension was a predictor of falls. There are few data about falls in patients who have experienced critical illness and existing studies have mainly focused on falls in the ICU[24,25] or during the acute hospitalisation shortly after ICU discharge.[26] The current study is one of the first to assess falls in the year following ICU discharge in a cohort of older patients. Muscle weakness, frailty, impaired mobility, cognitive impairment and postural hypotension are known risk factors for falls in elderly or recently hospitalised patients[27,28] and all can occur frequently following critical illness.[24] Postprandial hypotension may also be an unrecognised contributor to falls in older ICU survivors and our study suggests that it is more prevalent than orthostatic hypotension. It is unclear whether postprandial hypotension may be modifiable in this cohort — recent data suggest that inexpensive pharmacological therapies which slow gastric emptying or non-pharmacological approaches such as consuming smaller frequent meals, or protein preloading, are effective strategies for preventing or attenuating postprandial hypotension.[29,30] However, more longitudinal physiological studies of autonomic function following critical illness, particularly in the elderly, are needed.

Relationship to previous studies

In healthy individuals, ingestion of nutrient is associated with an increase in mesenteric blood flow and concurrent compensatory responses by the autonomic nervous system and cardiovascular system (arterial baroreceptor and gastrovascular reflexes leading to increased cardiac output and peripheral vasoconstriction), such that postprandial BP is maintained despite meal-induced splanchnic blood pooling.[5] Postprandial hypotension reflects an impairment of these compensatory reflex mechanisms, and patients who have autonomic impairment or are at an advanced age are at increased risk.[31,32] Furthermore, larger meal size[33] and faster rate of nutrient delivery into the small intestine (faster gastric emptying)[34] both elicit a greater haemodynamic response.

As many as 50% of critically ill patients have slow gastric emptying in the ICU,[35] but whether this persists after hospital discharge is unknown. The few previous studies of gastric emptying following critical illness have been limited in duration to the index hospital admission[36] or the first 3 months after ICU discharge,[37] and most of them used less sophisticated methods than ours to quantify gastric emptying, such as isotope breath tests.[37,38] Gastric emptying data in this cohort at both 3 and 12 months after critical illness were comparable to previous data obtained in 21 healthy participants of a similar age range who consumed an identical glucose drink.[39] However, a limitation of our study is that we did not measure gastric emptying during the ICU admission and, therefore, cannot ascertain whether gastric emptying was delayed in this cohort during their ICU stay.

Despite normal gastric emptying and low prevalence of cardiovascular autonomic dysfunction, postprandial hypotension was prevalent in this older cohort at 3 months after ICU discharge. Inferences about the prevalence of postprandial hypotension 12 months after ICU discharge are limited owing to the small size of the cohort, but the magnitude of the fall in systolic BP following ingestion of the glucose drink in the whole cohort was attenuated at 12 months compared with that at 3 months. This is in contradistinction to the increase in prevalence of postprandial hypotension observed in normal ageing.[40] Moreover, we did not detect changes in gastric emptying or cardiovascular autonomic scores over the same period. These findings suggest that alternative mechanisms may underlie an improvement in circulatory homeostasis following nutrient ingestion as older patients recover from critical illness. Potential mechanisms include changes in mesenteric blood flow,[14] plasma catecholamines[34] or gastrointestinal hormones, such as glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1,[41] which we did not measure. However, given the small sample size, any insights regarding mechanisms underlying postprandial hypotension in this cohort are limited.

Strengths and limitations

This study had several strengths, including the longitudinal design with a minimum follow-up period of 12 months after ICU discharge, the use of sophisticated methods (including scintigraphy) and a stringent definition of postprandial hypotension (a sustained fall in SBP of ≥ 20 mmHg for ≥ 30 min). The use of this conservative definition of postprandial hypotension minimised the possibility of false-positive diagnoses. However, there were several study limitations, including small sample size, single-centre design, predominantly male participants and the heterogeneous cohort of older ICU survivors, who had other potential causes of postprandial hypotension and cardiovascular autonomic dysfunction. These causes include age, complications of prolonged hospital admission, and comorbidities such as diabetes. However, none of the participants who had diabetes had postprandial hypotension at 12 months in this study. We do not have information regarding autonomic function or postprandial hypotension before or during the ICU admission for this cohort, so it is difficult to make conclusions about the role of critical illness as a causal factor per se. It is also important to note that about a third of the cohort was lost to follow-up at 12 months after ICU discharge, which is a potential confounder in many longitudinal studies of ICU survivors,[42] and we cannot exclude the possibility that those who participated at 12 months were more resilient, with survivorship bias affecting point estimates of all outcomes.[43] In addition, this cohort experienced only moderate illness severity (median APACHE II score of 16) and all patients were living independently at follow-up. It is plausible that postprandial hypotension, orthostatic hypotension and cardiovascular autonomic dysfunction are more prevalent in older ICU survivors who had a more severe critical illness.

Conclusion

This longitudinal, single-centre study suggests that in older survivors of critical illness, postprandial hypotension is prevalent 3 months after ICU discharge and increases the risk of falls in the year following ICU discharge. The prevalence of postprandial hypotension decreases with time in the year after ICU discharge.

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Competing interests

None declared.

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References

1 Schmidt H, Muller-Werdan U, Hoffmann T, et al. Autonomic dysfunction predicts mortality in patients with multiple organ dysfunction syndrome of different age groups. *Crit Care Med* 2005; 33: 1994-2002.
2 Schmidt H, Hoyer D, Hennen R, et al. Autonomic dysfunction predicts both 1- and 2-month mortality in middle-aged patients with multiple organ dysfunction syndrome. *Crit Care Med* 2008; 36: 967-70.
3 Kar P, Jones KL, Horowitz M, et al. Measurement of gastric emptying in the critically ill. *Clin Nutr* 2015; 34: 557-64.
4 Gungabissoon U, Hacquoil K, Bains C, et al. Prevalence, risk factors, clinical consequences, and treatment of enteral feed intolerance during critical illness. *JPEN J Parenter Enteral Nutr* 2015; 39: 441-8.
5 Jansen RW, Lipsitz LA. Postprandial hypotension: epidemiology, pathophysiology, and clinical management. *Ann Intern Med* 1995; 122: 286-95.
6 Kohara K, Jiang Y, Igase M, et al. Postprandial hypotension is associated with asymptomatic cerebrovascular damage in essential hypertensive patients. *Hypertension* 1999; 33: 565-8.
7 Aronow WS, Ahn C. Association of postprandial hypotension with incidence of falls, syncope, coronary events, stroke, and total mortality at 29-month follow-up in 499 older nursing home residents. *J Am Geriatr Soc* 1997; 45: 1051-3.
8 Fisher AA, Davis MW, Srikusalanukul W, Budge MM. Postprandial hypotension predicts all-cause mortality in older, low-level care residents. *J Am Geriatr Soc* 2005; 53: 1313-1320.
9 Collins KJ, Exton-Smith AN, James MH, Oliver DJ. Functional changes in autonomic nervous responses with ageing. *Age Ageing* 1980; 9: 17-24.
10 Bagshaw SM, Webb SA, Delaney A, et al. Very old patients admitted to intensive care in Australia and New Zealand: a multi-centre cohort analysis. *Crit Care* 2009; 13: R45.
11 Heyland DK, Garland A, Bagshaw SM, et al. Recovery after critical illness in patients aged 80 years or older: a multi-center prospective observational cohort study. *Intensive Care Med* 2015; 41: 1911-20.
12 Ferrante LE, Pisani MA, Murphy TE, et al. Functional trajectories among older persons before and after critical illness. *JAMA Intern Med* 2015; 175: 523-9.
13 Nguyen TAN, Ali Abdelhamid Y, Weinel LM, et al. Postprandial hypotension in older survivors of critical illness. *J Crit Care* 2018; 45: 20-6.
14 Sim JA, Horowitz M, Summers MJ, et al. Mesenteric blood flow, glucose absorption and blood pressure responses to small intestinal glucose in critically ill patients older than 65 years. *Intensive Care Med* 2013; 39: 258-66.
15 Trahair LG, Horowitz M, Stevens JE, et al. Effects of exogenous glucagon-like peptide-1 on blood pressure, heart rate, gastric emptying, mesenteric blood flow and glycaemic responses to oral glucose in older individuals with normal glucose tolerance or type 2 diabetes. *Diabetologia* 2015; 58: 1769-78.
16 Piha SJ. Cardiovascular autonomic reflex tests: normal responses and age-related reference values. *Clin Physiol* 1991; 11: 277-90.
17 Collins PJ, Horowitz M, Cook DJ, et al. Gastric emptying in normal subjects — a reproducible technique using a single scintillation camera and computer system. *Gut* 1983; 24: 1117-25.
18 Bagshaw SM, Stelfox HT, McDermid RC, et al. Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study. *CMAJ* 2014; 186: E95-102.
19 Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist* 1970; 10: 20-30.
20 Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969; 9: 179-86.
21 Johnson JA, Luo N, Shaw JW, et al. Valuations of EQ-5D health states: are the United States and United Kingdom different? *Med Care* 2005; 43: 221-8.
22 Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011; 364: 1293-1304.
23 American Diabetes Association. Classification and diagnosis of diabetes. *Diabetes Care* 2016; 39 Suppl 1: S13-22.
24 Trumble D, Meier MA, Doody M, et al. Incidence, correlates and outcomes associated with falls in the intensive care unit: a retrospective cohort study. *Crit Care Resusc* 2017; 19: 290-5.
25 Richardson A, Carter R. Falls in critical care: a local review to identify incidence and risk. *Nurs Crit Care* 2017; 22: 270-5.
26 Patman SM, Dennis D, Hill K. The incidence of falls in intensive care survivors. *Aust Crit Care* 2011; 24: 167-74.
27 Tinetti ME. Preventing falls in elderly persons. *N Engl J Med* 2003; 348: 42-9.
28 Mahoney J, Sager M, Dunham NC, Johnson J. Risk of falls after

hospital discharge. *J Am Geriatr Soc* 1994; 42: 269-74.

29 Ong AC, Myint PK, Potter JF. Pharmacological treatment of postprandial reductions in blood pressure: a systematic review. *J Am Geriatr Soc* 2014; 62: 649-61.

30 Deguchi K, Ikeda K, Sasaki I, et al. Effects of daily water drinking on orthostatic and postprandial hypotension in patients with multiple system atrophy. *J Neurol* 2007; 254: 735-40.

31 Vanis L, Gentilcore D, Lange K, et al. Effects of variations in intragastric volume on blood pressure and splanchnic blood flow during intraduodenal glucose infusion in healthy older subjects. *Am J Physiol Regul Integr Comp Physiol* 2012; 302: R391-9.

32 Kooner JS, Raimbach S, Watson L, et al. Relationship between splanchnic vasodilation and postprandial hypotension in patients with primary autonomic failure. *J Hypertens Suppl* 1989; 7: S40-1.

33 Puvi-Rajasingham S, Mathias CJ. Effect of meal size on post-prandial blood pressure and on postural hypotension in primary autonomic failure. *Clin Auton Res* 1996; 6: 111-4.

34 Trahair LG, Horowitz M, Jones KL. Postprandial hypotension is associated with more rapid gastric emptying in healthy older individuals. *J Am Med Dir Assoc* 2015; 16: 521-3.

35 Heyland DK, Tougas G, King D, Cook DJ. Impaired gastric emptying in mechanically ventilated, critically ill patients. *Intensive Care Med* 1996; 22: 1339-44.

36 Ott L, Young B, Phillips R, et al. Altered gastric emptying in the head-injured patient: relationship to feeding intolerance. *J Neurosurg* 1991; 74: 738-742.

37 Chapple LS, Weinel LM, Abdelhamid YA, et al. Observed appetite and nutrient intake three months after ICU discharge. *Clin Nutr* 2019; 38:1215-20.

38 Kar P, Plummer MP, Ali Abdelhamid Y, et al. Incident diabetes in survivors of critical illness and mechanisms underlying persistent glucose intolerance: a prospective cohort study. *Crit Care Med* 2019; 47: e103-11.

39 Marathe CS, Horowitz M, Trahair LG, et al. Relationships of early and late glycemic responses with gastric emptying during an oral glucose tolerance test. *J Clin Endocrinol Metab* 2015; 100: 3565-71.

40 Pham H, Phillips L, Trahair L, et al. Longitudinal changes in the blood pressure responses to, and gastric emptying of, an oral glucose load in healthy older subjects. *J Gerontol A Biol Sci Med Sci* 2019; doi: 10.1093/gerona/glz014 [Epub ahead of print].

41 Kar P, Cousins CE, Annink CE, et al. Effects of glucose-dependent insulinotropic polypeptide on gastric emptying, glycaemia and insulinaemia during critical illness: a prospective, double blind, randomised, crossover study. *Crit Care* 2015; 19: 20.

42 Tansey CM, Matte AL, Needham D, Herridge MS. Review of retention strategies in longitudinal studies and application to follow-up of ICU survivors. *Intensive Care Med* 2007; 33: 2051-7.

43 Palakshappa JA, Christie JD. Survivorship research: studying the past to define the future. *Crit Care Med* 2016; 44: 1422-3.