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MINIREVIEWS

Nutrient stimulation of mesenteric blood flow - implications for older critically ill patients

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Abstract

Nutrient ingestion induces a substantial increase in mesenteric blood flow. In older persons (aged ⩾ 65 years), particularly those with chronic medical conditions, the cardiovascular compensatory response may be inadequate to maintain systemic blood pressure during mesenteric blood pooling, leading to postprandial hypotension. In older ambulatory persons, postprandial hypotension is an important pathophysiological condition associated with an increased propensity for syncope, falls, coronary vascular events, stroke and death. In older critically ill patients, the administration of enteral nutrition acutely increases mesenteric blood flow, but whether this pathophysiological response is protective, or precipitates mesenteric ischaemia, is unknown. There are an increasing number of older patients surviving admission to intensive care units, who are likely to be at increased risk of postprandial hypotension, both during, and after, their stay in hospital. In this review, we describe the prevalence, impact and mechanisms of postprandial hypotension in older people and provide an overview of the impact of postprandial hypotension on feeding prescriptions in older critically ill patients. Finally, we provide evidence that postprandial hypotension is likely to be an unrecognised problem in older survivors of critical illness and discuss potential options for management.

Key words: Postprandial hypotension; Enteral nutrition; Critical care; Aged; Mesenteric ischaemia

Core tip: In older ambulatory persons, postprandial hypotension is an important pathophysiological condition associated with an increased propensity to coronary vascular events, stroke and death. In older critically ill patients, the administration of enteral nutrition acutely increases mesenteric blood flow, but whether this pathophysiological response is protective, or precipitates mesenteric ischaemia, is unknown. We herein describe the prevalence, impact and mechanisms and management of postprandial hypotension in older people. We finally provide an overview of the impact of postprandial hypotension on feeding prescriptions in and evidence that postprandial hypotension is likely to be an unrecognised problem in older survivors of critical illness.

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INTRODUCTION

Ingestion of nutrients initiates a complex process involving precise coordination between the gastrointestinal tract, autonomic and cardiovascular systems to increase intestinal blood flow, whilst simultaneously maintaining circulatory homeostasis[1,2]. Age and disease-related changes may compromise cardiovascular compensatory mechanisms, which, particularly in older persons, may result in a clinically relevant postprandial fall in blood pressure, known as postprandial hypotension (PPH). PPH is inconsistently defined but is generally regarded as a reduction in systolic blood pressure of $\geqslant$ 20 mmHg, or a decrease to $\leqslant$ 90 mmHg, that occurs within two hours of a meal and persists for at least 30 min[3]. This definition is empiric and derived from the definition of orthostatic hypotension[4]. It is important to recognise that although PPH frequently coexists with orthostatic hypotension, PPH is a distinct entity. However PPH may well occur more frequently, and have more substantive implications, than orthostatic hypotension[5,6].

EPIDEMIOLOGY

A recent meta-analysis reported that PPH occurs in about 20% of "healthy" older persons, about 30%-40% of nursing home residents, 20%-91% of hospitalised patients aged $\geqslant$ 65 years, about 40% of people with diabetes, and 40%-100% of patients with Parkinson's disease[7]. The wide range of reported prevalence in each group reflect the small cohort sizes and the confounding effect of lack of standardisation of methodology between studies; including the definition of PPH, composition of test meal, timing of meal ingestion, technique and duration of blood pressure measurement, and use of concomitant medications. However, it is clear that in each of these groups the prevalence of PPH is high and that the very elderly and patients with diseases associated with autonomic dysfunction are at particular risk. Surprisingly, the prevalence of PPH in elderly survivors of critical illness has not been evaluated.

CLINICAL IMPORTANCE OF POSTPRANDIAL HYPOTENSION

PPH is now recognised as an important pathophysiological condition, not only because of its high prevalence, but also due to the associated substantial morbidity and mortality[3]. In older people in the community, PPH is a strong predictor of syncope, falls, coronary events and stroke - irrespective of whether the individual has symptoms[8]. In a prospective study of 499 nursing home residents, Aronow *et al*[8] reported that the postprandial fall in systolic blood pressure was an independent risk factor for falls, coronary events, stroke and all-cause mortality. Supportive data are also provided by two case-control studies that report that the magnitude and prevalence of PPH are substantially greater in patients with a history of falls or syncope when compared to controls[9,10]. Furthermore, in a five-year study of nursing home residents, PPH was found to be an independent determinant of mortality (RR = 1.79; 95%CI: 1.19-2.68); with a "dose-response", such that all-cause mortality increased 13% for every 10 mmHg decrease in postprandial systolic blood pressure (RR = 1.13; 95%CI: 1.03-1.24)[11].

As indicated, preliminary data suggest that it is important to identify PPH even in those patients who are unaware of the condition. While PPH is associated with adverse outcomes, more than half (about 60%) of patients with PPH may be asymptomatic and, therefore, do not seek treatment[5,6]. For example, Kohara *et al*[12] studied 70 patients hospitalised with essential hypertension and reported that the prevalence of lacunar infarcts was increased two-fold in patients with asymptomatic PPH. The strong association between "asymptomatic" PPH and stroke has also been evident in larger cohorts of older people residing in nursing home facilities and ambulatory older people living in the community[8,13]. While this association does not establish causality, it provides a compelling rationale to diagnose PPH, which is a simple and inexpensive process[7], and to determine whether interventions that attenuate PPH mitigate the risk of adverse outcomes, such as cerebrovascular events[14]. The latter approach is to some extent compromised by the current lack of established effective management strategies[15].

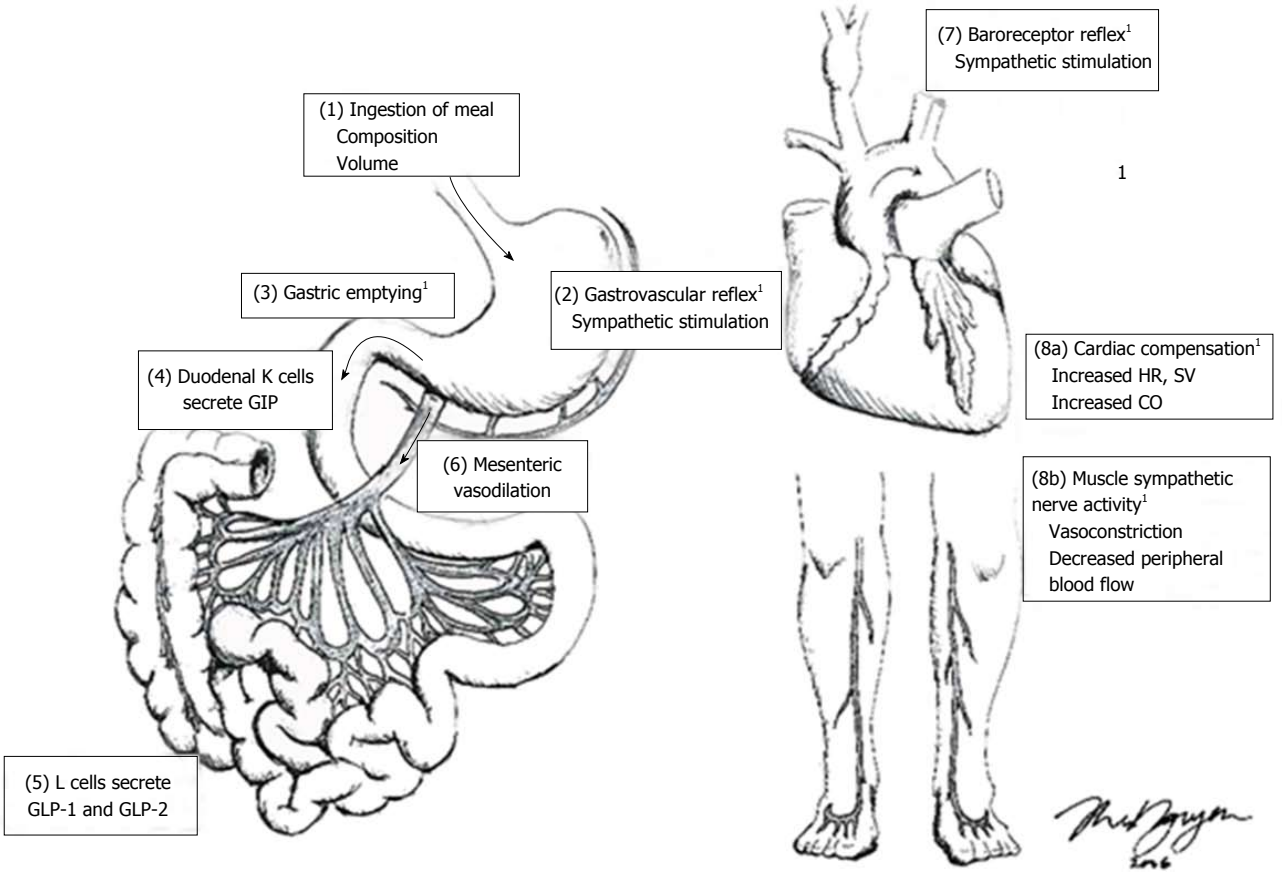

Figure 1 Factors involved in the regulation of postprandial blood pressure. (1) ingestion of a meal, with a greater carbohydrate load results in a greater postprandial hypotensive response; (2) Meal-induced gastric distension from the meal triggers stretch receptors in the stomach wall, increasing sympathetic nerve outflow; (3) gastric content is emptied into the small intestine, and, in response to the nutrient in the small intestine; (4, 5) gastrointestinal peptides are secreted from the small intestine (*e.g.*, GLP-1 and GLP-2, glucagon-like peptide-1 and 2; GIP, glucose insulinotropic polypeptide); (6) gastrointestinal peptides stimulate mesenteric vessel dilation; (7) this results in reduced circulating blood volume and the reduction in blood pressure is detected by baroreceptors; (8a) the "gastrovascular" and baroreceptor reflexes stimulate sympathetic activity to increase heart rate (HR), stroke volume (SV) and thus cardiac output (CO) to maintain postprandial blood pressure; (8b) skeletal vasculature constricts to decrease peripheral blood flow. [1]These factors are affected by age and have been identified as potential pathophysiological mechanisms of postprandial hypotension. Figure drawn by Ms. T. Nguyen. GIP: Glucose-dependent insulinotropic peptide; GLP: Glucagon-like peptide.

EFFECT OF NUTRIENT STIMULATION ON MESENTERIC BLOOD SUPPLY IN HEALTH

The presence of nutrients, particularly glucose and fats[16], in the small intestine stimulates secretion of several vasoactive gastrointestinal hormones that augment intestinal blood flow[17]. In response to direct contact with intraluminal nutrients, intestinal K-cells promptly secrete glucose-dependent insulinotropic peptide, and L-cells secrete glucagon-like peptide-1 and -2 (GLP-1 and GLP-2)[18] (Figure 1). There is a two-fold increase in blood flow through the superior mesenteric artery[3,19], such that up to 20% of total blood volume is diverted to the gastrointestinal tract, which facilitates digestion and absorption of nutrients[17]. The magnitude of this increase in mesenteric blood flow is dependent on meal size and the rate of nutrient delivery from the stomach into the small intestine[20,21]. In the research setting, the potential confounding effect of inter- and intra-individual differences in the rate of gastric emptying on PPH can be regulated by directly infusing nutrient into the small intestine[21,22]. Utilising this technique, it is apparent that mesenteric blood flow increases when nutrient is delivered at a greater rate and, particularly, when carbohydrate or fat are ingested when compared to protein[16,23].

PHYSIOLOGICAL HAEMODYNAMIC RESPONSES TO MEAL-INDUCED MESENTERIC BLOOD FLOW

In health, blood pressure is maintained even in the presence of postprandial mesenteric vasodilation *via* increases in cardiac contractility and peripheral vasoconstriction[3]. Meal-induced splanchnic blood pooling results in a temporary and virtual "hypovolaemia" that stimulates arterial baroreceptors[3], while gastric distension activates the "gastrovascular reflex"[24] (Figure 1). Together, these autonomic reflexes increase sympathetic nerve outflow to the heart and other vascular beds[5,16] to increase both heart rate and stroke volume, thereby, augmenting

cardiac output[3]. In parallel, the increase in muscle sympathetic nerve activity leads to a compensatory vasoconstriction of skeletal vasculature[25].

MECHANISMS UNDERLYING POSTPRANDIAL HYPOTENSION IN AMBULANT OLDER PERSONS

The pathophysiology of PPH reflects multiple factors that impair reflex cardiovascular compensation[3]. Given that mesenteric blood flow appears to be essentially unaffected by age[22], it has been postulated that autonomic dysfunction is the main, albeit not sole contributor, to PPH[7,26,27]. Masuda *et al*[28] estimated that healthy older people require a two to three-fold increase in sympathetic nerve activity to maintain postprandial blood pressure. However, with age, the sensitivity of the gastrovascular and baroreceptor reflexes diminishes[25,29], such that gastric distension may have minimal, or no effect, on plasma noradrenaline concentrations[3]. Consequently, the hypertensive and muscle sympathetic nerve activity responses following ingestion is blunted in apparently "healthy" older people[22,25]. In addition, PPH is common in individuals with autonomic impairment associated with primary autonomic failure, multiple system atrophy, Parkinson's disease or diabetes mellitus, conditions that are all prevalent in older people[30]. In autonomic failure, the postprandial increase in cardiac output is attenuated, indicative of a diminished compensatory response during mesenteric vasodilation[27].

PHYSIOLOGICAL RESPONSES TO ENTERAL NUTRITION IN THE CRITICALLY ILL

Administration of enteral nutrition (EN) is part of standard care of critically ill patients, although the optimal timing for the commencement of EN in patients with shock, and/or who are receiving substantive doses of catecholamines, remains controversial[31]. EN has several theoretical advantages over parenteral nutrition, including the stimulation of mesenteric blood flow and bowel contractility, as well as the release of trophic hormones[31]. In addition, early (within 24-48 h) initiation of EN supports commensal bacteria and favours maintenance of the structural and functional integrity of the gut mucosal barrier, including the gut-associated lymphoid tissue[32,33]. Consequently, feeding *via* the enteral route may limit bacterial overgrowth and attenuate translocation of gastrointestinal organisms and toxins[33,34]. However, in patients with established shock, postprandial nutrient-stimulated demand for mesenteric blood flow may potentially complicate systemic haemodynamics, while the increase in mesenteric blood flow may be deleterious *via* reperfusion injury[35]. The clinical dilemma as to whether EN protects against, or exacerbates, mesenteric ischaemia during critical illness, has been reviewed by several groups[35-37].

SLOWER GASTRIC EMPTYING IN CRITICALLY ILL PATIENTS MAY MITIGATE POSTPRANDIAL HYPOTENSION

Despite EN being a frequently administered intervention, there is a paucity of information regarding its effects on gastrointestinal peptides and mesenteric blood supply in the critically ill[38,39]. However, because of the frequent delay in gastric emptying associated with critical illness[40], the rate of exposure of nutrient to the small intestinal mucosa is diminished in many patients[41] that should, intuitively, attenuate vasoactive gastrointestinal peptide secretion. Our group has, however, reported increases in fasting and postprandial GLP-1 concentrations in the critically ill, particularly in those with feed intolerance[42]. This may represent the effect of undigested carbohydrates and fats remaining in the distal small intestine and colon, resulting in sustained secretion of gastrointestinal peptides. Alternatively, this may be secondary to an increased sensitivity to hormone secretion or decreased hormone clearance during critical illness.

IMPLICATIONS OF CHANGES IN MESENTERIC BLOOD SUPPLY DURING ENTERAL FEEDING

It has been suggested that administration of EN to those patients with haemodynamic compromise or hypoxia could be harmful[35]. According to this concept, fasting mesenteric blood supply is marginal, and the introduction of EN will increase demand beyond oxygen delivery capacity, thereby provoking mesenteric ischaemia[43,44]. While non-occlusive mesenteric ischaemia occurs in < 1% of critically ill patients, it carries substantial mortality (up to 80% in some series)[45].

The pathophysiology of non-occlusive mesenteric ischaemia in the critically ill is incompletely understood, but it is usually preceded by hypotension or hypovolaemia[46]. It has been suggested that during systemic hypotension mesenteric blood supply may be "sacrificed" to preserve systemic blood pressure and, in the presence of artheromatous plaques, which are normally associated with subclinical stenosis, this leads to critical ischaemia[47]. It has also been proposed that disordered autoregulation of mesenteric vasculature causes intense vasospasm of the superior mesenteric artery, even when systemic blood pressure is normal, which may be exacerbated during reperfusion[48]. The tips of the intestinal villi are considered to be especially sensitive to ischaemia, particularly given their reliance on a so-called "counter-current exchanger system" for oxygen delivery[36]. Arterial blood is supplied *via* the central arterial vessel that arborises at the tip of the villus forming a dense subepithelial network of capillaries and

oxygen cross-diffuses from the central supplying vessel to the peripheral limb of the vascular hairpin loop[49]. It has been proposed that when mesenteric blood flow is compromised the velocity of blood flow in the hairpin vascular loops is decreased leading to extravascular oxygen shunting at the base of villi[49], which causes local oxygen deficits at the villi tips, ultimately resulting in ischaemic injury and cell death[36,49].

The tips of intestinal villi are essential for nutrient absorption, and it has been hypothesised that non-specific symptoms of gastrointestinal intolerance represents one of the earliest signs of injury[46]. The presence of unabsorbed nutrient in the bowel lumen results in fluid shifts, bacterial overgrowth and fermentation, potentially causing marked bowel distension[46]. Patients may, therefore, initially present with nausea, diarrhoea, bloating and abdominal distension. According to this theory, as the bowel wall is stretched further, there is a progressive increase in capillary sludging and a reduction in mucosal perfusion[46]. The resultant increased mural and vascular permeability allows translocation of fluid, bacteria and toxins across the bowel wall, which induces third-space fluid shifts and activates a cascade of cytokines and oxidative radicals that exacerbate the ischaemic episode[48]. Furthermore, changes frequently associated with age, such as the presence of congestive heart failure, dysrhythmias or cardiogenic shock, are likely to exacerbate the processes in the development of mucosal ischaemia, thereby identifying older critically ill patients as a high-risk group[46]. However, previous case series of critically ill patients with non-occlusive mesenteric ischaemia include a large proportion of relatively young patients[50,51], which appears inconsistent with the proposed events in this model of pathophysiology.

Moreover, there is conflicting data, which suggest that during a period of systemic hypotension EN is protective and may reduce, or even prevent, non-occlusive mesenteric ischaemia[43]. A number of studies in animal models have demonstrated that small intestinal nutrient stimulates superior mesenteric artery blood flow and mucosal microcirculatory flow[34,43,52-54]. However, it should be recognised that these studies frequently use relatively young animals and an "acute insult" model[55]. Therefore, extrapolation of these data to older critically ill humans, who characteristically have considerable co-morbid illnesses and have been receiving liquid EN for a number of days, should be made highly circumspectly.

There is also a concern that changes in mesenteric blood supply stimulated by EN will lead to redistribution of cardiac output to the mesenteric circulation, thereby, "stealing" blood/oxygen from other organs including the heart and brain[43]. It is well established that PPH is associated with coronary vascular events and stroke in the "healthy" ambulant older persons and hospitalised patients with hypertension potentially due to this "stealing" phenomenon[3]. Whether this phenomenon occurs in the critically ill, and has clinical implications, is unknown.

NUTRIENT STIMULATES MESENTERIC BLOOD FLOW DURING CRITICAL ILLNESS

To improve understanding of mesenteric blood flow during enteral feeding in the critically ill several investigators have "bypassed" the stomach and delivered nutrient directly into the small intestine. Revelley *et al*[38] reported that a standard polymeric nutrient liquid administered *via* a postpyloric tube to nine patients one-day post-cardiopulmonary bypass, who were also receiving catecholamine support, was associated with an approximately 30% increase in postprandial hepatosplanchnic blood flow with minimal impact on systemic haemodynamics. Rokyta *et al*[56] also reported that standard polymeric nutrient liquid infused *via* a postpyloric tube to ten patients with severe sepsis (mean age 61 years and n = 8 receiving catecholamine support) increased hepatosplanchnic blood flow. These investigators found that blood pressure was unaffected by nutrient administration, but that there were modest increases in cardiac output, measured using pulmonary artery thermodilution, when EN was commenced[56]. However, both studies used indocyanine green clearance to measure hepatosplanchnic blood supply, which is dependent on adequate hepatic perfusion and function, and may well be less predictable in the critically ill than in health. Furthermore, both groups utilised a mixed nutrient liquid delivered at a rate (0.75 kcal/min), which is less than normal physiological gastric emptying (1-4 kcal/min)[21] and standard feeding regimens[57,58]. Accordingly, this rate is not known to stimulate changes in mesenteric blood flow in ambulatory older people[22], and is not the rate of gastric emptying in many critically ill patients[59]. Our group evaluated the effect of liquid glucose (2 kcal/min) infused directly into the small intestine in critically ill patients aged $\geqslant$ 65 years[39]. Compared to healthy age-matched persons, we observed that postprandial mesenteric blood flow measured by duplex ultrasound is attenuated in older critically ill patients (n = 11, but only one patient had established shock and required exogenous noradrenaline), which was associated with reduced glucose absorption, while mean arterial pressure was unaffected by nutrient infusion at this rate[39].

In summary, while there are limited data relating to the acute effect of nutrient on mesenteric blood flow, it appears that nutrient does increase macrovascular blood flow. In older critically ill patients with shock, there is no clear evidence that EN precipitates or protects against mesenteric ischaemia, or exacerbates hypotension, in this group. Nonetheless, feeding prescriptions that limit delivery to $\leqslant$ 1.5 kcal/min of a mixed nutrient liquid are likely to be well tolerated.

PREVALENCE AND OUTCOMES OF OLDER PEOPLE IN THE ICU

Given the aging population and improved survival to older age, there is an increasing demand for health care services in older persons, including services provided in the intensive care unit (ICU) for critically ill patients[60,61]. Recent multicentre cohort studies indicate that > 50% of ICU admissions are for patients aged ⩾ 65 years, with 8%-13% of admissions being the very old (aged ⩾ 80 years)[60,62]. Indeed, the prevalence of older critically ill patients admitted to ICUs is projected to rise by 3%-5% annually[60,62]. The increased rate of hospitalisation and admission to ICU in this group is attributable, in part, to the higher prevalence of chronic illness and organ impairment associated with older age[63].

Mortality and health care resource utilisation during, and following, hospital stay in older ICU survivors are substantial[62]. Approximately 16% of ICU patients die in hospital, with older patients being two- to three-fold more likely to die, making up about 70% of ICU non-survivors[60,62]. Six-months after hospital discharge, almost half of ICU survivors have presented to the emergency department and one-third required hospital readmission[62]. Within five years of hospital discharge, one-third of survivors of critical illness die, with about 70% of ICU non-survivors being aged ⩾ 65 years[62]. Those who survive critical illness have a greater reduction in physical function post-ICU requiring more rehabilitation services and utilisation of long-term care facilities[62,64]. Accordingly, it is evident that older survivors of ICU represent a group that may benefit from increased follow-up and novel interventions, particularly when considering the burden associated with health care utilisation following critical illness.

POTENTIAL FOR PPH IN OLDER SURVIVORS OF CRITICAL ILLNESS

All critically ill patients, regardless of age, are at high risk of acute autonomic nerve dysfunction due to the insult critical illness inflicts on organs, which disrupts the inter-organ communication network[65]. Spectral analysis of heart rate variability is frequently used to assess sympathetic-parasympathetic balance and cardiorespiratory interactions non-invasively[65]. While the precise prevalence of autonomic dysfunction in the critically ill is unknown it appears to be is poor prognostic marker for patients within the ICU[65]. Acute autonomic dysfunction, as evidenced as attenuation in heart rate variability, has been reported to be associated with the development of multiple organ dysfunction, cardiac arrhythmias, and death, and it can persist for prolonged periods even after discharge from hospital[66-68]. Schmidt and colleagues prospectively followed 90 critically ill patients with score-defined multiple organ dysfunction (56 patients were on catecholamine support), and reported about 95% of patients had significantly reduced heart rate variability, which was not affected by the administration of sedatives or catecholamines[65]. These investigators also reported that heart rate variability was comparable in young (< 40 years, n = 9), middle aged (40-60 years, n = 31) and older (> 60 years, n = 45), but baroreflex sensitivity declined with age[65]. Given that the baroreceptor reflex and cardiac autonomic function are fundamental to the maintenance of postprandial blood pressure, it is intuitively plausible that older patients who survive critical illness and have autonomic dysfunction represent a group at risk of PPH. However, there is limited data as to the prevalence of PPH in survivors of critical illness and it is also possible that delayed gastric emptying or attenuated superior mesenteric blood flow, which are both observed during critical illness, persist after ICU, and this would mitigate the risk of PPH.

POTENTIAL INTERVENTIONS FOR PATIENTS WITH PPH

Management of PPH can be non-pharmacological, or pharmacological and attenuate PPH by targeting the mechanism(s) involved in the pathophysiology of PPH, as specified in Figure 1[15]. Interventions, such as consuming smaller, more frequent meals, reducing carbohydrate content and protein "pre-loads", to reduce the rate of glucose absorption in the small intestine may be effective, as this has been postulated to reduce the magnitude and duration of increased mesenteric blood flow[23]. The simple task of drinking approximately 350 mL of water immediately prior to nutrient ingestion, to maximise gastric distension, attenuates PPH, probably *via* the gastrovascular reflex[69]. Gastric emptying can be slowed with the use of guar and other "pre-load" stimulants[15]. Inhibition of gastrointestinal peptides may also be achieved *via* the use of alpha-glucosidase inhibitors (*e.g.,* acarbose) or somatostatin analogues (*e.g.,* octreotide)[15,70]. Alternatively, sympathetic nerve activity can be directly stimulated *via* postprandial exercise or caffeine[15]. However, the evidence to support the efficacy of these interventions is limited as studies have, for the main part been acute and limited to small cohorts, often including individuals who do not clearly meet the criteria for diagnosis of PPH. Nevertheless, the use of inexpensive interventions, such as eating smaller meals and drinking water may be sufficient to attenuate PPH.

CONCLUSION

PPH is recognised as an important pathophysiological condition, which is prevalent in older people (aged ⩾ 65 years) living within the community, and is associated with considerable morbidity and mortality. Demographic changes have resulted in an older population within the ICU and this group is likely to be particularly susceptible to PPH due to their co-morbid conditions, as well as the frequent critical illness-associated autonomic dysfunction. While administration of EN will acutely increase me-

senteric blood flow in this group, whether this pathophysiological response is protective, harmful, or has no effect on blood pressure, remains uncertain. Current management strategies for PPH are limited. Further work is required to determine the prevalence of this condition in older survivors of critical illness and evaluate novel interventions in this cohort.

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