Review

Understanding gastrointestinal perfusion in critical care: so near, and yet so far

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Abstract

An association between abnormal gastrointestinal perfusion and critical illness has been suggested for a number of years. Much of the data to support this idea comes from studies using gastric tonometry. Although an attractive technology, the interpretation of tonometry data is complex. Furthermore, current understanding of the physiology of gastrointestinal perfusion in health and disease is incomplete. This review considers critically the striking clinical data and basic physiological investigations that support a key role for gastrointestinal hypoperfusion in initiating and/or perpetuating critical disease.

Keywords: gastric tonometry, sepsis, shock, splanchnic circulation

Introduction

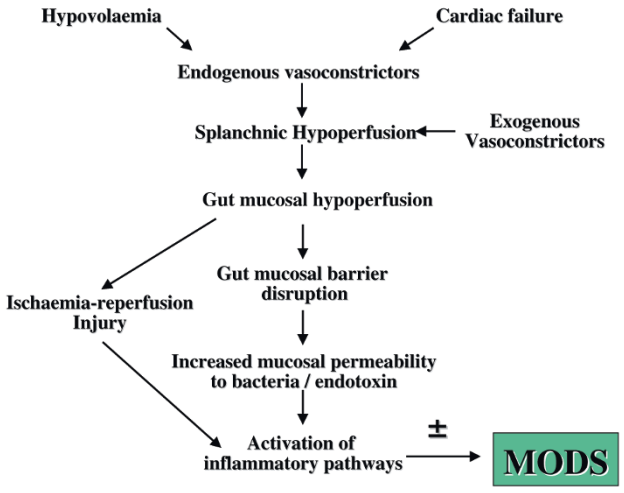
Largely circumstantial evidence continues to implicate the gastrointestinal tract in the pathogenesis of the systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome. The present review explores why the role of gastrointestinal perfusion has become an important focus of critical care and anaesthesiology research. Specifically, we consider conflicting, unresolved clinical data put forward in support of the idea that the gut is the 'motor of critical disease'. We also consider why current, albeit incomplete, understanding of gastrointestinal circulatory physiology supports this concept.

The idea that the gastrointestinal tract provides the 'spark' and/or 'fuel' for critical disease has been pursued since the series of clinical studies conducted in the 1960s by Fine and coworkers [1,2], who proposed that a gut-mediated factor, perhaps endotoxin, contributed to sepsis. However, although this attractive idea has gained further support [3,4], pinpointing the exact role of the gastrointestinal tract has proved complex.

One model proposed to explain the involvement of the gut in this process is a two-step mechanism (Fig. 1). First, gastrointestinal perfusion and therefore tissue oxygenation is compromised. Then, as a result of tissue damage, disruption of the mucosal barrier and access to the systemic circulation of toxic entities occurs. The entities proposed include bacteria, bacterial components (eg endotoxin) and chemicals normally found in the bowel lumen. An alternative concept is that the second step involves ischaemia–reperfusion injury of a large viscus, the gastrointestinal

ACE = angiotensin-converting enzyme; ICU = intensive care unit; NO = nitric oxide; P_{CO_2} = partial carbon dioxide tension; pHi = intramucosal pH; SIRS = systemic inflammatory response syndrome; SMA = superior mesenteric artery.

Figure 1



The 'gut hypothesis' for the pathogenesis of critical illness. MODS, multiple organ dysfunction syndrome.

tract, with consequent massive release of cytokines and other proinflammatory mediators. The present review does not focus on the controversies that surround translocation or increased permeability of the gastrointestinal mucosa, or on the evidence for a mechanism that involves ischaemia–reperfusion.

In the clinical setting the results of a number of studies are offered as an example of evidence for the 'gut hypothesis' (Fig. 1). The majority of these studies used gastric tonometry – the only clinical tool for monitoring gastrointestinal perfusion that is widely available at present. Gastric tonometry, using gastric intramucosal pH (pHi) as an index of gastric perfusion, is a highly sensitive but relatively nonspecific predictor of outcome after high-risk major surgery [5], cardiac surgery [6], in a cross-section of patients admitted to the intensive care unit (ICU) [7–9] and in ICU patients with sepsis [10] or acute circulatory failure [11]. However, these data do not establish a causal role for gut hypoperfusion in these situations. The link between gastric perfusion and abnormal tonometry-derived variables is complex. If one accepts that tonometry data reflect perfusion state, abnormal perfusion may still represent an epiphenomenon rather than a causative mechanism. In many ways these clinical studies in the critically ill and high-risk surgical patient serve only to highlight our incomplete physiological understanding of the gastrointestinal tract. We review persuasive data from both human-based and laboratory-based studies that suggest that the splanchnic circulation is important in both health and disease, maintaining regulatory mechanisms that are not obviously linked to gastrointestinal homeostasis alone. Before presenting this data, we briefly review the laboratory and clinical techniques that have been used for the assessment of gastrointestinal perfusion. A particular focus is on gastric tonometry, the only technology that has accumulated a substantial body of clinical data.

Assessment of gastrointestinal perfusion

A number of techniques are available for the assessment of gastrointestinal perfusion. Several methods measure portal blood flow or total liver blood flow either directly or indirectly. These include plasma indocyanine green clearance [12] and portal vein catheterization with measurement of blood flow blood flow, oxygen saturation and lactate [13]. Although these techniques have contributed to our understanding of basic physiology, they are not widely used clinically and, in addition, measure total hepatosplanchnic perfusion. We do not focus on these methods any further.

A number of techniques that have not reached the clinical arena are utilized widely in research in this field, and are mentioned in this context throughout the present review. These include Doppler flowmetry of both individual mesenteric vessels and of the serosa and mucosa of the gut [14], reflectance spectrophotometry to index gut mucosal haemaglobin concentration and saturation [15], and the use of oxygen electrodes to assess tissue oxygen levels in the colon [16]. A gut oximeter attached to the antimesenteric boder of the intestine has also been used in animal studies [17]. Radioactive, colour-labelled or fluorescent microspheres can be used in animal studies; when the animal is killed at the end of the study, the distribution of the spheres quantifies relative blood flow to different tissue beds against a reference level [18].

The only practical technique for assessing gastrointestinal perfusion that has entered clinical practise is gastrointestinal tonometry for the measurement of gut intraluminal CO_2 (Fig. 2). It is worth at this point exploring the relationship between gastrointestinal intraluminal CO_2 and blood flow.

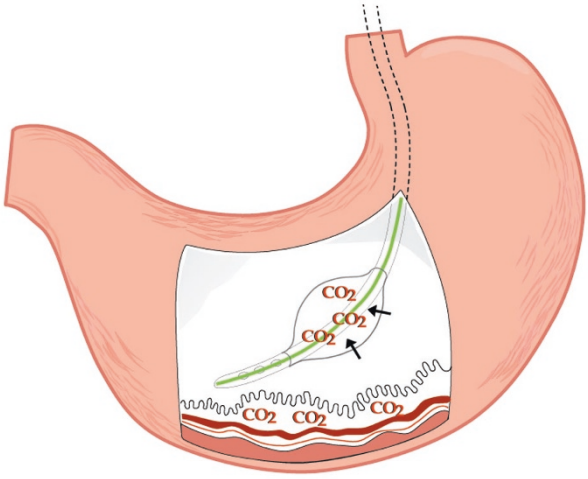
The assumption that intraluminal gut CO_2 is elevated when local perfusion is compromised is based on the concept that in situations where gastrointestinal perfusion is reduced oxygen delivery falls below a critical level, resulting in anaerobic cellular metabolism that leads to local lactic acidosis and generation of CO_2. An alternative or additional explanation may be inadequate washout of CO_2 due to low flow. When gastrointestinal blood flow is reduced by restriction of superior mesenteric artery (SMA) blood flow in the absence of the hormonal milieu that occurs with systemic hypovolaemia, mucosal pH decreases (CO_2 increases) only when flow is less than 50% of baseline [19]. However, this relationship may not hold in hypovolaemia and shock, where vasoactive mediators released in response to decreased intravascular volume are likely to have significant effects on the microcirculation.

Temperature can be an additional confounding factor when the CO_2 is measured in the gaseous phase in the stomach, and this is indexed against arterial CO_2 measured in the liquid phase. If the two samples are at different temperatures, a methodological error is introduced [20]. It has been suggested that in some cases the Haldane effect may be responsible for increased CO_2 levels in situations of increased oxygen extraction in the absence of decreased perfusion [21]. Clearly local metabolic factors that alter the position of the haemaglobin CO_2 dissociation curve could result in changes in measured gastric CO_2 in the absence of any alteration in local CO_2 production. Although the assumption is made that the CO_2 is of mucosal origin, and this is supported by histological damage to the mucosa in shocked patients, it is possible that the CO_2 could be derived from the serosal or muscular levels of the gastrointestinal tract. There are some data to suggest that altered substrate metabolism in the gastrointestinal mucosa may also influence CO_2 production. A lower gastric pHi was observed in swine that were haemorrhaged and resuscitated with a haemaglobin substitute presented in a maltose-containing preparation than those that were resuscitated with a nonsugar-containing preparation [22]. However, hydoxyethyl starch presented in a glucose-containing carrier solution produced less derangement of pHi than the same starch presented in a saline carrier (Wilkes NJ, Woolf R, Mutch M, Stephens R, Mooney L, Mallett SV, Peachey T, Mythen MG, unpublished data).

The development of gastric tonometry as a practical clinical technique has been limited by both methodological drawbacks and problems of interpretation. The original technique of manual saline tonometry was limited by the inconvenience of having to obtain and process samples manually, by slow equilibration times and by errors associated with measurement in the blood gas analyzer. The newer technique of automated semicontinuous air tonometry uses infrared spectrophotometry to measure CO_2. This system also has the advantage that the partial carbon dioxide tension (PCO_2) in the intragastric balloon equilibrates more rapidly with the PCO_2 in the stomach, and accurate readings are available within 30 min of commencing monitoring.

The vast majority of clinical outcome and intervention studies use the derived index of gastric pHi. This is obtained by using a formula to produce a value that is claimed to be representative of the tissue pH in the gastric mucosa. However, this assumes that the tissue bicarbonate is equivalent to the arterial bicarbonate. If this is not so, then the derived pH will be inaccurate. Another way of considering this is that the tissue CO_2 signal is being confounded by systemic acid–base disturbances (eg metabolic acidosis) that are known to be independently predictive of outcome.

Figure 2



Tonometry in the stomach. CO_2 diffuses into the gastric tonometer balloon.

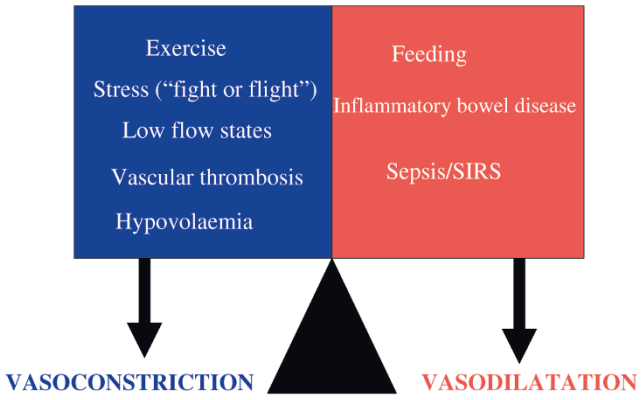
Recent consensus is that presenting the result as the arithmetic difference between the PCO_2 measured in the stomach and the arterial or end-tidal PCO_2, the CO_2 gap (gastric PCO_2 – arterial PCO_2, or gastric PCO_2 – end-tidal PCO_2), will avoid the problems outlined above [23]. Confirmation that the established clinical correlates with pHi are also true for the CO_2 gap is awaited.

Assessment of gut luminal CO_2 can be achieved using other techniques and at other sites. Tonometry has also been conducted in the colon [24] in human clinical studies and in the oesophagus [25] in animals in an attempt to develop an easily accessible site for assessing gastrointestinal perfusion. The sublingual mucosa is an attractive site for clinical measurement because of its ease of access when compared with other parts of the gastrointestinal tract. However the anatomical basis of sublingual blood flow is significantly different from that of the more distal gut, and it is unclear whether this area has the same susceptibility to hypoperfusion as other gut regions in times of stress. Sublingual capnometry using a CO_2 electrode placed on the sublingual mucosa has been investigated in humans with limited success [26].

An overview of the physiology of gastrointestinal perfusion

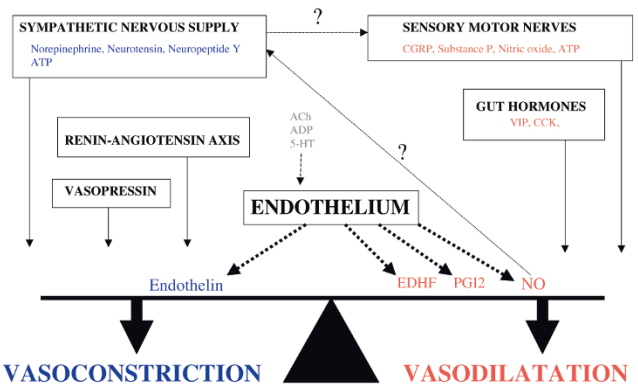
Under normal circumstances, in addition to the fundamental role of the splanchnic circulation in maintaining liver and gut perfusion to maintain mucosal integrity, the splanchnic bed also acts as a ‘circulatory sink’ [27]. The redistribution of blood flow that occurs during feeding and exercise are routine haemodynamic challenges for the splanchnic circulation. Exploration of how splanchnic perfusion copes at

Figure 3



A dynamic balance between vasodilatation and vasoconstriction in the gastrointestinal blood supply exists during both health and disease.

Figure 4



A complex interplay of neural, hormonal and endothelial-derived factors regulates the balance of gastrointestinal perfusion between vasodilatation and vasoconstriction. Question marks indicate possible interactions; dashed lines indicate endothelium-derived production. ACh, acetylcholine; CCK, cholecystokinin; CGRP, calcitonin gene-related peptide; EDHF, endothelium-derived hyperpolarizing factor; 5-HT, 5-hydroxytryptamine; PG, prostaglandin; VIP, vasoactive intestinal peptide.

these extremes of normal homeostatic function illustrates the regulatory mechanisms at play (Fig. 3).

We concentrate on splanchnic rather than hepatic perfusion [28], the microvascular perfusion of which has been considered in detail elsewhere [29]. Unless stated otherwise, the studies quoted were conducted using laboratory animal models.

The hepatosplanchnic circulation receives 30% of total cardiac output. With increasing age, splanchnic blood flow declines both absolutely and as a fraction of total cardiac output [30]. Splanchnic anatomy is described in detail elsewhere [31]. Briefly, the mesenteric circulation consists of the muscularis propria, submucosa and mucosa, which are arranged in parallel [32]. Resistance arterioles regulate blood flow to the splanchnic bed, so at constant hydrostatic pressure flow is inversely proportional to resistance. Although these arterioles partake in a markedly less impressive autoregulatory system than in the kidney or brain, they do enable a partial compensation for falls in blood flow [33]. The tone of these vessels depends on the complex balance between neurally mediated sympathetic vasoconstriction, the local action of vasoregulatory substances that are under the influence of the apparently paradoxically named 'sensory-motor' nerves, the parasympathetic cholinergic nerve supply, the enteric nervous system and endothelial-derived agents [34] (Fig. 4).

In most models, norepinephrine (noradrenalin) is the key sympathetic-mediated vasoconstrictor acting with the cotransmitters ATP [35] and neuropeptide Y [36], the latter contributing to perhaps 30% of sympathetic vasoconstriction [37]. The vasodilatory calcitonin gene-related peptide [38] is the main neurotransmitter released at sensory-motor nerves, among many other putative agents. The enteric nervous system includes the nonadrenergic noncholinergic system that supplies perivascular myenteric nerves [39]; nitric oxide (NO) is a putative neurotransmitter in this system, in addition to the well-established endothelium-derived role in maintaining basal vascular tone [40]. NO inhibits the synthesis [41] and potent vasoconstrictor action [42] of another endothelial-derived factor, endothelin-1 [43], which belongs to a family of cytokines that exhibit many other roles [44]. Infusion of endothelin-1 produces mesenteric vasoconstriction in the rat, an effect that is attenuated by bosentan, an endothelin-receptor antagonist [45]. Inhibition of NO synthesis not only reveals endothelin to have a tonic pressor role [46], but also increases intestinal epithelial permeability [47]. Human studies show that endothelin-1 [48] and N^G-monomethyl-L-arginine (L-NMMA) both reduce splanchnic blood flow, but prior administration of L-NMMA prevents the vasoconstriction normally seen with endothelin-1 [40]. In damaged or absent endothelium in which there is impaired NO production, sympathetic-mediated vasoconstriction has been reported to be augmented, whereas paradoxical vasoconstriction is seen on application of established vasodilatory agents [49]. Such pharmacological interplay may be part of an even more complex system, given that there is evidence for neuromodulation occurring between NO, sympathetic nerves and other sensory-motor neurotransmitters [38,50,51]. Furthermore, there is intriguing data indicating that gastric perfusion can be altered by flow characteristics,

and not simply by volume status. Pulsatile cardiopulmonary bypass results in reduced disturbance in pHi as compared with nonpulsatile cardiopulmonary bypass [52].

Recent biomechanical modelling, based on morphometric mapping of the mesentery, indicated that approximately 40% of the mesenteric circulation is contained in venules, which represent the bulk of the mesenteric microcirculation [53]. Precapillary and postcapillary sphincters determine the tone of these capacitance vessels [54]. The combined action of such capillary sphincters and the resistance arterioles effects intraorgan redistribution [55].

Splanchnic oxygen consumption is 20–35% of total body oxygen consumption [56]. In general, animal models show that oxygen consumption is maintained, even at substantially lower blood flow, by the ability to increase oxygen extraction; only at very low blood flow is oxygen uptake dependent on blood flow [57,58]. This reserve is facilitated by microvascular adaptation; a relatively underperfused, extensive network of collateral capillary beds [59] becomes an additional conduit during periods of decreased oxygen delivery [60]. Mucosal permeability may therefore be protected to a large degree, only becoming compromised when oxygen uptake is below 50% of control [61]. More recent data from human studies [62] suggest that oxygen supply dependency may occur with as little as 30% reduction in gastrointestinal blood flow, with mucosal supply dependency (identified using continuous flow gastric tonometry) occurring before global splanchnic supply dependency can be identified (using portal venous CO_2 measurement). Data from studies in humans using tonometry suggest that the mucosa may respond differently to alternative causes of reduction in oxygen delivery. Although stagnant hypoxia is readily detected [63], sensitivity to anaemic hypoxia seems to be much lower [64].

Feeding

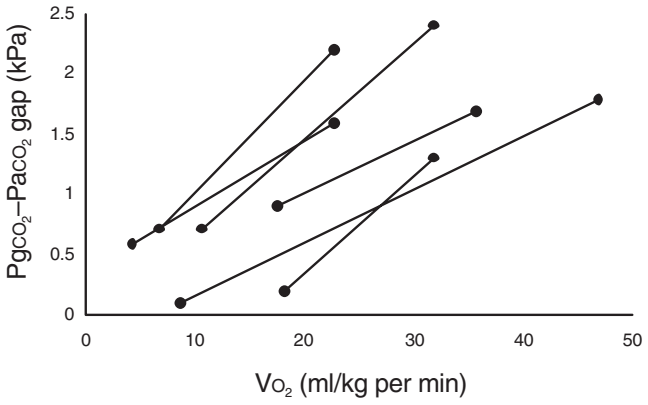
The anticipation and ingestion of food results in neurally mediated sympathetic increases in heart rate, cardiac output, plasma norepinephrine levels and peripheral (forearm) vascular resistance [65]. Within 15 min of food ingestion, SMA blood flow can double from 500 to 1000 ml/min [66], depending on caloric load [67], food volume and type. For example, oral alcohol causes an increased SMA blood flow compared with alcohol-free control [68]. Elevation in SMA blood flow correlates closely with amino-terminal neurotensin and norepiniphrine [67]. Sensory-efferent/motor nerves may play a key role in 'fine-tuning' this process; distension of the large intestine induces SMA smooth muscle hyperpolarization [69] and hence increased blood flow. This may partly explain the observation that the site of feeding can produce differential mesenteric blood flow effects [70]. Fasting for 1 day produces significant mucosal atrophy in the rat [71].

Despite the gut being the largest endocrine organ in the body, the local and cardiovascular effects of many of the gut-derived hormones that are stimulated by feeding have been described relatively recently, and their roles remain unclear [72]. Established humoral agents including vasoactive intestinal peptide [73] and cholecystokinin [74] promote vasodilatation. During ingestion, systemic blood pressure and cardiac output are maintained by increased sympathetic drive, a feature that is absent in patients with autonomic failure [66]. Within 5–30 min after a meal, all cardiovascular responses to feeding subside, except that increased mesenteric blood flow is sustained whereas skeletal muscle blood flow decreases in resting animals [75]. Thus, digestion is accompanied by an increase in total body, myocardial, splanchnic and intestinal oxygen consumption.

The increased metabolic demands of active absorption are proportionally greater than the increases in splanchnic blood flow, suggesting that the active gut may incur an oxygen debt in the same way that we consider the whole body does during exercise and physiological stress. Although the exact mechanism of the absorptive small intestine villi is disputed across species [76–78], numerous authors support the idea that these villi are particularly susceptible to deleterious circulatory or hypoxic changes [79]. The villi exhibit an oxygen countercurrent exchange mechanism, producing relative hypoxia at the luminal tip compared with at its base, even under normal conditions [80,81]. The potential vulnerability of such relatively hypoxic tissue may be potentiated by the villus architecture, which theoretically promotes the phenomenon of plasma skimming, and hence lower haematocrit and oxygen delivery [82], although experimentally this is not seen at reduced perfusion pressures [83].

In the clinical setting there is evidence that the increased metabolic requirements of an absorbing gut coupled with inadequate perfusion due to hypovolaemia or vascular insufficiency may result in a critical imbalance between oxygen supply and demand. The clinical syndrome of mesenteric angina occurring after oral intake is well recognized. Angiography of some of these patients reveals critical arterial stenosis. In patients with stenoses a proportion have an increased difference between their arterial and intragastric P_{CO_2} (an elevated P_{CO_2} gap) at rest, suggesting poor perfusion. Tonometry during moderate exercise demonstrated an abnormal CO_2 gap in all patients with stenoses in one study, and this abnormality was absent in control individuals [84]. Revascularization resulted in normalization of perfusion in all patients. The clinical importance of this in a critical care setting is highlighted by case reports that describe patients who have sustained massive bowel infarction soon after initiation of enteral feeding.

Figure 5



Gastric–arterial CO_2 (P_{gCO_2}–P_{aCO_2}) gap before and after exercise to high oxygen consumption (V_{O_2}). Data from Chieverley-Williams S, Hurley R, Cox M, McCorkell S, Grocott MPW, Goldstone J and Mythen MG (unpublished data).

Despite the current consensus that early enteral feeding is beneficial [85,86], the clinical evidence is largely drawn from subset analyses of randomized controlled trials [87], which did not demonstrate an overall outcome benefit, but did show a reduction in specific complications. The possibility that unidentified complications are increased in other subsets cannot be discounted in view of the equivocal overall outcome. There may exist a subset of patients in whom the increased metabolic demands incurred by active absorption of nutrients and increased motility result in critical ischaemia and infarction. Case reports of small-bowel necrosis after jejunal feeding offer support for this idea [88]. It is interesting to speculate whether this group could be identified by tonometry, perhaps in combination with a test of gastric functional response. Good experimental support for this idea is provided in a canine model in which the entire vascular supply to the jejunoileum was isolated [19]. Decreased SMA flow during nutrient delivery only to the jejunum resulted in increased mucosal perfusion at that level (as measured by laser Doppler flowmetry and reflectance spectrophotometry). However, concomitantly, perfusion to the distal ileum was reduced. Thus, a redistribution of mesenteric blood occurred, or 'intramesenteric steal' as coined by the authors.

Exercise

In contrast to feeding, acute exercise is associated with large increases in cardiac and active skeletal muscle blood flows, but reduced blood flow to skin, kidneys and organs perfused by the splanchnic circulation [89]. Using SMA and coeliac artery duplex ultrasound, a 50% reduction in the hepatosplenic and a 25–40% reduction in the mesenteric blood flow were demonstrated [90,91]. Simultaneous indocyanine green dye elimination measurements were consistent with the duplex data [90]. Results from studies using gastric tonometry also support the concept of a decrease in gastrointestinal perfusion occurring with exercise. Oarsmen subjected to 30 min of maximal exercise all had a significantly reduced gastric pHi, and this was proportionally greater than the reduction in arterial pH [92]. We have produced similar results using bicycle ergometer as an exercise challenge (unpublished data) (Fig. 5).

Reduction in splanchnic blood flow occurs in proportion to relative exercise intensity. Low-intensity exercise (heart rate 90 beats/min) reduces splanchnic blood flow [93], whereas strenuous exercise can result in clinically significant gut ischaemia [94]. Increased sympathetic nervous system outflow appears to be the primary mediator of reduced blood flows to the splanchnic vasculature [95]. However, angiotensin II receptor antagonists increase blood flow throughout the gut during exercise [96], and the vasoconstrictors endothelin [48] and vasopressin probably also make important vasoconstrictive contributions [97].

Human and animal studies have shown that splanchnic blood flow is reduced less from resting levels during acute exercise after programmed endurance exercise training. The mechanisms that are involved in these adaptations produced by such training include reductions in sympathetic nervous system outflow, plasma angiotensin II and vasopressin concentrations, which result in less splanchnic and renal vasoconstriction [97].

An excellent illustration of how important adaptive splanchnic circulatory changes are during normal function is provided by studies that examine how splanchnic circulatory changes during digestion are affected by exercise. In healthy adults, exercise performed during the digestion phase does not affect the intestinal hyperaemia seen due to increased splanchnic flow. Using this knowledge has helped to provide a strategy for avoiding postprandial hypotension in elderly patients, an important clinical problem given its estimated high incidence (8% of syncopal episodes) and strong association with increased incidence of falls, syncope, new coronary events, new strokes and total mortality at long-term follow up [98]. As predicted from our knowledge of splanchnic circulation during feeding, acute exercise should ameliorate the pooling of splanchnic blood during feeding, and hence reduce postprandial hypotension. Indeed, in nursing home residents with postprandial hypotension, postprandial walking transiently increased cardiac output, but orthostatic hypotension or falls did not occur [99].

Critical care

How does normal homeostasis of gut perfusion alter in high-risk surgery or critical care diseases? Adequate splanchnic perfusion is seriously challenged during the commonly encountered critical care scenarios of circulatory

shock and septic shock (like) states, but for rather different underlying reasons. Of course, clinically these two scenarios also often overlap in a dynamic manner, and therefore many ICU scenarios are likely to be considerably more complicated than the models discussed here. Unless stated otherwise, all studies quoted were conducted in animals.

Circulatory shock

In contrast to sepsis, circulatory shock causes splanchnic hypoperfusion with no initial change in splanchnic oxygen consumption, regardless of whether the aetiology is cardiac or acute hypovolaemia. By diverting blood supply mediated by sympathetic adrenergic stimulation [100], both the liver (which can redistribute an additional 1 l of blood to the systemic circulation under cardiovascular stress) and the gut are an efficient means of ensuring that vital organs are perfused during acute hypovolaemia [101,102], illustrating much the same general principle as that of exercise. Gastric tonometry during induced short-term hypovolaemia in healthy volunteers demonstrated a reduced gastric pHi and this resolved with resuscitation [63]. Interestingly, this was the only significant clinical indicator of hypovolaemia, with heart rate, blood pressure and peripheral perfusion showing no change after a 20–25% blood volume venesection. Although simulated [103] and actual hypovolaemia [101] in healthy human volunteers showed that splanchnic vasoconstriction exists beyond the period of restoration of normal systemic haemodynamics after apparently adequate fluid resuscitation, the importance of the duration of such insults remains unclear. The question remains as to the cost the gut incurs as a result of sustained redistribution, or extreme hypoperfusion.

Furthermore, there is some evidence that intriguingly suggests that splanchnic hypoperfusion may actually be the result of, or at least exacerbated by, the combination of the neural response to injury plus haemorrhage, rather than hypovolaemia alone [104]. The degree of haemorrhage is increased in the presence of afferent nerve stimulation [105]. Whether afferent nerve stimulation in these animal studies simulates the pain/stress response and/or modulates central cardiovascular and baroreflexes [106] requires further investigation. It is interesting, however, to consider the obvious clinical correlate of this idea, in which neural blockade by local nerve block has been shown to reduce blood loss [107] and epidural blockade to improve lower limb graft survival [108]. However, thoracic epidural analgesia during major vascular surgery does not improve splanchnic perfusion, as monitored by gastric and sigmoid colon tonometry [109]. Laboratory studies indicate that the site and spread of epidural block are critical, with thoracic sympathetic blockade causing either no change in splanchnic perfusion [110] or increased splanchnic venodilatation, whereas lumbar blockade increases splanchnic sympathetic outflow and hence vasoconstriction, probably via the baroreceptor reflex [111].

At the local and cellular levels, the complex interplay between those factors described above in determining normal vascular tone probably plays the key role in determining whether the response to hypoperfusion is sustained. The splanchnic circulation certainly has important humorally mediated differences in response to hypoperfusion compared with the systemic circulation. Both vasopressin and angiotensin II have markedly greater effect in the mesenteric bed than elsewhere. In particular, angiotensin II is believed to play a crucial role in mediating intense splanchnic vasoconstriction. This appears to be regardless of whether the underlying aetiology is cardiogenic or haemorrhagic [112]. Splanchnic vasoconstriction is not abolished by ablation of the α-adrenergic sympathetic response [113] or mesenteric arterial denervation [114]. Nephrectomy [115], angiotensin-converting enzyme (ACE) [112,115] and specific angiotensin II receptor inhibition [116,117] prevent splanchnic vasoconstriction. Furthermore, direct infusion of angiotensin II in rats [118] and angiotensin I in humans causes splanchnic vasoconstriction, which is again reversed by ACE inhibition [119]. No clinical studies have been able to show a similar effect of ACE inhibitors on splanchnic perfusion. Splanchnic perfusion as determined by gastric tonometery was not altered by enalaprilat in adults [120] or captopril in infants [121] after cardiac surgery, although a small study of trauma patients [122] did show a benefit. As alluded to above, the mechanisms(s) that underlie such acute changes may be very different from those that are involved in chronic adaptation to low-flow states. In patients with biventricular cardiac failure, ACE inhibitors have no effect on splanchnic blood flow [123].

Vasopressin also plays an important role in producing the vasoconstriction that is seen in haemorrhage [113,124], even at relatively low levels of hypovolaemia with sympathetic blockade [125]. Antagonism of vasopressin results in higher SMA blood flow during haemorrhage [124]. Experimental models of hypovolaemia in humans, induced by head-up tilt, lower body negative pressure or epidural, show marked plasma vasopressin increases, but temporally these occur only after renin–angiotensin activation [126]. β-Blockade, which has been shown to reduce myocardial ischaemia and improve perioperative and postoperative outcome [127], elevates vasopressin levels in both euvolaemic and hypovolaemic rats [128]. Clonidine, which has also been shown to reduce myocardial ischaemia perioperatively [129], prevents sympathetic-mediated splanchnic vasoconstriction [130], including in humans [131]. Given that the splanchnic perfusion is the last to be restored after adequate fluid resuscitation, cellular changes induced by hypoperfusion that outlast the period of insult may well be the key step in perpetuating mucosal gut damage, persistent gut dysfunction and the generation of a systemic inflammatory response. The importance of reperfusion injury in the gut is reviewed elsewhere [132].

Sepsis/systemic inflammatory response syndrome

The hallmark of the human splanchnic circulation in sepsis/SIRS is increased total hepatosplanchnic blood flow [133–135], with higher splanchnic oxygen extraction [136] and consumption [137]. The effect on mesenteric blood flow *per se* is less clear [138]. However, oxygen consumption, delivery and extraction ratio may also depend on the duration of the sepsis state, as indicated by an endotoxin model. Oxygen consumption and delivery (but not oxygen extraction ratio) in the small intestine increased early in sepsis, only to decrease 20 h after the onset of sepsis [139]. A confounding factor in that study was the likely lack of fluid resuscitation, resulting in a haematocrit rise that may well be deleterious to the splanchnic microcirculation.

'Cytopathic hypoxia' causes this increase in hepatosplanchnic blood flow during sepsis, and many possible cellular mechanisms have been postulated [140,141]. Whether generated by initial hypoperfusion, trauma or even direct endotoxaemic damage [142], the resultant panendothelial injury that alters endothelial-derived functions generates and perpetuates an inflammatory response [143].

One problem in building an overall picture of the pathophysiology of sepsis/SIRS is the variety of methods that are employed in generating the sepsis-like response in laboratory models. These differences are probably important, particularly in interpreting the role and modulation of the splanchnic vasculature. Indeed, many endotoxin-mediated models of sepsis show decreased mesenteric perfusion, in contrast to models in which live bacterial innoculation results in the hyperdynamic response. However, *in vitro*, both *Escherichia coli* haemolysin and endotoxin models of sepsis produce abnormal capillary blood flow distribution, with decreased perfused capillaries [144], with evidence of impaired tissue oxygenation indicated by an increase in the mucosal–arterial Pco_2 gap, despite the maintenance of mesenteric oxygen delivery [145]. Furthermore, relatively increased haemoglobin concentration values and oedema formation occurred, suggesting postcapillary vasoconstriction and capillary leakage. This attractive model [145] serves to illustrate the probable microvascular changes that are induced by sepsis, which are supported by current understanding of the splanchnic microvasculature [53].

Both animal and human studies show that norepinephrine, NO [146], endothelin [147] and angiotensin II [148] levels are markedly elevated in sepsis/SIRS. In addition, other vasoactive mediators such as vasoactive intestinal peptide [149], eicosanoids, platelet-activating factor and bradykinin have been implicated, but, despite successful modulation of these factors in animal models of sepsis, results in humans are disappointing [150]. In particular, NO is a key element in generating the septic response [151,152]. However, nonspecific inhibition of NO in humans on a large scale did not improve outcome (unpublished data). NO inhibition reverses hypotension, but cardiac output is reduced and the overall effect on organ perfusion is unclear [153]. This is despite the often impressive (but also inconsistent) effects of NO inhibitors on reversing systemic hypotension and splanchnic hypoperfusion in many bacterial and endotoxin models of sepsis [154–156]. This mirrors the finding that blockade of NO synthase or gene deletion of NO synthase can exacerbate intestinal inflammation in experimental models, due to the indiscriminate inhibition of both inducible and constitutive NO [157,158]. The effect of timing of these interventions on restoring splanchnic perfusion seems important [159], given that experimental intestinal dysfunction results in an early (within 20 min) [160], severe decrease in endothelium-derived NO [161]. In contrast to the scenario of decreased NO, greater NO production is thought be responsible for decreased norepinephrine-mediated vasopressor activity during septic shock [162].

In septic patients, the greatest severity of disease has been correlated to the highest concentration of endothelin-1 [163], although the mechanism involved in the increase of endothelin-1 concentration during sepsis is largely unknown. Oldner *et al* [164] have shown that bosentan (a nonpeptide endothelin $[ET]_A$ and ET_B receptor antagonist) restores both systemic and gut oxygen in a porcine endotoxic model of sepsis. In this model, gut oxygen consumption increased despite the profound reduction in gut oxygen delivery. Restoration of splanchnic oxygen delivery in response to bosentan treatment was not associated with an increase in oxygen consumption, suggesting that oxygen consumption was not dependent on oxygen delivery in the gut. However, that study contrasts with others conducted over longer periods of time in that, although splanchnic perfusion *per se* was not investigated, endothelin antagonists exacerbated endotoxic mediated hypotension [165] and increased mortality [166]. As illustrated by quantative assessments of NO and vasopressin during prolonged exposure to endotoxin or bacteria, cellular function may be profoundly altered, thereby producing a markedly different, and therefore incomparable, picture to the early response.

Given the marked increase also seen in angiotensin II, there is interesting, albeit limited, evidence that both vasopressin and angiotensin may induce endothelin release from *in vitro* endothelial cells [167]. In addition, ACE inhibitors potentiate forearm vasculature dilatation induced by infusion of acetylcholine in healthy human volunteers [168]. Although vasopressin has little effect in normal humans, its role in sepsis is complex. The effect on splanchnic perfusion of the large initial rise and subsequent rapid decline in plasma vasopressin seen in animal models is not known. Finally, impaired autonomic function

in sepsis [169], if present, has a potentially important, deleterious influence on splanchnic perfusion. The effects of inotropes and vasopressors on gastrointestinal perfusion are complex and tonometry-derived results are often not consistent with results obtained using other techniques or laboratory models. This area has been well covered in a recent review [170].

Can improvement in gastrointestinal perfusion improve outcome?

That the majority of studies using tonometry predict outcome is certainly striking. This is all the more impressive given the inability of the commonly measured physiological variables (cardiac output and oxygen delivery excepted) to predict outcome. However, to date there is little convincing evidence that gastric tonometry-driven therapeutic intervention can alter outcome. An early study conducted in patients newly admitted to an ICU [8] demonstrated that the application of a protocol designed to increase oxygen delivery in response to an abnormal gastric pHi improved outcome in those with a normal pHi on admission, but had no effect on those who already had an abnormal pHi.

Commencement of corrective therapy in the already critically ill patient, by definition after a major insult, is considered by many to be equivalent to shutting the stable door after the horse has bolted; otherwise stated, prevention of (or rapid response to) an abnormal pHi (before or early in the course of the insult) may be much more effective than attempting to treat an established abnormal pHi. In cardiac surgical patients intraoperative oesophageal Doppler optimization of stroke volume reduced the incidence of an abnormal gastric pHi when compared with standard fluid management [6]. Whether this algorithm would improve outcome if instituted only in response to abnormal pHi is unknown. Intervention in response to an abnormal pHi that occurs intraoperatively in patients undergoing elective infrarenal aortic aneurysm repair did not improve outcome [171]. The treatment protocol in this study was somewhat different, however, and was not demonstrated to improve pHi. The hypothesis that pHi-guided therapy can improve outcome was therefore not tested. One complex study that combined optimization of oxygen delivery and tonometry guidance [172] suggested that monitoring and reacting to abnormal gut perfusion produced greater benefit than that obtained by optimizing oxygen delivery alone. More recently, a large randomized controlled trial of patients recruited on ICU admission used additional fluid therapy and dobutamine in response to a low pHi, and failed to demonstrate any outcome difference between control and protocol groups [173]. Once again the treatment algorithm was ineffective at improving pHi and the therapy was instituted after the insult. An adequately powered intraoperative study with an effective treatment algorithm is awaited to answer this important clinical question definitively.

Conclusion

Current physiological understanding of splanchnic perfusion suggests a key role for the splanchnic circulation in the regulation of cardiovascular homeostasis. Gastrointestinal perfusion is often compromised early relative to other vascular beds in situations including critical illness, major surgery and exercise, all of which are characterized by increased demands on the circulation to maintain tissue oxygen delivery. Perhaps more importantly, this relative hypoperfusion often outlasts the period of the hypovolaemic insult or low-flow state. The relationship between gastric tonometry and gastrointestinal perfusion is complex. However, this is the only currently available clinically practical monitor that we have. The ability of pHi to predict outcome has repeatedly been demonstrated. CO_2 gap, now the accepted variable, has not yet been conclusively demonstrated to have the same predictive ability. Convincing data that demonstrate the ability of tonometry-guided therapy to improve outcome remains elusive.

The striking association between outcome and gastric pHi provides an important clue to the pathophysiology of critical illness. Greater understanding of the complex physiological basis of gastrointestinal perfusion during both health and disease will hopefully open up further potential therapeutic avenues.

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