ABSTRACT

Objective: To review the clinical and experimental methods of detecting intestinal ischaemia and to assess their value in current clinical practice.

Data sources: Relevant articles and published reviews on intestinal ischaemia and/or infarction.

Summary of review: The incidence of acute mesenteric ischaemia has increased substantially over the last few decades. Death rates of 70% to 90% have been reported for this condition. Improved management depends upon prompt diagnosis and early aggressive treatment. Despite mounting evidence that ischaemic intestinal injury may be frequent and may be a cause of multi-organ failure, accurate monitoring of the intestinal circulation in critically ill patients continues to be a distant goal.

The need for a reliable, specific test of intestinal ischaemia has been recognised for many years. Numerous potential monitors have been evaluated including intraluminal pCO$_2$, abdominal CT, abdominal MRI and specific plasma enzymes, but few have shown potential to be clinically useful. At present no specific test for intestinal ischaemia and/or infarction is in routine clinical use. Development of a specific test to monitor for intestinal injury would be of great clinical value. Further work will inevitably lead to the development of useful markers.

Conclusions: Accurate detection of intestinal ischaemia in the critically ill patient is often difficult. While numerous tests have been examined to diagnose and monitor intestinal ischaemia and/or infarction most exhibit an unacceptably low specificity and sensitivity. (Critical Care and Resuscitation 2001; 3: 176-180)

Key words: Intestinal ischaemia, monitoring, critical illness, intraluminal pCO$_2$
oxygen delivery in shock states. In addition, splanchnic vasoconstriction has been observed to persist long after fluid resuscitation has restored normal systemic haemodynamic parameters. These observations suggest that the intestine is very likely to be prone to ischaemia and/or infarction in the face of severe and persisting shock.

The clinical and pathological response of the intestine to ischaemia

Classically, the initial clinical response to total vascular obstruction is characterised by intense intestinal spasm with severe abdominal pain, but without signs of peritonism. Bowel sounds may be absent, intermittent or hyperactive. Subsequent sloughing of the mucosa results in bleeding which may be clinically evident. When ischaemia is prolonged the bowel wall becomes friable, full thickness necrosis and perforation may occur, and gas bubbles may appear in the mesenteric veins. Following perforation, signs of peritonitis will be evident.

Since the early clinical features are non-specific, the diagnosis is often delayed until full thickness infarction has occurred, by which time the intestine is unsalvageable and the prognosis for the patient (with or without surgery) is poor.

At a cellular level, following vascular occlusion, the epithelial cells of the villi become swollen and slough into the intestinal lumen. This process advances from the tip to the base of the villus, and at the end of a period of total ischaemia lasting 120 minutes there is complete destruction of the villi as well as the upper portions of the crypts. Progressive histological signs of inflammation and infarction (e.g. neutrophil infiltration, cell lysis) are seen in the crypts and submucosal layers. Intestinal permeability to macromolecules increases in association with intestinal infarction and consequently compounds present in high concentration in the bowel lumen will diffuse through the bowel wall and can be detectable in the circulation.

Diagnostic tests of intestinal damage

Radiology

A plain X-ray of the abdomen is generally of little value in the early diagnosis of intestinal infarction and of no use in the diagnosis of ischaemia. Once intestinal necrosis occurs, linear streaks of gas in the bowel wall or gas in the portal vein may be evident. These appearances are late signs, associated with a grave prognosis and are consequently of limited clinical value.

Computerised tomography (CT) of the abdomen may reveal signs of an infarcted bowel wall, which is often thicker and shows no enhancement after intravenous contrast. Free intraperitoneal fluid and intramural gas can usually be seen in more advanced cases. Similarly, using magnetic resonance imaging (MRI) the infarcted bowel wall does not show contrast enhancement. Consequently, advanced medical imaging can have a high diagnostic accuracy, but only after infarction has occurred.

Intraluminal pCO₂

Measurement of gastric intraluminal pCO₂ has been proposed as a sensitive indicator of bowel hypoperfusion. A variation on the original technique, employing air as the equilibration medium, has some advantages. Initially, a calculated intramusosal pH (pHᵢ) was derived from the luminal pCO₂ and the systemic bicarbonate concentration; however it has been recognised that use of the systemic bicarbonate is not helpful in the interpretation. More recently, interpretation has rested on intraluminal pCO₂ alone. Using a continuously reading pCO₂ sensor placed directly into the small bowel lumen, very rapid increases of pCO₂ have been observed following various degrees of interruption of intestinal blood flow.

Gastric tonometry, however, has not gained wide acceptance in clinical practice. There are several reasons for this, including a lack of response of abnormal results to treatment (intraluminal pCO₂ does not alter profoundly or rapidly in response to therapeutic interventions), a lack of specificity (e.g. some patients who have a high intragastric CO₂ recover without complication) and a relatively high catheter cost. Furthermore, local CO₂ measurements can only reflect the local conditions where the monitor is situated; they do not give any direct indication of a remote area of intestinal ischaemia or infarction. While it has become apparent that the stomach is a much less sensitive site for monitoring intestinal ischaemia than the ileum in clinical practice, ileal access is not easy. Moreover, a marketed product is not available for naso-jejunal pCO₂ monitoring.

Faecal examination

Faecal examination is not an attractive prospect for the monitoring of intestinal ischaemia. Furthermore, patients may have an ileus or total obstruction and produce no faecal sample. Equally, feeding or intestinal hurry resulting in diarrhoea may confuse the results. However, as villi are shed into the intestinal lumen as an early response to intestinal ischaemia, it is possible that the investigation of faeces might provide a test which would have value.

Administration of a small intestine mucosal toxin to rats results in an increase in faecal intestinal alkaline phosphatase on the first day after treatment followed by
a marked reduction for the subsequent three days. After five days the faecal alkaline phosphatase activity increases again, presumably reflecting intestinal regeneration. Also high levels of angiotensin-converting enzyme (ACE) are found in the brush border of human small bowel, suggesting the potential usefulness of faecal ACE determination as an index of enterocyte damage. Currently however, faecal determination of alkaline phosphatase or angiotensin-converting enzyme have not been used in the clinical assessment of intestinal ischaemia.

**Blood testing**

In concept, a specific and sensitive blood test for intestinal ischaemia or early infarction would be very useful in the evaluation of an adequate intestinal circulation. However, up until now both routine and specialised blood tests have failed to satisfy these requirements and none have entered routine clinical practice. A neutrophilia and metabolic acidosis are common but are non-specific findings. The diagnostic triad of leukocytosis, base deficit and elevated serum phosphate concentration has been proposed as a distinctive characteristic of intestinal infarction. However, these changes often occur late and are also nonspecific. The plasma lactate is commonly raised but this is also nonspecific.

In an animal model of intestinal ischaemia, an elevation in serum levels of the mucosal enzyme alkaline phosphatase (ALP) and the seromuscular enzymes creatine phosphokinase (CK), lactate dehydrogenase (LDH) and serum aspartate amino transferase (AST) has been reported. An elevation in serum N-acetyl hexosaminidase (a lysosomal acid hydrolase), has also been reported in association with intestinal ischaemia, as well as with acute rejection of transplanted small intestine.

De Toma G *et al*, reviewed the serum changes of a number of markers in an animal model of bowel ischaemia in a search for a clinically useful blood test for intestinal infarction. Serum levels of CK, LDH, AST, ALP, alanine amino transferase (ALT), gamma glutamyl transferases (GGT), glucose, urea nitrogen, creatinine, amylase, sodium and potassium were measured following an experimentally induced acute mesenteric infarction. They noted that mesenteric infarction resulted in a significant increase in serum LDH, AST, ALP and total CK. However, none of these enzymes were specific for intestinal infarction. Other studies have also addressed the same problem investigating serum levels of LDH, CK, AST, ALP, diaminodioxidase and hexosaminidase. However, none have entered clinical practice either because of low specificity and sensitivity or due to an inability to detect intestinal ischaemia before the onset of gangrene.

Recently, the alpha isoenzyme of glutathione S-transferase (GST) has been found to be highly specific to small bowel and liver. It has been found to be 100% sensitive and 86% specific for mesenteric ischaemia in an animal model, although the same sensitivity and specificity have not been reported in humans. Cytosolic beta-glucosidase has also been found to rise rapidly after intestinal ischaemia and appeared to be a sensitive marker. However, it has a low specificity, as closed-loop obstruction of the small bowel also results in increased serum levels of this enzyme.

Creatine phosphokinase (CK) isoenzymes have been demonstrated in the mucosa and muscles throughout the entire gastrointestinal system in both man and dogs. CK-MM, presumably from striated muscles, is most prevalent in the oesophagus. In other portions of the bowel all three isoenzymes are present in equal proportions. In the mucosa, the levels of CK-MM and CK-BB are higher than CK-MB.

Of the 26 different variables potentially able to predict intestinal infarction in man, Fried and co-workers considered CK-BB to be the best (e.g. 63% sensitivity and 100% specificity), whereas total CK and CK-MB did not identify patients with infarction. The CK-BB isoenzyme is very labile and has been reported to lose 95% of its activity within 90 minutes at 37 degrees centigrade, and may have a profound influence on the results if blood is not rapidly cooled before being assayed. Further investigation of CK-BB in animal models of intestinal infarction has confirmed that CK-BB becomes elevated within 3 hours of infarction and peaks by 6 hours before it falls, even in the presence of progressive irreversible infarction. In contrast, CK-MB rises more slowly and does not peak until 24 hours after the onset of vascular occlusion. The authors suggest that recognition of this pattern of rise of the CK isoenzymes could be of useful diagnostic significance. It has also been found that CK-BB levels are significantly increased in babies with necrotising enterocolitis, and remain elevated until recovery, while normal levels are often observed in unaffected babies and in those with diarrhoea who do not develop necrotising enterocolitis. However, in a case report of bowel infarction complicating acute aortic dissection, the marked rise in CK observed, was 100% CK-MM.

Intestinal fatty acid binding protein (I-FABP) is present in high concentration in enterocytes (especially concentrated in the cells of the villus) and is specific to the small intestine. I-FABP is not normally detectable in the serum but is released into the peripheral circulation after reversible intestinal ischaemic injury. Consequent-
ly, I-FABP has the potential to be a useful biochemical test of early, and therefore reversible, mesenteric ischaemia. In an animal model of bowel ischaemia, I-FABP was found to be present in the serum within 15 minutes after segmental mesenteric arterial ligation. It has also been shown to be elevated in a rat model of necrotising enterocolitis and to be a sensitive marker of small bowel allograft rejection.

Phospholipase A$_2$ (sPLA$_2$) has recently been implicated as a key enzyme of local inflammation after gastrointestinal ischaemia-reperfusion (I/R). Activation of sPLA$_2$ appears to be an important step in the pathogenesis of distant organ injury after splanchnic hypoperfusion, a process that appears to involve polymorphonuclear cell priming in the gastrointestinal bed. Phospholipase A$_2$ (PLA$_2$) activity has been found to accumulate rapidly in the preservation media containing ischämic rat intestinal grafts, confirming a relationship between ischaemia and PLA$_2$ secretion. The phospholipase secreted from the bowel has been reported to differ from classic type IIa PLA$_2$ and consequently detection of this specific phospholipase in the blood could be a useful indicator of significant intestinal injury.

REFERENCES