Clinical practice review

Monitoring Intestinal Ischaemia

C. CORKE, K. GLENISTER
Intensive Care Unit, The Geelong Hospital, and Deakin University, Geelong, VICTORIA

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 monitor-ing 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* n*umerous 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

The clinical diagnosis of intestinal ischaemia and/or infarction remains a challenge and when delayed often results in considerable morbidity and mortality.[1,2] However, reliable tests to detect intestinal injury, early, are unavailable in clinical practice. Various imaging and biochemical techniques have been evaluated but all have proved inadequate. The search for an easily applied, specific and sensitive test that enables one to identify intestinal ischaemia and/or infarction at an early stage continues.

It has been suggested that gastrointestinal injury may be an important cause of multiple organ failure by way of inflammatory mediator release and/or translocation of bacterial products. Disruption of bowel motility or absorption, as a consequence of ischaemia, may also complicate nutritional management. While the importance of bowel ischaemia as a cause of organ dysfunction in critically ill patients remains to be clarified, there is substantial agreement that bowel injury in critically ill patients should be avoided or minimised. Currently, our inability to monitor bowel injury makes such an aim difficult to achieve.

The counter current arrangement of the villous blood flow enhances nutrient absorption, but results in a low mucosal oxygen saturation at villous tips, rendering the intestinal mucosa vulnerable to the effects of reduced

Correspondence to: Dr. C. Corke, Intensive Care Unit, The Geelong Hospital, Geelong, Victoria 3220.
(e-mail: charliec@barwonhealth.org.au)

oxygen delivery in shock states.[3] In addition, splanchnic vasoconstriction has been observed to persist long after fluid resuscitation has restored normal systemic haemodynamic parameters.[4,5] These observat-ions 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 perit-onitis 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.[6] Intestinal permeability to macromolecules increases in association with intestinal infarction[7,8] 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.[9]

Intraluminal pCO_2

Measurement of gastric intraluminal pCO_2 has been proposed as a sensitive indicator of bowel hypoperfusion. A variation on the original technique, employing air as the equilibration medium, has some advant-ages.[10,11] Initially, a calculated intramusosal pH (pH_i) was derived from the luminal pCO_2 and the systemic bicarbonate concentration; however it has been recogn-ised that use of the systemic bicarbonate is not helpful in the interpretation. More recently, interpretation has rested on intraluminal PCO_2 alone.[12] Using a continu-ously reading pCO_2 sensor placed directly into the small bowel lumen, very rapid increases of pCO_2 have been observed following various degrees of interruption of intestinal blood flow.[12,13]

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 pCO_2 does not alter profoundly or rapidly in response to thera-peutic interventions), a lack of specificity (e.g. some patients who have a high intragastric CO_2 recover without complication) and a relatively high catheter cost. Furthermore, local CO_2 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,[14] in clinical practice, ileal access is not easy. Moreover, a marketed product is not available for naso-jejunal pCO_2 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.[15] 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.[16] 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.[17] 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), lactic dehydrogenase (LDH) and serum aspartate amino transferase (AST) has been reported.[18] An elevation in serum N-acetyl hexosaminidase (a lysosomalacid hydrolase), has also been reported in association with intestinal ischaemia, as well as with acute rejection of transplanted small intestine.[19]

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.[20] Other studies have also addressed the same problem investigating serum levels of LDH, CK, AST, ALP,[18,21] diamine oxidase[22] and hexosaminidase.[23] 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,[24] 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.[25]

Creatine phosphokinase (CK) isoenzymes have been demonstrated in the mucosa and muscularis throughout the entire gastrointestinal system in both man and dogs.[26] 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.[26]

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.[27] The CK-BB isoenzyme is very labile and has been reported to lose 95% of its activity within 90 minutes at 37 degrees centigrade,[28] 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.[28,29] 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 iso-enzymes could be of useful diagnostic significance.[29] 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.[30] However, in a case report of bowel infarction complicating acute aortic dissection, the marked rise in CK observed, was 100% CK-MM.[31]

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.[32,33] 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.[34] It has also been shown to be elevated in a rat model of necrotising enterocolitis[35] and to be a sensitive marker of small bowel allograft rejection.[36]

Phospholipase A_2 ($sPLA_2$) has recently been implicated as a key enzyme of local inflammation after gastrointestinal ischaemia-reperfusion (I/R).[37] 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.[37] Phospholipase A_2 (PLA_2) activity has been found to accumulate rapidly in the preservation media containing ischemic rat intestinal grafts, confirming a relationship between ischaemia and PLA_2 secretion.[38] The phospholipase secreted from the bowel has been reported to differ from classic type IIa PLA_2[39,40] and consequently detection of this specific phospholipase in the blood could be a useful indicator of significant intestinal injury.

Received: 8 June 2001
Accepted: 28 July 2001

REFERENCES

1. Bradbury AW, Brittenden J, McBride K, Ruckley CV. Mesenteric ischaemia: a multidisciplinary approach. Br J Surg 1995;82:1446-1459.
2. Deehan DJ, Heys SD, Brittenden J, Eremin O. Mesenteric ischaemia: prognostic factors and influence of delay upon outcome. J R Coll Surg Edinb 1995;40:112-115.
3. Mythen MG, Webb AR. The role of gut mucosal hypoperfusion in the pathogenesis of post-operative organ dysfunction. Intensive Care Med 1994;20:203-209.
4. Oud L, Haupt MT. Persistent gastric intramucosal ischemia in patients with sepsis following resuscitation from shock. Chest 1999;115:1390-1396.
5. Edouard AR, Degremont AC, Duranteau J, Pussard E, Berdeaux A, Samii K. Heterogeneous regional vascular responses to simulated transient hypovolemia in man. Intensive Care Med 1994;20:414-420.
6. Wagner R. Ischamische Schadigung and postischamische Regeneration der Dunndarmschleimhaut. Fortschr Med 1980;98:1077-1082.
7. Schlichting E, Grotmol T, Kahler H, Naess O, Steinbakk M, Lyberg T. Alterations in mucosal morphology and permeability, but no bacterial or endotoxin translocation takes place after intestinal ischemia and early reperfusion in pigs. Shock 1995;3:116-124.
8. Kong SE, Blennerhassett LR, Heel KA, McCauley RD, Hall JC. Ischaemia-reperfusion injury to the intestine. Aust NZ J Surg 1998;68:554-561.
9. Klein HM, Klosterhalfen B, Kinzel S, et al. CT and MRI of experimentally induced mesenteric ischemia in a porcine model. J Comput Assist Tomogr 1996;20:254-261.
10. Creteur J, De Backer D, Vincent JL. Monitoring gastric mucosal carbon dioxide pressure using gas tonometry: in vitro and in vivo validation studies. Anesthesiology 1997;87:504-510.
11. Venkatesh B, Morgan J, Jones RD, Clague A. Validation of air as an equilibration medium in gastric tonometry: an in vitro evaluation of two techniques for measuring air PCO2. Anaesth Intensive Care 1998;26:46-50.
12. Knichwitz G, Rotker J, Mollhoff T, Richter KD, Brussel T. Continuous intramucosal PCO2 measurement allows the early detection of intestinal malperfusion. Crit Care Med 1998;26:1550-1557.
13. Morgan TJ, Venkatesh B, Endre ZH. Continuous measurement of gut luminal PCO2 in the rat: responses to transient episodes of graded aortic hypotension. Crit Care Med 1997;25:1575-1578.
14. Walley KR, Friesen BP, Humer MF, Phang PT. Small bowel tonometry is more accurate than gastric tonometry in detecting gut ischemia. J Appl Physiol 1998;85:1770-1777.
15. Lehmann FG, Hufnagel H, Lorenz Meyer H. Fecal intestinal alkaline phosphatase: a parameter for toxic damage of the small intestinal mucosa. Digestion 1981;21:156-62.
16. Letizia C, Picarelli A, De Ciocchis A, et al. Angiotensin-converting enzyme activity in stools of healthy subjects and patients with celiac disease. Dig Dis Sci 1996;41:2268-2271.
17. Feretis CB, Koborozos BA, Vyssoulis GP, Manouras AJ, Apostolidis NS, Golematis BC. Serum phosphate levels in acute bowel ischemia. An aid to early diagnosis. Am Surg 1985;51:242-244.
18. Thompson JS, Bragg LE, West WW. Serum enzyme levels during intestinal ischemia. Ann Surg 1990;211:369-373.
19. Maeda K, Schwartz MZ, Bamberger MH, Daniller A. A possible serum marker for rejection after small intestine transplantation. Am J Surg 1987;153:68-74.
20. De Toma G, Marzano D, Salvatore P, et al. Enzymatic and metabolic changes in peripheral serum after superior mesenteric artery ligation in dogs. Ital J Surg Sci 1983;13:269-273.
21. Kazmierczak SC, Lott JA, Caldwell JH. Acute intestinal infarction or obstruction: search for better laboratory tests in an animal model. Clin Chem 1988;34:281-288.
22. Wollin A, Navert H, Bounous G. Effect of intestinal ischemia on diamine oxidase activity in rat intestinal tissue and blood. Gastroenterology 1981;80:349-355.
23. Polson H, Mowat C, Himal HS. Experimental and clinical studies of mesenteric infarction. Surg-Gynecol-Obstet 1981; 153:360-2.

24. Delaney CP, O'Neill S, Manning F, Fitzpatrick JM, Gorey TF. Plasma concentrations of glutathione S-transferase isoenzyme are raised in patients with intestinal ischaemia. Br J Surg 1999;86:1349-1353.
25. Morris S, Hays W, Enomoto M, et al. Serum cytosolic beta-glucosidase elevation and early ischemic injury to guinea pig small intestine. Surgery 1999;125:202-210.
26. Graeber GM, Cafferty PJ, Wolf RE, Harmon JW. An analysis of creatine phosphokinase in the mucosa and the muscularis of the gastrointestinal tract. J Surg Res 1984;37:376-382.
27. Fried MW, Murthy UK, Hassig SR, Woo J, Oates RP. Creatine kinase isoenzymes in the diagnosis of intestinal infarction. Dig-Dis-Sci 1991; 36:1589-93.
28. Smirniotis VE, Labrou AT, Tsiftses DD. Plasma level of the creatine phosphokinase BB isoenzyme during experimental intestinal ischemia. Ann Vasc Surg 1989;3:8-10.
29. Graeber GM, Cafferty PJ, Reardon MJ, Curley CP, Ackerman NB, Harmon JW. Changes in serum total creatine phosphokinase (CPK) and its isoenzymes caused by experimental ligation of the superior mesenteric artery. Ann Surg 1981;193:499-505.
30. Samaniego Munoz M, Sanchez Navarro MR. CK-BB serica. Marcador bioquimico en la enterocolitis necrotizante neonatal. An Esp Pediatr 1996;44:577-580.
31. Cavaliere F, Martinelli L, Guarneri S, Morelli M, Possati GF, Schiavello R. Creatine-kinase isoenzyme pattern in colonic infarction consequent to acute aortic dissection. A case report. J Cardiovasc Surg Torino 1993;34:263-265.
32. Kanda T, Fujii H, Fujita M, Sakai Y, Ono T, Hatakeyama K. Intestinal fatty acid binding protein is available for diagnosis of intestinal ischaemia: immunochemical analysis of two patients with ischaemic intestinal diseases. Gut 1995;36:788-791.
33. Kanda T, Fujii H, Tani T, et al. Intestinal fatty acid-binding protein is a useful diagnostic marker for mesenteric infarction in humans. Gastroenterology 1996;110:339-343.
34. Gollin G, Marks C, Marks WH. Intestinal fatty acid binding protein in serum and urine reflects early ischemic injury to the small bowel. Surgery 1993; 113:545-51.
35. Gollin G, Marks WH. Elevation of circulating intestinal fatty acid binding protein in a luminal contents-initiated model of NEC. J Pediatr Surg 1993;28:367-370.
36. Marks WH, Gollin G. Biochemical detection of small intestinal allograft rejection by elevated circulating levels of serum intestinal fatty acid binding protein. Surgery 1993;114:206-210.
37. Koike K, Moore EE, Moore FA, Carl VS, Pitman JM, Banerjee A. Phospholipase A2 inhibition decouples lung injury from gut ischemia-reperfusion. Surgery 1992;112:173-180.
38. Sonnino RE, Pigatt L, Schrama A, Burchett S, Franson R. Phospholipase A2 secretion during intestinal graft ischemia. Dig Dis Sci 1997;42:972-981.
39. Fukushima T, Serrero G. Characterization of calcium-independent cytosolic phospholipase A2 activity in the submucosal regions of rat stomach and small intestine. Lipids 1994;29:163-169.
40. Mansbach CMd, Pieroni G, Verger R. Intestinal phospholipase, a novel enzyme. J Clin Invest 1982;69:368-376.