Review article: diagnosis and management of mesenteric ischaemia with an emphasis on pharmacotherapy

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SUMMARY
Mesenteric ischaemia results from decreased blood flow to the bowel, causing cellular injury from lack of oxygen and nutrients. Acute mesenteric ischaemia (AMI) is an uncommon disorder with high morbidity and mortality, but outcomes are improved with prompt recognition and aggressive treatment. Five subgroups of AMI have been identified, with superior mesenteric artery embolism (SMAE) the most common. Older age and cardiovascular disease are common risk factors for AMI, excepting acute mesenteric venous thrombosis (AMVT), which affects younger patients with hypercoaguable states. AMI is characterized by sudden onset of abdominal pain; a benign abdominal exam may be observed prior to bowel infarction. Conventional angiography and more recently, computed tomography angiography, are the cornerstones of diagnosis. Correction of predisposing conditions, volume resuscitation and antibiotic treatment are standard treatments for AMI, and surgery is mandated in the setting of peritoneal signs. Intraarterial vasodilators are used routinely in the treatment of non-occlusive mesenteric ischaemia (NOMI) and also are advocated in the treatment of occlusive AMI to decrease associated vasospasm. Thrombolytics have been used on a limited basis to treat occlusive AMI. A variety of agents have been studied in animal models to treat reperfusion injury, which sometimes can be more harmful than ischaemic injury. Chronic mesenteric ischaemia (CMI) usually is caused by severe obstructive atherosclerotic disease of two or more splanchnic vessels, presents with post-prandial pain and weight loss, and is treated by either surgical revascularization or percutaneous angioplasty and stenting.

INTRODUCTION
Intestinal ischaemia refers to the process whereby blood flow to the bowel is decreased with cellular injury consequent to diminished supply of oxygen and nutrients.\(^1\) Intestinal ischaemia can be classified temporally (acute vs. chronic), by location (small bowel vs. colonic) and by vessel (artery, arteriole, vein, venule) involved. The focus of this article will be acute mesenteric ischaemia (AMI), which can be further subcategorized: superior mesenteric artery embolus (SMAE), non-occlusive mesenteric ischaemia (NOMI), superior mesenteric artery thrombosis (SMAT), focal segmental ischaemia (FSI) and acute mesenteric venous thrombosis (AMVT). This article will review briefly the epidemiology, pathophysiology and clinical presentation of mesenteric ischaemia, but an emphasis will be placed on diagnosis and treatment with particular attention to pharmacologic therapy.

Epidemiology
AMI is an uncommon occurrence, accounting for approximately 0.1% of hospital admissions.\(^1\) A rising
incidence in the past quarter century has been attributed to a heightened awareness of gastrointestinal ischemic disease as well as an increase in the number of people at risk for AMI because of aging populations and advances in the treatment of cardiovascular diseases allowing patients to survive what previously were fatal conditions. The overall mortality rate remains high at 71%; however, survival rates are significantly improved when AMI is diagnosed and treated in an expeditious manner (under 24 h) especially when mesenteric angiography and splanchnic vasodilators are used. The most common cause of AMI is SMAE, accounting for approximately 50% of the cases, with NOMI following at 25%. SMAT (10%), MVT (10%) and FSI (5%) are responsible for the remainder of cases.

**Pathophysiology**

Knowledge of the anatomy of the splanchnic circulation is inherent to an understanding of intestinal ischemia. The major branches of the celiac, superior mesenteric and inferior mesenteric arteries and the organs that they supply are reviewed in Table 1.

Extensive collateralization between splanchnic vessels serves as a protective mechanism against ischemia. The inferior and superior pancreaticoduodenal arteries anastomose the CA and SMA; rarely these two main vessels are connected via the arc of Buhler. Three major anastomoses between the SMA and IMA exist: the marginal artery of Drummond, the central artery and the arc of Riolan. On angiography, the ‘meandering artery’ represents a dilated central artery or arc of Riolan and may be diagnostic of an occluded SMA or IMA. The internal and external iliac arteries, femoral artery and aorta also form anastomoses with the IMA. In general, the stomach, duodenum and rectum rarely are compromised by vascular events because of extensive collateral blood supply, while the splenic flexure and sigmoid colon are particularly vulnerable to ischemic injury because of a relative paucity of collateralization.

In addition to the protection offered from collateral blood supply, the bowel has several other mechanisms to prevent ischemic injury. A network of intramural submucosal vessels helps preserve segments of bowel even when extramural arterial supply has been diminished severely. Further, redistribution of intramural blood supply occurs with ischemia, favouring preservation of the mucosa. It has been demonstrated that the bowel can endure a 75% decrease in its blood supply for up to 12 h without significant injury. Two mechanisms may account for this observation: first, under normal physiologic conditions, only 20% of the mesenteric capillaries are open and utilizing oxygen at any one time; second, when oxygen delivery is decreased, the bowel adapts by increasing oxygen extraction. When the aforementioned parameters are exceeded, however, these compensatory mechanisms are overwhelmed and no longer protective.

Blood flow to the intestine is regulated by the sympathetic nervous system, humoral factors including angiotensin II and vasopressin, and local factors such as prostaglandins and leukotrienes. As reviewed by Brandt and Boley, when a major intestinal artery is obstructed, a reduction in pressure in the distal arterial bed below systemic pressure triggers the opening of collaterals. After several hours, however, the distal arteries begin to vasoconstrict resulting in an increased pressure, which consequently decreases collateral flow. Vasoconstriction initially is reversible, but may become irreversible after a prolonged period even if the ischemic event has been identified and corrected. In addition to hypoxia, reperfusion is another important etiologic factor in ischemic injury and plays a greater role when periods of ischemia are short; reperfusion injury will also be reviewed.

**Pathology**

A wide range of microscopic and gross pathologic findings is found in intestinal ischemia. Non-transmural necrosis (mucosal necrosis, submucosal oedema, haemorrhage and ulceration) is seen with a more subacute course, and these less severe lesions heal in time. On the other hand, bowel that has suffered transmural necrosis (infarction), gangrene or...
perforation, needs to be surgically resected; these lesions are more typically found in AMI than colonic ischaemia. Findings of intermediate severity may lead to transmural necrosis or result in fibrosis and stricture.8

Clinical aspects

Risk factors for AMI include age greater than 50 years, cardiovascular conditions including atherosclerotic disease, congestive heart failure and other low-output states, arrhythmias, valvular disease, recent myocardial infarction and hypotension.1 NOMI increasingly has become recognized after cardiopulmonary bypass in elderly patients9 and in haemodialysis patients.10 Hypercoaguable states, underlying vasculitides and intra-abdominal malignancy also have been linked to the development of AMI, particularly acute MVT. Medications and drugs such as digitalis, phenylephrine, amphetamines, vasopressin and cocaine may cause potent splanchnic vasoconstriction and have been linked to the development of NOMI.11

The overwhelming majority of patients with AMI experience abdominal pain: a more acute onset usually is observed with SMAE as opposed to the other causes of AMI.1 The classic teaching of 'pain out of proportion to findings on physical exam' often is observed in the early stages of AMI, when the abdomen is soft and even non-tender. Distention and severe tenderness with rebound and guarding develop as a consequence of bowel infarction. The rapidity with which these concerning findings develop is a function of the degree of ischaemic injury; additionally, a small proportion of patients with NOMI never experience pain, and distention is more common in this group.1 Forceful bowel evacuation may be noted by patients with SMAE. Occult bleeding is seen in 3/4 of patients with AMI, whereas gross bleeding is rare in patients with AMI and usually indicates right colon involvement.1 In the elderly, AMI more frequently manifests with non-specific symptoms such as mental status change (29%) and tachypnea (35%) while abdominal pain is seen less often than in younger patients.12 Late signs and symptoms of intestinal ischaemia include nausea, vomiting, haematemesis, fever, obstruction, back pain and shock.13

Diagnosis

Angiography. Selective catheter angiography has long been the gold standard for diagnosis of AMI. In a review of mesenteric angiography in the diagnosis of AMI, sensitivities in five of six studies have ranged between 90–100%; specificity was reported in two of these studies to be 100%.2 Not only can a diagnosis of AMI and its aetiology be established confidently by conventional angiography, but intra-arterial vasodilators can be administered and a vascular ‘roadmap’ in occlusive disease can be obtained that can aid in planning revascularization procedures. The exquisite sensitivity and therapeutic potential of angiography combine to effect a significantly improved mortality rate with a reported range of 18–53%.2 Preoperative angiography is, therefore, a valuable tool, although even the most partisan advocates of angiography would agree that it should never significantly delay what may be life-saving surgery. Disadvantages of traditional angiography are its limited availability and potential renal toxicity as well as its expense and time constraints.

Computed tomography and magnetic resonance angiography. More recently, computed tomography angiography (CTA) has been shown to be a very promising method to diagnose AMI, and is beginning to challenge traditional angiography as the diagnostic test of choice for AMI. Kirkpatrick et al. utilized biphasic multidetector row CT to image 62 patients with a clinical suspicion of AMI.14 CT scans were examined for multiple specific and non-specific findings. CT angiograms were assessed for suggestion of emboli and thrombi in the CA, SMA or IMA. The scan was considered positive for the diagnosis of AMI if the radiologist’s final impressions were recorded as ‘consistent with,’ ‘concerning for’ or ‘diagnostic of’ mesenteric ischaemia although the criteria for categorization was unclear. Patients were later divided into study and control groups: the former group included 26 patients who were ultimately diagnosed with AMI by surgery, pathology or both (except for one diagnosed presumptively by imaging studies and managed conservatively). This method yielded 100% sensitivity and 89% specificity. When the data were re-examined using a combination of defined radiologic criteria the authors determined that a calculated specificity of 94% and a sensitivity of 96% could be achieved. The contribution of the angiographic component aside from other CT findings also was studied: angiographic findings were believed to independently alter the course of 19% of patients with AMI either by making the diagnosis of AMI when CT alone did not or by identifying a vascular
event that required revascularization. A mortality rate of 42% in studied patients with documented AMI was observed. While these data are very encouraging, the authors of this study believe that CTA may fall short of standard angiography in terms of diagnosing NOMI as well by its inability to allow treatment with intra-arterial vasodilators.

Magnetic resonance angiography (MRA) is another of the newer imaging modalities used as a diagnostic test for mesenteric ischaemia. At this time, MRA lacks adequate resolution to diagnose NOMI secondary to low-flow states or to identify distal embolic disease. In evaluation of CMI, however, contrast-enhanced MRA has demonstrated excellent sensitivity and specificity for the detection of major splanchnic vessel stenoses and occlusions, although sensitivity is attenuated for smaller peripheral vessels and specificity may be lower for IMA stenosis. The findings of splanchnic artery occlusions, however, are not alone sufficient to diagnose CMI; to this end, functional MRA also has been studied: the normal increase in post-prandial SMV flow compared with SMV flow in the fasting state has been shown to be less in patients with CMI compared with controls. Additionally, the ratio of post-prandial SMV flow increase to SMA flow increase is less in patients with CMI compared with controls. While not yet routinely available, functional MRA may hold promise for the future in helping to diagnose CMI. The major advantage of MRA over CT angiography or conventional angiography is its lack of renal toxicity.

Other radiologic tests. Although poorly sensitive (30%) and non-specific, plain films of the abdomen are nevertheless almost always obtained in the work-up of patients with suspected intestinal ischaemia and may be complementary to CT imaging. In many hospitals, however, CT scanning has replaced plain film use. Early in the course of AMI, abdominal films usually are normal. In late-stage AMI, one may observe an ileus, ‘thumbprinting,’ formless or focally dilated thickened loops of small bowel, pneumatosis, and more rarely portal or mesenteric venous gas. The main purpose of plain films is to identify other causes of abdominal pain that might mandate a therapeutic approach different from that for AMI.

Standard CT of the abdomen lacks sufficient sensitivity to be used as a diagnostic test for AMI. In a comprehensive study evaluating CT as a diagnostic modality for AMI, CT scans from a control group were compared retrospectively with CT scans from patients with documented AMI. CT scans were ‘positive’ if any one of the following criteria were met: SMA or SMV occlusion, pneumatosis intestinalis, portal venous gas, lack of bowel wall enhancement or solid organ infarction. Using this method, specificity was determined to be 92%, while sensitivity was calculated at only 64%, and thus CT has been considered unacceptable as a diagnostic test for AMI. One exception to this opinion is when the aetiology of the ischaemia is secondary to MVT, which CT has demonstrated a sensitivity of 100% for acute MVT and 93% for chronic MVT.

Doppler ultrasound in the diagnosis of mesenteric ischaemia has excellent specificity, but its sensitivity is limited by four significant factors: first, only the proximal portions of the main splanchnic vessels can be studied; second, vessel occlusions or stenoses identified by this technique are not diagnostic of intestinal ischaemia given that complete occlusions in two or even all three vessels can be seen in asymptomatic patients; third, blood flow through the SMA is highly variable which can make interpretation of this test difficult; fourth, NOMI cannot be diagnosed by Doppler ultrasound.

Serologic markers. While laboratory tests often are abnormal in patients with AMI, they are neither sufficiently sensitive nor specific to diagnose AMI early enough to improve prognosis. This holds true for serum levels of inorganic phosphate and standard enzyme determinations such as creatinine kinase, lactate dehydrogenase, aspartate transferase and alkaline phosphatase (including the intestinal isoenzyme). More specific enzymes including diamine oxidase and hexosaminidase also lack sufficient sensitivity and specificity to diagnose AMI. More recently, the α-subunit of glutathione S-transferase, a family of cytosolic enzymes widely distributed in the intestine, has been shown to be a promising marker for intestinal ischaemia. Similarly, intestinal fatty acid binding protein (I-AFBP), accounting for 2% of intestinal protein and located at mucosal villi tips, may be a useful test in both adults with intestinal ischaemia and neonates with necrotizing enterocolitis.

As reviewed by Kurland et al., metabolic acidosis is neither sensitive nor specific enough to be used as an aid in diagnosing AMI. Leukocytosis is a common finding in AMI, with an elevated white blood cell count over 15 000/mL seen in more than 75% of patients with AMI. Thus, a normal WBC cannot reliably
exclude AMI but neither can an elevated one clinch the diagnosis given its lack of specificity.

Other diagnostic tests. Peritoneal lavage in animal studies has revealed elevated WBC, inorganic phosphate, LDH, aldolase, alkaline phosphatase and lactic acid, but this diagnostic technique has not been extensively studied in humans. Other diagnostic tests. Peritoneal lavage in animal studies has revealed elevated WBC, inorganic phosphate, LDH, aldolase, alkaline phosphatase and lactic acid, but this diagnostic technique has not been extensively studied in humans.21

Tonometry is a technique that permits the indirect measurement of intestinal intramural pH (pHt). A decrease in pHt reflects a decrease in oxygen delivery to the gut and results from a shift to anaerobic metabolism with subsequent cellular acidosis. Grum et al. used a canine model to show that pHt dropped precipitously when blood flow (oxygen delivery) was decreased below 60% of baseline.25 Tonometry has been applied to predict multiple organ failure and death in the intensive care unit setting,26 to help diagnose chronic mesenteric ischaemia27 and to assess for colonic ischaemia after abdominal aortic surgery.28

Laparoscopy may be used as a diagnostic test for mesenteric ischaemia with two caveats: first, intraperitoneal pressure exceeding 20 mmHg decreases SMA blood flow,29 and second, mucosal injury may exist and be unappreciated in the absence of serosal evidence of ischaemia, leading to a false negative conclusion.21 The latter is explained by the mucosal-to-serosal shunting of blood flow that occurs with increased intestinal intraluminal pressure. Upper endoscopy to evaluate for mesenteric ischaemia is limited by the reach of the instrument; colonoscopy in the diagnosis of colonic ischaemia, however, has become routine.21 As reviewed by Kurland et al., endoscopists should be aware that intraluminal pressures above 30 mmHg have been shown to decrease blood flow to the colon and the small bowel. Of note, when CO2 was used to insufflate the colon in dogs, the period of distention and elevated pressure was shorter than when room air was used because CO2 is more readily absorbed than is air. Further, blood flow actually was increased with CO2 insufflation, owing to its vasodilating properties.30 While the practice of using CO2 has not been widely adopted into practice, every effort should be made to minimize the period of colonic distention during colonoscopy to avoid the potential of iatric ischaemic injury.

Intravenous fluorescein has been used both endoscopically and intraoperatively to define areas of ischaemia; the underperfused ischaemic areas of bowel demonstrate proportionally less fluorescence than does the bowel with normal blood flow.21 Radioisotope studies, laser Doppler flowmetry, reflectance spectrophotometry and superconducting quantum interference devices (SQUID) are other experimental modalities that have been studied in the diagnosis of intestinal ischaemia although not yet been applied clinically.21, 31

Treatment

General principles of treatment of acute mesenteric ischaemia. All patients with suspected AMI should undergo volume resuscitation and treatment with broad-spectrum antibiotics as well as correction of any potential underlying mechanisms of AMI such as arrhythmias or congestive heart failure.1 Bacterial translocation has been shown to occur during AMI owing to loss of mucosal integrity.32 Experimental studies have shown decreased mortality with peri-ischaemic event fluid resuscitation and antibiotic treatment.33 Typically, intravenous antibiotic coverage for both Gram-negative and anaerobic organisms is used, but one study in rats with SMA transection comparing gentamicin and metronidazole suggested that antibiotic coverage for anaerobes and not Gram-negative bacteria may be more important in the treatment of mesenteric ischaemia.34 Animals treated with either enterically injected or intravenous metronidazole or a combination of metronidazole and gentamicin survived significantly longer than animals treated with gentamicin alone. The authors hypothesized that metronidazole was more effective for several reasons: first, anaerobic bacteria may play a more important role than Gram-negative aerobes in early ischaemic injury in the setting of decreased blood and oxygen delivery; second, metronidazole may be effective at eliminating aerobic bacteria as well as anaerobic bacteria while the reverse cannot be said of gentamicin; or third, Gram-negative aerobes may be important in early ischaemic injury but gentamicin is not effective against them under anaerobic conditions. Metronidazole was slightly more effective when injected enterally, perhaps pointing to a need for high intraluminal concentrations, which may not be as readily achieved with intravenous administration in the setting of blood flow obstruction.34

Occlusive acute mesenteric ischaemia: superior mesenteric artery embolism and superior mesenteric artery thrombosis. SMAE generally arise from ventricular or left atrial thrombi, often in the setting of atrial fibrillation. Many
patients have histories of peripheral arterial emboli, and concomitant peripheral emboli are seen in 20% of patients. Typically, SMAE are found at points of normal anatomic narrowing, frequently just distal to the origin of a major vascular branch. They are classified as ‘major’ emboli when found proximal to the origin of the ileocolic artery and ‘minor’ if distal to this point or in one of the distal branches of the SMA. Angiographically, SMAE are characterized by rounded filling defects that result in occlusions to flow; evidence of atherosclerotic disease is seen to a lesser extent with emboli than with thrombosis.1

SMAT is found most commonly in areas of severe atherosclerotic disease, usually at the origin of the SMA. A 20–50% of patients with SMAT report postprandial pain and weight loss compatible with CMI. Coronary artery disease, stroke and peripheral artery disease are frequent comorbidities. Angiography typically demonstrates an occlusion 1–2 cm distal to the origin of the SMA. Sometimes it can be difficult to differentiate an acute thrombosis from one that is chronic and incidental: the finding of collateral vessels that provide good filling of the SMA argues against an acute thrombosis, and other aetiologies for the patient’s symptoms should be sought. Alternatively if collateral vessels cannot be appreciated or adequate collateral filling of the SMA is not seen then the thrombosis must be considered to be acute and appropriate treatment begun.1

Treatment of occlusive AMI is highly dependent upon the presence or absence of peritoneal signs: when such signs are present, a patient must undergo an exploratory laparotomy. Surgical interventions include resection of necrotic and perforated bowel with thromboembolotomy, patch angioplasty, endarterectomy and bypass procedures,35 depending on individual vascular anatomy and cause of the occlusion, e.g. embolus or thrombus. In the case of bowel perforation, peritoneal lavage with saline and antibiotics is performed to reduce bacterial load. ‘Second-look’ operations are recommended in cases where there is questionable bowel viability during the first surgery, in an attempt to minimize the amount of bowel initially resected. The time in between the index surgery and the second-look procedure is used to maximize bowel survival, e.g. antibiotics, fluid replacement and correction of adverse comorbidities. Percutaneous transluminal angioplasty also has been successful in one case report of a patient with SMAT and peritoneal signs,36 but generally is not advocated given the significant risk of re-thrombosis.

Thrombolytics
In patients without suspected peritonitis, thrombolytics have been used successfully to treat SMA emboli and to a lesser extent, thrombi. The pertinent literature, however, consists of only case reports and small case series; agents that have been used include streptokinase, urokinase and tissue plasminogen activator (t-PA) (Table 2). To date, no studies have directly compared any of these agents to each other or to other treatments.

Pharmacology of thrombolytics
Plasmin, a key element in the body’s endogenous fibrinolytic system, is a protease that dissolves thrombi by breaking down fibrin and other proteins of the clotting cascade including fibrinogen (precursor to

Table 2. Specific thrombolytics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Source</th>
<th>Mechanism of action</th>
<th>Dose</th>
<th>Half-life</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
<td>protein produced by Group C β-haemolytic streptococci and purified for clinical use</td>
<td>forms complex with plasminogen, which then cleaves the Arg560–Val561 ‘activator bond’ to convert both complexed and free plasminogen to plasmin</td>
<td>250 000 U (2.5 mg) intra-arterial bolus or low-dose continuous infusion with 5000–10 000 U/hr</td>
<td>12–18 min</td>
<td>least expensive, risk of allergic reaction (3%), sufficient dose must be given to overcome possible neutralization with antibodies to streptococcus, acts on both bound and free plasminogen</td>
</tr>
<tr>
<td>Urokinase</td>
<td>cultured from human kidney cells</td>
<td>directly activates plasminogen by cleaving Arg560–Val561</td>
<td>200 000–250 000 U intra-arterial bolus, followed by infusion of 60 000–120 000 U/hr</td>
<td>15–20 min</td>
<td>expensive, acts on both bound and free plasminogen</td>
</tr>
<tr>
<td>Tissue plasminogen activator (t-PA)</td>
<td>recombinant human serine protease</td>
<td>binds to fibrin and is activated by cleavage of an arginine–isoleucine bond after which it activates plasminogen by cleavingArg560–Val561</td>
<td>20 mg ‘slow’ intra-arterial bolus, followed by a subsequent 20 mg bolus 12 h later</td>
<td>2–6 min</td>
<td>most expensive, ‘fibrin-selective’ as acts primarily on fibrin-bound plasminogen</td>
</tr>
</tbody>
</table>

*Doses that have been reported in case studies and series.
fibrin) and coagulation factors V and VIII.37 Plasminogen is converted to plasmin by the cleavage of a single arginyl–valyl bond, also known as the Arg560–Val561 ‘activator bond’.38 Endogenous t-PA and urokinase serve as plasminogen activators: t-PA converts predominantly fibrin-bound plasminogen to plasmin; urokinase, produced by human kidney cells, helps keep hollow organs such as the ureter, free from thrombi. Fibrinolysis is regulated primarily by inhibitors of both plasmin and plasminogen;37 however, when thrombolytics are used, these inhibitory controls become overwhelmed, and haemorrhage is thus a feared side effect. Because of its fibrin specificity, t-PA is theoretically safer in terms of haemorrhagic risk, but this advantage has not been borne out clinically. Contraindications to thrombolytic therapy relate primarily to increased risk of bleeding, including recent surgery, trauma or severe GI bleeding; severe hypertension; active bleeding or haemorrhagic disorder; previous CVA or active intracranial process; and pregnancy or puerperium.39

The largest case series of thrombolytic therapy for AMI40 evaluated 10 patients who presented with acute abdominal pain of 5–18 h duration; all had angiographically proven SMAE, two with major and eight with minor emboli. No patients had peritoneal signs on examination, and all had normal abdominal plain films. Urokinase (200 000 U) was infused directly into the embolus, followed by infusion of urokinase at 100 000 U/h into the SMA proximal to the embolus until angiographic resolution of the embolus; infusion times ranged between 8 and 32 h. All patients received simultaneous systemic heparin at 1000 U/h, which was continued for 4 days after urokinase treatment and was followed by warfarin indefinitely, if fibrinolysis was successful. Response to treatment was assessed by repeated clinical assessment and angiography 4–6 h after beginning treatment and thereafter at regular intervals as appropriate, depending on clinical and radiologic results. Resolution of the occlusion was defined by normal angiography or the presence of only tiny non-obstructing emboli with normal blood flow. Follow-up angiography showed successful lysis of emboli in 90% of patients, and resolution of abdominal pain within 1 h of infusion in 70% of patients. One of these seven patients underwent exploratory laparotomy because of equivocal physical examination findings and was found to have normal bowel. All three patients who continued to have abdominal pain and/or developed peritoneal signs and the one patient who did not have successful thrombolysis under-

went surgery with bowel resection. The one death in this group was believed secondary to cardiac insufficiency and was without demonstrable abdominal pathology. The authors of this study believed resolution of abdominal pain within 1 h to be the most significant factor in predicting the success of fibrinolysis and also cautiously pointed out that in contrast to classic dogma, duration of symptoms prior to diagnosis and treatment did not seem to be related to outcome. No complications occurred from urokinase therapy, and no patient suffered from recurrent embolism or post-ischaemic stenoses in follow-up over an average period of 11 months.

Many questions with regard to fibrinolysis remain to be studied including optimal agent and dose, method of delivery (pulse-spray, intraembolic, slower infusions), length of treatment, whether treatment should vary depending on emboli location or duration of symptoms, role of adjunctive anticoagulation and its optimal duration, criteria to help define need for surgery and the best means of routine post-lytic evaluation.

Vasodilators

Both canine and human studies have shown vasodilator therapy to be beneficial for AMI secondary to SMAE or SMAT because splanchnic vasoconstriction accompanies acute embolic and thrombotic mesenteric disease. Vasodilators rarely are used alone in these situations, however, unless patients are judged to be poor operative candidates. As previously reviewed, mesenteric vasoconstriction may develop and persist for hours, causing irreversible ‘non-occlusive’ ischaemia, even after surgery or thrombolytic therapy for SMAE or SMAT.

The beneficial effect of papaverine was demonstrated in a small study of dogs with iatrogenic SMA occlusion, comparing dogs treated with intra-arterial saline (n = 5) with dogs treated with intra-arterial papaverine (n = 10).41 Twenty-four-hour survival was 20% in the saline group compared with 100% in the papaverine group. Further, bowel infarction was demonstrated in control group dogs except the one who survived, while all dogs in the papaverine group had normal intestines. Serial angiograms showed partial resolution of mesenteric vasoconstriction and better preservation of collateral blood flow in the dogs treated with papaverine.

A subsequent canine study by the same group compared animals with iatrogenic SMAE treated with intra-arterial saline (n = 3), intra-arterial papaverine...
(n = 5), intra-arterial streptokinase (n = 5) or both papaverine and streptokinase (n = 5). Post-treatment angiograms and pathologic examination revealed that although the group treated with streptokinase had the most vigorous response in terms of embolus lysis, the group treated with papaverine had less vasoconstriction, better perfusion and less bowel necrosis than any of the other three groups. Interestingly, the vasodilative and thrombolytic effects of the papaverine and streptokinase, respectively, were attenuated in the group treated with both agents. Fondacaro et al. found that the vasodilators prostacyclin, prostaglandin D₂ and 2-chloroadenosine each reversed the digoxin-induced ischaemia and hypoxia experimentally created in a canine model. Clinically, Boley et al. demonstrated a decreased mortality rate of 54% (compared with 70–80% mortality in traditionally managed patients) when an aggressive approach utilizing early angiography and papaverine was taken in the management of patients with suspected AMI.

Because of these successful experimental and clinical outcomes, papaverine is used frequently both pre- and post-operatively to reduce the splanchnic vasoconstriction that typifies NOMI and accompanies SMAE, SMAT and even AMVT. To date, however, no randomized controlled studies have been conducted to confirm the efficacy of this approach. Studies in which embolectomy and papaverine was taken in the management of patients with suspected AMI.

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Pharmacology of papaverine. Papaverine is a non-selective vasodilator extracted from the poppy plant (genus Papaver); it inhibits phosphodiesterase, resulting in increased levels of intracellular cyclic AMP (cAMP), the net effect of which is smooth muscle cell relaxation. In its use as a vasodilator for AMI, papaverine is administered as a bolus dose of 60 mg directly into the SMA, followed by a constant infusion of 30–60 mg/h. Priscoline, an α-receptor antagonist, sometimes is administered prior to papaverine to assess mesenteric responsiveness to vasodilation. Few systemic side effects from papaverine are found owing to its high first pass metabolism of 90%. Complete AV block is a contraindication to papaverine treatment as large doses may depress AV conduction.

Proponents of vasodilator therapy recommend that preoperative intra-arterial papaverine be started during the index angiography if possible, and continued for 12–24 h postoperatively if no second-look surgery is planned, and through the second procedure if one is planned. In either case, angiography should be done before removal of the catheter to confirm that vasospasm does not persist. Complications from repeated angiographic studies include acute tubular necrosis, local haematomas and catheter dislodgement.

The concept of postocclusive vasoconstriction and thus the benefit of vasodilators in treating occlusive mesenteric ischaemia has been challenged by some experimental studies. Bulkley et al. found in rats that collateral blood flow to segments of bowel undergoing very brief arterial occlusions (70–90 s) was dependent primarily upon vasodilation within the ischaemic vascular bed. In a canine model, this same group subsequently demonstrated that intra-arterial vasodilator treatment of similarly brief bowel vascular occlusion had only a minimal effect on vascular resistance within the ischaemic bed but significantly diluted the non-ischaemic bed: perfusion pressure was thus decreased in the non-ischaemic bed and in the collaterals feeding the ischaemic bed. Bulkley’s studies are flawed by the artificial and extreme brevity of vascular occlusion, making his results inapplicable to the clinical situation.

Meilahn et al. conducted a study to examine the effect of continued infusion of vasodilator during a prolonged period of vascular occlusion. Via arterial ligation, ischaemia was induced in rat ileum so that only collateral vessels from adjacent non-ischaemic bowel supplied blood flow to this area; a 48-h continuous SMA infusion of papaverine (at two different doses), isoproterenol, norepinephrine or normal saline was administered. Bowel viability was assessed blindly by both gross and histological examination. Although both papaverine and isoproterenol resulted in increased SMA blood flow acutely without change in systemic blood pressure, viable bowel lengths in both papaverine groups and the isoproterenol group were shorter than those of the control group. The authors explained this finding by postulating that the non-ischaemic vasculature preferentially was dilated, thus destroying the previously established flow gradient created by the preferential dilation of the ischaemic bed over the non-ischaemic bed. They concluded that this study was relevant only for permanent occlusions.

Glucagon is another potentially therapeutic agent that has been studied in experimental models of occlusive mesenteric ischaemia. Glucagon is an endogenous
peptide synthesized in the A cells of the pancreatic islets of Langerhans and has three main actions: relaxation of smooth muscle with consequent vasodilation (particularly in the small intestine); cardiac inotropy and chronotropy; and the promotion of glycogen catabolism, gluconeogenesis and ketogenesis. Several animal studies have demonstrated marked improvement in SMA blood flow when glucagon was utilized in the setting of a post-ischaemic event. Clark and Gewertz, however, found that glucagon given before, during and after occlusion of the SMA may potentiate reperfusion injury in rats with SMA occlusion, an effect which they hypothesized was secondary to glucagon’s action to increase metabolism. In contrast, Gangadharn et al. showed improved intestinal viability when glucagon was administered early in the reperfusion phase after segmental ischaemia was relieved; the authors attribute the difference in findings to the timing of glucagon’s administration.

Non-occlusive mesenteric ischaemia. NOMI results from vasoconstriction that initially serves as a protective mechanism in the setting of a cardiovascular event such as acute myocardial infarction with shock, arrhythmias, congestive heart failure, hypovolemia associated with burns, pancreatitis, haemorrhage and sepsis; cirrhosis and renal failure/dialysis are also risk factors. Splanchnic vasoconstrictors such as α-adrenergic agents and digitalis also have been linked to NOMI. The incidence of NOMI has decreased significantly in recent years, likely owing to improved monitoring capabilities of hemodynamic parameters in the intensive care setting as well as the widespread use of vasodilating agents in the management of congestive heart failure and myocardial infarction. Vasoconstriction which initially is reversible may become irreversible if it is not corrected quickly, even after removal of the precipitating cause. Angiographically, four signs help to reliably diagnose NOMI: narrowing at the origins of SMA branches, alternating dilation and narrowing in the intestinal branches (the ‘string-of-sausages’ sign), spasm of the vascular arcades and impaired filling of intramural vessels.

An algorithm for management of NOMI proposed by Boley et al. over 25 years ago is still the treatment regimen with the best survival rates. As soon as angiographic diagnosis is established, intra-arterial papaverine is initiated with a bolus of 60 mg and then infused at a dose of 30–60 mg/h. If peritoneal signs remain absent or remit within 20–30 min after papaverine infusion has begun, then papaverine is continued and repeat angiography is performed in 24 h to document absence of or improvement in vasospasm. Papaverine infusion may be stopped at this point or continued for up to 5 days if vasospasm persists; optimally an angiogram would be repeated daily during infusion. If peritoneal signs are newly noted or persist after papaverine is started, then exploratory laparotomy is mandated with resection of bowel as needed. Second-look procedures are done if bowel viability is in question. Papaverine is continued perioperatively and postoperatively for 24 h or until the time of the second look operation.

Experimental treatment in non-occlusive mesenteric ischaemia

Bailey et al. have demonstrated that mesenteric vasoconstriction is mediated in large part by the renin–angiotensin axis. Bailey and colleagues showed in pigs subjected to prolonged pericardial tamponade, that blockade of this pathway either by intravenously infused angiotensin converting enzyme inhibitor (ACEi) or by bilateral nephrectomy protected the small bowel from ischaemia. Further, phenoxybenzamine, an α-adrenergic inhibitor was not protective against the development of ischaemic changes; this finding contradicts the theory that the sympathetic nervous system primarily regulates mesenteric vasoconstriction. These findings may be difficult to extrapolate to hypovolemic-induced ischaemia given the different pathophysiology of tamponade-induced cardiogenic shock. A subsequent experimental study supported this study’s findings: intra-arterial captopril given at the beginning of shock reduced the extent of tamponade-induced mesenteric ischaemia in piglets. The narrow window of time in which the ACEi must be administered to be effective, however, limits its clinical application, although the prophylactic use of ACEi in high-risk patients is an intriguing idea. The risk of systemic hypotension with an ACEi also needs to be considered in the clinical setting. Glucagon, histamine and perhexiline also have been shown to restore blood flow and oxygen consumption via vasodilation in dogs with digoxin-induced mesenteric vasoconstriction. Iloprost, a synthetic derivative of prostacyclin, has been shown to be beneficial in patients with peripheral vascular disease; it is a potent inhibitor of platelet...
aggregation and may also promote fibrinolysis by decreasing an inhibitor of plasminogen activation. Additionally, in low doses, it has been shown to increase SMA blood flow and oxygen delivery in septic shock. Kang et al. recently conducted an experimental study to examine the effect of intravenous iloprost in NOMI secondary to cardiac tamponade: compared with a control group given normal saline, the iloprost group was found to have increased SMA blood flow, decreased intestinal mucosal hypercarbia and increased pH; interestingly, mucosal oxygen consumption did not change significantly during its use. Unfortunately, the intestine was not studied at the conclusion of the experiment, thus making the significance of these findings less clear.56

Ovine corticotropin releasing factor, sauvagine and urotensin I are three chemically related peptides that have been shown to be selective mesenteric vasodilators in a canine model. Each intravenously administered peptide improved mesenteric blood flow and decreased mesenteric vascular resistance in animals subjected to mesenteric hemodynamic changes induced by intravenous digoxin.57 In a follow-up canine study, intravenous urotensin I was found to be as effective as intra-arterial papaverine in correcting mesenteric blood flow and oxygen kinetics. Systemic side effects were not observed with intravenous urotensin I, but as expected, hypotension was marked when papaverine was given intravenously at sufficient doses to restore mesenteric blood flow to baseline values.58 While these studies are certainly intriguing, these peptides have yet to be examined for a possible clinical role in the treatment of NOMI in humans.

Finally, gastric inhibitory peptide (GIP) is a member of the secretin–glucagon–vasoactive intestinal polypeptide family of gastrointestinal hormones and has been shown to increase SMA blood flow selectively in a canine model.59 GIP has yet to be studied in NOMI.

**Mesenteric venous thrombosis.** MVT may have an acute, subacute or chronic presentation. Patients with MVT are typically younger than those with other types of mesenteric ischaemia. MVT is associated with a myriad of hypercoagulable states (including protein C, protein S or antithrombin III deficiency, factor V Leiden mutation, anticardiolipin antibodies, malignancy, estrogens and pregnancy, and peripheral deep vein thrombosis), portal hypertension, intra-abdominal inflammation and sepsis, post-operative states, and trauma. MVT secondary to cirrhosis or neoplasm tends to start at the site of obstruction and propagate peripherally, while the opposite sequence is observed in hypercoagulable states. If collateral blood flow does not permit venous drainage around the obstructed vessel, the bowel will become congested and oedematous. Coincidental arterial vasoconstriction may occur and cause bowel infarction. Standard CT is the current diagnostic test of choice for MVT, unlike its use in patients with arterial occlusive or non-occlusive mesenteric ischaemia.1

Treatment of MVT generally involves surgery, anticoagulation or both. Surgical intervention includes resection of necrotic bowel and/or thrombectomy; thrombolytics have been used successfully in case reports. Papaverine and second-look operations are advocated as appropriate, using similar guidelines as for arterial causes of AMI.1 Traditionally it has been taught that peritoneal signs warrant immediate surgical intervention, but Brunaud et al. in a retrospective review of patients with acute MVT found that peritoneal signs do not always indicate transmural necrosis, and may be seen with only mucosal necrosis, a situation which may be reversible with anticoagulation alone. Based on his comparison of patients who were treated surgically with those who were treated medically, he suggested that non-operative management of acute MVT may be a reasonable option provided the initial CT diagnosis is unequivocal and if bowel infarction has not led to transmural necrosis and bowel perforation.60

Current recommendations for continued anticoagulation are based on whether an underlying hypercoagulable state is discovered, in which case lifelong coumadin is advocated.39 If no underlying thrombotic state is found, then anticoagulation is generally recommended for 3–6 months. Chronic MVT is primarily found in the setting of portal hypertension and is generally asymptomatic or presents with gastrointestinal bleeding from varices; treatment is aimed at control of haemorrhage.1

**Focal segmental ischaemia.** FSI is generally not a life-threatening condition as only short segments of bowel are involved and adequate collateral blood flow generally limits transmural necrosis. The aetiology of FSI is varied and includes atheromatous emboli, strangulated hernias, immune complex disorders and vasculitis, blunt abdominal trauma, segmental thrombosis, radiation therapy and oral contraceptives.1 Partial necrosis may manifest as acute enteritis, chronic enteritis (often

difficult to distinguish from Crohn’s disease) or a stricture. Definitive treatment of FSI is resection of the involved bowel.1

Chronic mesenteric ischaemia. CMI, also known as intestinal angina or claudication, almost always is caused by severe mesenteric atherosclerotic disease; over 90% of patients have occlusion of at least two of the major splanchnic vessels, and over 50% have occlusion of all three.1 Abdominal pain results from ischaemia in the small intestine as blood is ‘stolen’ from this organ to meet the heightened need for gastric blood flow as food enters the stomach. Classically, patients complain of abdominal pain that begins approximately 30 min after eating and gradually remits over the next 1–3 h; fear of eating (sitophobia) often leads to food avoidance and consequent weight loss. Diagnosis is made by clinical history, angiographic findings of at least two-vessel occlusion and the absence of any other cause for symptoms.

The mainstay of treatment for CMI is surgical bypass, although percutaneous angioplasty and stenting procedures have also been studied. Therapeutic outcomes may be difficult to assess as success has been defined in different ways, including graft patency, relief of symptoms and long-term survival. As reviewed in one recent article, means of 85% for long-term pain relief, 86% for graft patency and 7% for mortality rate were found for surgical revascularization.61 Presently, only retrospective reviews of percutaneous angioplasty and stenting are available and are hampered not only by their inherent suboptimal study design but also by lack of homogeneity in terms of patient population, procedural technique, post-procedural assessment and length of follow-up. Additionally, it may be difficult to compare surgery with percutaneous procedures as usually more vessels are bypassed in surgery than are treated percutaneously; further, generally only stenosed and not occluded vessels are treated percutaneously. Although initial success rates for percutaneous angioplasty and stenting are reported to range between 63 and 100%,1,62 long-term efficacy is generally less than that for surgery; one recent study reported recurrent symptoms in 34% of patients at 3 years.61 More recently, a study looking at patients treated with only angioplasty plus stenting found success rates equivalent to those of surgery (83% symptomatic relief at 15 months, 92% stent patency at 6 months and a 10% complication rate).62 More data are likely needed before definitive conclusions can be reached.

Experimental treatment of reperfusion injury. As mentioned previously, reperfusion injury may be more detrimental than primary ischaemic injury, especially when ischaemia is short-lived. Reperfusion injury is likely multifactorial, but oxygen radicals and polymorphonuclear cells (PMNs) are thought to be integral. Xanthine oxidase-derived oxygen radicals stimulate leukotriene B4 (LTB4) and platelet activating factor (PAF) production, which in turn promote neutrophil adherence and migration; these leukocytes mediate microvascular injury by the release of proteases and physical disruption of the endothelial barrier.7 Because the two main effectors of reperfusion injury are reactive oxygen metabolites and PMNs, it follows that they are also the major foci of experimental studies aimed at reducing reperfusion injury.

Antioxidants

Oxidants including superoxide, hydrogen peroxide and hydroxyl radicals, are logical targets in the prevention and treatment of reperfusion injury, with many different antioxidants having yielded promising results in animal models.7 As reviewed by Zimmerman, superoxide dismutase (SOD), an enzyme that scavenges O2\(^-\), has been reported to diminish increased mucosal permeability associated with reperfusion injury. Further, it has been shown that pretreatment with both SOD and non-enzymatic scavengers of the hydroxyl radical lessens ischaemia-induced reperfusion injury. Allopurinol, a xanthine oxidase (XO) inhibitor and thereby an indirect inhibitor of oxidant production, has been shown repeatedly to decrease epithelial necrosis and mucosal permeability. At high doses, allopurinol and other XO inhibitors also may attenuate ischaemia/reperfusion injury by directly scavenging oxygen radicals.7 Melatonin, caffeic acid phenethyl ester (CAPE), bilirubin, diclofenac sodium and ethyl pyruvate also have been shown to reduce ischaemic/reperfusion injury in animal models via their antioxidant effects.63–67

Biologic agents

Neutrophils are the primary cells mediating in reperfusion injury. They are a source of oxygen radicals and are also believed to be the primary mediators of
increased mucosal permeability via secretion of such enzymes as elastase. Thus, much attention in the research of treatment and prevention of reperfusion injury has focused on reducing neutrophil recruitment and adhesion. PAF receptor antagonists used in a feline model produced significant reduction in the rate of leukocyte adherence and emigration normally observed after reperfusion of ischemic mesenteric venules. Various monoclonal antibodies directed against membrane glycoproteins that mediate neutrophil adhesion to vascular endothelium also have been studied. Most recently, pretreatment with antibody directed against the intercellular adhesion molecule-1 (ICAM-1) in rats with experimentally induced intestinal ischemia has been shown to decrease not only mucosal damage, but also levels of both tumor necrosis factor-alpha (TNF-α) and myeloperoxidase (MPO). TNF-α is a cytokine released from neutrophils that may be involved in the further recruitment of neutrophils, while MPO is an enzyme found almost exclusively in neutrophils and therefore another means to measure their activity. In rats with SMA occlusion-induced ischemia, treatment with heparin-binding epidermal growth factor (EGF)-like growth factor has been shown to down-regulate the expression of ICAM-1, vascular cell adhesion molecule-1 (VCAM-1), as well as decrease neutrophil and macrophage infiltration in injured tissue. Hepatocyte growth factor has also shown to offer intestinal protection in treatment of ischemia reperfusion injury by preventing the activation of enterocyte caspase, resulting in the reduction of crypt apoptosis and cellular necrosis.

Other

Nitroglycerin serves as an exogenous donor of nitric oxide, which is believed to suppress PAF, inhibit neutrophil activation and infiltration, and scavenge reactive oxygen species. Nitroglycerin’s potentially protective role in intestinal ischemia and reperfusion injury, however, has been limited by hypotension when given intravenously. Prophylactic use of intraluminally delivered nitroglycerin in rats with SMA occlusion for 1 h followed by reperfusion for 4 h was found to decrease intestinal injury, improve bile flow and blunt a decrease in blood pressure that accompanies reperfusion.

Glycine has been shown to improve mucosal viability in rats with the ischemia-reperfusion injury by preventing the induction of apoptosis. Glucagon-like peptide-2α, a synthetic protease-resistant analogue of glucagon-like peptide has a cytoprotective effect in injured intestinal epithelium by augmenting mucosal DNA and protein content and has been shown to enhance intestinal mucosal mass and absorptive function after ischemia-reperfusion injury in rats. Similarly, interleukin-11, a multifunctional cytokine, was found to increase intestinal absorptive function after ischemia-reperfusion injury. Pancreatic proteases also have been associated with ischemia-reperfusion injury, and it is hypothesized that these enzymes have both a direct proteolytic digestive action on the protein core of the ischemic enterocytes and that they also may have a role in the conversion of xanthine dehydrogenase to xanthine oxidase, a primary source of free radicals. While the use of pancreatic protease inhibitors in animal models has been encouraging, they are unlikely to be of benefit clinically in AMI given that pretreatment is required for their efficacy. Liquid perfluorocarbons are biologically inert substances with the capability to dissolve oxygen, up to 40% by volume, compared with whole blood which dissolves only 20% by volume. Thus, intraluminally delivered perfluorocarbons have been studied as a means to transport higher concentrations of oxygen, and have been shown to decrease significantly ischemic injury. Serious side effects such as coagulopathy and ARDS have limited further research to experimental studies.

CONCLUSION

Mesenteric ischemia is a relatively uncommon cause of abdominal pain, but one with significant mortality. In the proper clinical setting, it is crucial to maintain a high index of suspicion so that a correct diagnosis may be made and treatment initiated expeditiously. There are many different variants of AMI, the most common of which is SMAE. For most types of AMI, the diagnostic test of choice is CT angiography or conventional angiography; MVT may be diagnosed accurately with standard CT. Treatment also is dependent upon the type of AMI, but in most situations any patient with peritoneal signs should be operated upon without delay. Medical treatments include antibiotics, vasodilators, thrombolytics, anticoagulants, with a host of experimental agents being studied for both primary ischemia and reperfusion injuries.
REFERENCES


