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EDITORIAL

Challenges in diagnosing mesenteric ischemia

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Abstract

Early identification of acute mesenteric ischemia (AMI) is challenging. The wide variability in clinical presentation challenges providers to make an early accurate diagnosis. Despite major diagnostic and treatment advances over the past decades, mortality remains high. Arterial embolus and superior mesenteric artery thrombosis are common causes of AMI. Non-occlusive causes are less common, but vasculitis may be important, especially in younger people. Because of the unclear clinical presentation and non-specific laboratory findings, low clinical suspicion may lead to loss of valuable time. During this diagnostic delay, progression of ischemia to transmural bowel infarction with peritonitis and septicemia may further worsen patient outcomes. Several diagnostic modalities are used to assess possible AMI. Multi-detector row computed tomographic angiography is the current gold standard. Although computed tomographic angiography leads to an accurate diagnosis in many cases, early detection is a persistent problem. Because early diagnosis is vital to commence treatment, new diagnostic strategies are needed. A non-invasive simple biochemical test would be ideal to increase clinical suspicion of AMI and would improve patient selection for radiographic evaluation. Thus, AMI could be diagnosed earlier with follow-up computed tomographic angiography or high spatial magnetic resonance imaging. Experimental *in vitro* and *in vivo* studies show promise for alpha glutathione S transferase and intestinal fatty acid binding protein as markers for AMI. Future research must confirm the clinical utility of these biochemical markers in the diagnosis of mesenteric ischemia.

Key words: Acute mesenteric ischemia; Diagnosis; Biological markers; Intestinal fatty acid binding protein; Alpha-glutathione S transferase

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INTRODUCTION

Mesenteric ischemia accounts for approximately 1% of acute abdomen hospitalizations and occurs in one in 1000 patients presenting to emergency rooms[1,2]. Despite growing recognition of this entity and interest in preventing irreversible ischemia, identification and early diagnosis is challenging because early symptoms are non-specific[3]. Despite major diagnostic and treatment advances over the past decades, low clinical suspicion leads to persistently high mortality rates of 40% to 70% for acute mesenteric ischemia (AMI)[4]. Early diagnosis is necessary to commence appropriate treatment, whereas diagnostic delay contributes to poor patient outcomes. A 24-h delay decreases survival rates by 20%[5]. Therefore, development of new diagnostic strategies is of great importance. Ideally, a highly specific and sensitive, non-invasive marker is needed to identify patients earlier.

MESENTERIC ISCHEMIA

Etiology and clinical presentation

In 70% to 80% of cases, intestinal ischemia is caused by an arterial embolus or thrombosis within the superior mesenteric artery. In cases of embolic occlusion, the absence of a well-developed collateral circulation causes earlier ischemia and transmural necrosis compared to other causes of mesenteric ischemia. Less common causes are venous thrombosis and non-thrombotic mechanical causes such as strangulated hernia[6]. Patients with a history of arterial emboli, vasculitis, deep venous thrombosis, hypercoagulable state, or chronic postprandial pain are at increased risk[7]. Vasculitis is a common cause of mesenteric ischemia in younger people with auto-immune disease[8]. Finally, case reports implicate vascular anomalies as a cause of mesenteric ischemia[9,10].

There are a wide variety of clinical presentations for mesenteric ischemic. Classically, AMI is associated with a dramatic onset of severe abdominal pain disproportionate to physical exam findings. Peritonitis and septicemia develop once the ischemia has progressed transmurally[3]. Postprandial pain, nausea and weight loss often occur in patients with chronic mesenteric ischemia and superior mesenteric artery thrombosis[3]. In chronic mesenteric ischemia, the association of pain with meals leads to fear of eating and subsequent weight loss[7].

Early diagnosis is challenging because of the wide variability in clinical presentation of mesenteric ischemia.

Laboratory findings

Classically, patients with mesenteric ischemia have leukocytosis, metabolic acidosis, an elevated D-dimer and elevated serum lactate[3]. Although profound leukocytosis with peripheral white blood cell counts exceeding 20 × 10^9/L have been reported, this finding is not useful to distinguish AMI from other diagnoses[11,12]. In a prospective clinical trial, Acosta *et al*[13] investigated the classically described metabolic acidosis. In their study, initial blood gas analysis showed metabolic alkalosis more frequently than metabolic acidosis; this finding results from profound vomiting during early bowel ischemia. D-dimer is also purported as an important tool in diagnosing AMI. However, D-dimer, an enzymatic degradation product of fibrin that is released during intravascular coagulation and fibrin deposition, may be present with AMI as well as several other conditions[14]. A recent trial demonstrated that serum D-dimer detection does not differentiate patients with AMI from those with non-acute mesenteric ischemia, and that there is no difference in serum D-dimer levels between resectable and unresectable bowel necrosis lesions[15]. L-lactate is associated with late-stage mesenteric ischemia with extensive transmural intestinal infarction, body tissue hypoperfusion, anaerobic metabolism and death[16]. Some studies report absence of systemic plasma L-lactate elevation in cases of extensive intestinal ischemia. This absence of L-lactate is probably explained by the liver's capacity to clear large quantities of L-lactate from the porto-mesenteric circulation[17]. A recent study by Thuijls *et al*[18] confirmed that plasma L-lactate level, base excess and leukocyte count cannot be used as markers of mesenteric ischemia. In that study, fifty consecutive patients suspected of having intestinal ischemia provided blood and urine samples. Plasma L-lactate level, base excess and leukocyte count were nondiscriminatory in determining whether patients had intestinal ischemia or other disease such as stomach perforation, pancreatitis or perforated appendicitis. Leukocyte counts in that study did not differ significantly between groups (13.9 × 10^9/L in the mesenteric ischemia group versus 12.7 × 10^9/L in the control group).

Table 1 Sensitivity, specificity and likelihood ratios for laboratory findings classically associated with mesenteric ischemia

Marker	Sensitivity	Specificity	Positive likelihood-ratio (95%CI)	Positive likelihood-ratio (95%CI)
WBC count[1]	0.80	0.50	1.57 (1.07, 2.27)	0.41 (0.20, 0.83)
pH[1]	0.38	0.84	2.49 (0.82, 7.51)	0.71 (0.45, 1.14)
D-dimer[1]	0.89	0.40	1.48 (1.28, 1.71)	0.30 (0.14, 0.64)

[1]Evennett *et al*[19]. WBC: White blood cell.

Table 1 shows that classically described laboratory findings cannot be used as markers for AMI because of their insufficient likelihood ratios[19]. These laboratory findings are not sensitive or specific enough to establish or exclude the diagnosis of AMI. Elevations in AMI serum markers usually occur only after transmural bowel infarction, and therefore, cannot be used for early diagnosis[7].

Imaging techniques

The American Gastroenterological Associated guideline (2000) states that mesenteric angiography is the gold standard for the diagnosis of mesenteric ischemia[7]. When the clinician is aware of possible AMI, angiography is accurate and increases survival[20]. However, catheter angiography is invasive and time consuming. Furthermore, the unavailability of this diagnostic modality at most hospitals leads to a critical delay. At the time of the 2000 guideline, computed tomography (CT)-angiography (CTA) seemed promising, but there was limited experience with this modality then. Over the last decade, however, there has been a major shift toward CTA because it is less invasive, less time- and resource-consuming, and more readily available. Today, CTA has replaced angiography as the gold standard in diagnosing mesenteric ischemia with a sensitivity and specificity of 0.96 and 0.94, respectively[21,22]. These sensitivity and specificity results were obtained in a dedicated study with structural CT evaluation for all AMI characteristics. Generalizability of these outstanding diagnostic values is questionable because it is unlikely whether all AMI characteristics are evaluated by specialized radiologists at all practice locations.

Wiesner *et al*[23] described a group of 291 patients who presented with acute abdomen and underwent multidetector-row computed tomographic scans. All original computed tomographic diagnoses were made

during several radiologists' daily routines. The sensitivity and specificity of multidetector-row CTA for the diagnosis of AMI were 0.79 and 0.98, respectively. These statistical measures may better reflect daily practice. In these cases, no focused structural radiological search for characteristics of intestinal ischemia was performed. There were different examination protocols because of variation in suspected diagnosis. Arterial phase scanning was not performed regularly if there was no specific clinical indication. Based on the current evidence, CTA is acceptable and accurate in diagnosing AMI; however, early identification of patients remains a challenge. Early identification could alert the radiologist to perform structural evaluations of CT scans specific for AMI, so as to increase the sensitivity of CTA[21].

NEW DIAGNOSTIC STRATEGIES

New diagnostic strategies aim for early identification (*e.g.*, biochemical markers) or seek to optimize accurate diagnosis using existing modalities such as contrast-enhanced magnetic resonance angiography (CE-MRA). CE-MRA of the splanchnic vessels is an evolving technology which is theoretically appealing because it is non-invasive and avoids the nephrotoxicity and allergic risks associated with iodinated contrast agents[22]. Dynamic CE-MRA yielded a sensitivity and specificity of 0.95 and 1.00, respectively, in a clinical trial designed to diagnose severe stenosis or occlusion of the origins of the celiac axes and superior mesenteric artery[24]. However, this modality is limited to identification of more distally located occlusions and does not have the same spatial resolution and acquisition time as CTA[14]. If better spatial resolution becomes available in the future, CE-MRA has the potential to become the diagnostic modality of choice.

Non-contrast-enhanced 7 tesla magnetic resonance imaging (7T-MRI) is a recently developed diagnostic modality. A study using an *in vivo* rat model for mesenteric ischemia demonstrated that 7T-MRI allows for the identification of pathological findings of ischemic colitis and histopathological correlation[25]. Further research is needed to substantiate these promising results in human clinical situations.

Biochemical markers for early detection

In AMI, ischemia starts at the mucosa and extends toward the serosa[16]. An ideal biomarker for mesenteric ischemia should originate at the mucosa to detect ischemia at the earliest stage. According to a recent review by Evennett *et al*[19], intestinal fatty acid binding protein (I-FABP), alpha-glutathione S transferase (GST) and D-lactate are the most promising plasma markers for mesenteric ischemia. Fatty acid binding proteins comprise a class of low molecular weight (14-15 kDa) cytosolic proteins. I-FABP is a small cytosolic protein found in tissues involved in uptake and consumption of fatty acids. It is highly expressed in cells on the luminal side of small intestinal villi. I-FABP is released into the circulation and renally cleared upon enterocyte membrane integrity loss. These characteristics, combined with localization at the initial site of destruction in mesenteric ischemia, make I-FABP a useful urinary and plasma marker for enterocyte damage[26]. Urinary and plasma I-FABP levels are significantly elevated in patients with intestinal ischemia compared to healthy controls[27]. Furthermore, I-FABP levels were increased in patients with small intestinal necrosis, but not patients without intestinal ischemia in a patient population with suspected ischemia due to small bowel obstruction[28]. I-FABP has been reported as a specific and sensitive marker for postoperative intestinal necrosis[25]. A recent clinical trial demonstrated a high sensitivity and specificity of 0.90 and 0.89, respectively, for urinary I-FABP[18]. The rapid clearance of plasma FABPs (calculated half-life time of eleven minutes[29]) into urine plus urinary FABP accumulation following intestinal damage make urinary FABP more diagnostically useful compared to plasma FABP[26]. These findings suggest that further research is needed to confirm the diagnostic value of I-FABP in cases of mesenteric ischemia.

Other potential early markers of AMI are alpha-GSTs, a family of cytosolic enzymes involved in detoxification and released from a variety of cells following cell membrane damage[30]. GST is involved in detoxification of a range of toxic compounds within the cell by conjugation to glutathione. Alpha-GST is known to be highly active both in the liver and the small intestine mucosa[16]. Alpha-GST has pooled sensitivity and specificity for diagnosing AMI of 0.68 and 0.85, respectively. A limitation of alpha-GST is that hypotensive patients with multiple organ failure and hepatic ischemia may also have elevated alpha-GST levels with concomitant ASAT and ALAT abnormalities.

A third suggested marker for AMI is D-lactate, which originates from bacteria such as *Escherichia coli* in the intestinal lumen[17]. It was hypothesized that *D*-lactate levels increase during mesenteric ischemia due to bacterial translocation and overgrowth following mucosal injury. However, a recent review showed a pooled sensitivity and specificity for *D*-lactate of only 0.82 and 0.48, respectively. Therefore, *D*-lactate cannot be used as a marker for AMI, given the superiority of alternatives such as I-FABP and alpha-GST.

CONCLUSION

AMI is a rare condition with a non-specific clinical presentation which makes early diagnosis challenging. Despite technical advances in imaging leading to more accurate diagnosis, AMI is often diagnosed late or even missed due to low clinical suspicion; therefore, a high mortality rate results.

A readily available, simple, highly sensitive and specific marker to identify patients with AMI early would be of great importance in selecting candidates for CTA. Future research must confirm the clinical utility of promising biochemical markers such as I-FABP and GST.

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