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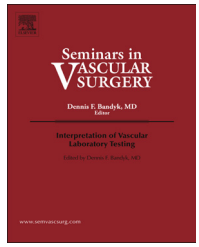

Plasma biomarkers for early diagnosis of acute intestinal ischemia

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ABSTRACT

Determining the severity of acute mesenteric ischemia or reperfusion injury can be problematic, as early visceral hypoperfusion is difficult to detect by traditional laboratory testing. Likewise gauging the success of resuscitation and therapeutic intervention is also challenging to determine by laboratory analysis alone. Investigators continue to actively search for plasma biomarkers that will aide clinicians in identifying the early microvascular changes associated with visceral splanchnic malperfusion in an effort to allow for earlier diagnosis and expedient intervention in order to minimize overall intestinal ischemia and reperfusion injury for the potential of improving clinical outcomes.

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1. Introduction

Acute mesenteric ischemia (AMI) defines a complex of conditions presenting as interruption in the splanchnic circulation, including de novo atherosclerosis, arterial thromboembolism, venous thrombosis, or development of shock states that promote nonocclusive ischemia. The common thread among these conditions is circulatory malperfusion and the accompanying hypoxia at the cellular level. If allowed to progress, the disruption in intestinal blood flow results in activation of a systemic inflammatory cascade, in turn, leading to cellular death and eventual bacterial translocation. Mortality from AMI typically ranges from 60% to 80%, with some reports citing an increased incidence during the last several decades [1–3]. A number of factors have been associated with increased mortality, including advanced age, duration of symptoms, and chronic medical illness [4,5]. Diagnosis of the condition may be particularly confounding, as the presentation, clinical signs, and serum markers are often nonspecific to the gravity of the illness. Treatment likewise is treacherous, as reperfusion after successful revascularization can be associated with additional cellular injury and hemodynamic instability. The resulting disparity in diagnosis, combined with an often unpredictable reperfusion reaction, has impaired the development of consensus clinical pathways for AMI management.

2. Pathophysiology of Intestinal Ischemia

The splanchnic circulation accepts approximately 25% cardiac output at rest and can demand an additional 10% in a postprandial state. More than two-thirds of this blood flow is directed to the mucosal and submucosal layers of the intestines to facilitate nutrient exchange, however, the intestines accommodate varying states of circulatory flow [6,7]. The unique arteriolar architecture of villi permits a pattern of countercurrent blood flow for effective autoregulation that allows the intestines to maintain a constant level of oxygen uptake. Because the digestive demands on mesenteric blood

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flow vary considerably, oxygen exchange depends on the capacity of the villi to increase extraction and recruit additional capillary beds to maintain circulatory homeostasis. In circumstances of malperfusion or shock, the circulation transit time across the villi is prolonged, resulting in arterial shunting. With prolonged ischemic insult or reperfusion injury, the countercurrent exchange intensifies injury to the villus–crypt axis, resulting in cellular dysfunction and cell death occurring initially at the mucosal villous tip. The changes associated with AMI occur at two specific stages, sometimes described as the "no flow" or ischemic injury and the "reflow" or reperfusion injury. Intuitively, the "no flow" phenomena describe a condition impaired or absent arterial circulation before revascularization, while the "reflow" phenomena require reestablishment of circulation and oxygenation. Parks and Granger [8] described this relationship, reporting on the intensity of small intestinal injury noted during the period of reperfusion and documenting that the return of oxygen supports the development of cytotoxic oxidants. These oxidants stimulate leukocyte recruitment and activation, followed by increased microvascular permeability and a loss of endothelial integrity. If allowed to persist for longer periods, the mucosal barrier begins to degenerate or slough. Accompanying this process is intravascular hemoconcentration, leukocyte plugging, vasomotor dysfunction, and capillary narrowing; all of which lead to endothelial swelling and microvascular thrombosis. With restoration of blood flow, the intestinal enterocyte is subject to oxygen free radical–mediated damage or reperfusion injury, which can manifest as damage to the microvasculature, release of iron stores, production of inflammatory cytokines, and complement activation.

3. Clinical Features

The classic presentation for AMI includes a description of diffuse or periumbilical pain frequently out of proportion to physical examination. Abdominal symptom onset is typically more sudden (hours) in conditions associated with acute arterial occlusion or thromboembolism, while venous disorders often present in a more insidious manner. Absence of abdominal pain as a presenting symptom can occur in one quarter of patients. Alimentary tract emptying is also relatively common, manifesting as nausea with emesis or diarrhea. Altered mental status and dehydrated conditions are common among the elderly. With progressive dehydration, there is development of tachycardia and tachypnea. Circulatory collapse or shock again and often harbor poor outcomes. Suspicion for the condition and timely initiation of therapy is paramount to successful treatment.

4. Laboratory Analysis

4.1. *Nonspecific Serum Markers*

Although laboratory assays are often abnormal in the setting of splanchnic hypoperfusion or reperfusion injury, the pattern can be as perplexing as the clinical presentation. Conventional recommendations for laboratory assessment of AMI include evaluation of white blood cell count, physiologic acid–base status (pH, increased anion gap, base excess), aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and amylase levels. Additional standard serology testing might include assessment of lactate dehydrogenase and creatine kinase [9,10].

Unfortunately, all of these more traditional serum markers alone are highly inaccurate in determining early intestinal ischemia or reperfusion injury. For the most part, each of these markers is generally associated with initiation of regional or systemic inflammation and related to activation of macrophages in response to cellular injury. More commonly, the finding of multiple abnormal test values among these conventional laboratory measures generally suggest a rapidly progressive or advanced degree of visceral ischemia in a setting of a systemic inflammatory response. Therefore, with clinical applications, in order to increase the diagnostic yield of these nonspecific markers, it may be more sensible to consider serial laboratory testing, especially in the early phases of mesenteric malperfusion, combined with ongoing clinical evaluations to determine if AMI may be developing.

4.2. *Investigative Biomarkers*

4.2.1. *Lactate*

Although linked with muscle ischemia of all types, lactate has been a recognized marker of intestinal ischemia AMI for >50 years [11]. Only recently have the conjugated forms of lactate, L and D stereoisomers, been evaluated as biomarkers to diagnose AMI. L-lactate is produced by all human cells and is the product of glycolosis, especially in circumstances associated with restricted perfusion and oxygen delivery. L-lactate is rapidly metabolized by the liver and elevations of L-lactate can occur in normal physiologic circumstances, such as vigorous exercise. Early elevation of L-lactate is generally not noted, as the liver is capable of clearing large amounts of L-lactate passed to it from the portal circulation. Thus, its value as an early detector of splanchnic shunting is limited. When noted, elevation of L-lactate levels most often indicates intestinal ischemia at later stages after hypoperfusion has initiated transmural infarction and metabolic acidosis [12,13].

D-lactate levels represent normal bacterial biochemical metabolism, such as found in the coliform flora of intestine. Elevations of D-lactate have been noted in conditions not associated with critical illness, such as gastric bypass surgery, short gut syndrome, and probiotic usage [14]. Because bacterial translocation is noted to occur with progressive AMI, it was postulated that D-lactate would increase as mucosal injury worsened and homeostasis of the gut flora colonies changed. However, pooled research records sensitivities of 82%, but substantially lower specificities, as low as 36% [15,16]. These findings may in part reflect that D-lactate is an ineffective marker for the early (<1 hour) or hyperacute phase of mesenteric malperfusion. Several studies have demonstrated that increases in D-lactate levels are uncommon during the early phase of ischemia/reperfusion; however, at later periods (>3 hours), investigators more frequently noted elevations in D-lactate levels, which often persist as long as 48 hours in some reviews [17,18]. This may

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