Clinical and experimental studies on treatment of acute mesenteric ischemia

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Chapter 1

A surgical approach to acute mesenteric ischemia

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\textit{Surgical intervention in acute mesenteric ischemia – the golden standard}

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Abstract

Bowel ischemia may arise from a number of causes affecting the arterial and venous compartments of the mesenteric circulation. The rapid onset of acute mesenteric ischemia and the potential rapidity with which bowel infarction may occur explain the lethality of this disease. This review addresses the causes and consequences of arterial obstruction, focusing on the acute phenomenon of mesenteric ischemia. Therapeutic strategies are dependent on reversible or irreversible ischemic damage on bowel integrity. Surgery is far the most favorable treatment, as it includes the assessment of intestinal viability, determination or conformation of the underlying cause, revascularization, and resection of the nonviable intestine. A variety of operative procedures are described to restore blood flow and secure the viability of the remaining bowel. In this context, a number of new treatment modalities are reported, which have been introduced in the last decades of the previous century. These treatment modalities may benefit a certain population of patients with acute mesenteric artery occlusion and may improve outcome of this lethal disease.
Introduction

Whereas great advances in diagnosis and treatment have been obtained over the past decades, there is still no reason to express optimism concerning acute mesenteric ischemia. Continued poor outcome of most of the patients with acute mesenteric ischemia makes this disease a dreaded condition with mortality rates up to 90%\(^1\). Since the first report of mesenteric ischemia described almost two hundred years ago\(^2\), successful diagnosis and treatment has always been a great challenge for any physician to salvage the intestine and subsequently the life of the patient.

Tiedman\(^3\) and Virchow\(^4\), in 1843 and 1847 respectively, described acute mesenteric ischemia as a clinical entity, but it was Elliott\(^5\) in 1895 who reported the first patient to recover from resection of necrotic and gangrenous bowel. Schnitzler\(^6\) in 1901 described our present-day understanding of chronic mesenteric ischemia; a patient with years of postprandial pain who at autopsy had infarction of the small intestines from a thrombus superimposed on atherosclerosis of the superior mesenteric artery. In the early 1900s, more articles and reviews appeared in the literature which identified accurately the spectrum of mesenteric ischemia: occlusions of the mesenteric arteries or veins by means of embolism, thrombosis or atherosclerosis, with chronic or acute appearance were described\(^7,8\). However, it lasts until 1943 that Thorek documented precisely bowel necrosis in the absence of arterial or venous obstruction, which may represent the first report of a patient with nonocclusive mesenteric ischemia\(^9\). During this period Rendich and Harrington\(^10\) suggested that radiographic examination might be helpful in the diagnosis of mesenteric ischemia. In the 1950s Shaw and Rutledge\(^11\) but also Klass\(^12\) reported a patient in whom embolectomy of the superior mesenteric artery without resection of bowel was followed by survival. The first successful revascularization procedure - a thromboendarterectomy - for superior mesenteric artery thrombosis with survival was described by Shaw and Maynard\(^13\) in 1958, and remains unequaled present-day. Until present day, the revascularization procedures have been expanded including aortomesenteric and iliomesenteric bypasses and balloon dilations of stenotic and occluded arteries, however, the prognosis after mesenteric arterial thrombosis appears to be worse than that after mesenteric arterial embolism. The involvement of at least two of the major splanchnic arteries may be relevant in the poor prognosis of this etiological subset of mesenteric ischemia\(^14\).

In 1967, Aakhus and Brabrand\(^15\) first suggested the value of angiography in diagnosing acute superior mesenteric artery insufficiency. Early diagnosis of acute mesenteric ischemia was difficult before intestinal infarction had occurred, because physical findings, radiographic examination and laboratory tests were, and still are, non-specific. Subsequently, in 1973, Boley and coworkers\(^16\) proposed an aggressive radiographic and surgical approach to acute mesenteric ischemia, with the liberal use of angiography in patients at risk and the infusion of papaverine through the angiographic catheter as part of the treatment of both occlusive and nonocclusive mesenteric arterial insufficiency. Jamieson and coworkers\(^17\) described the pioneering thrombolysis of acute superior mesenteric artery embolism in 1979, which was soon followed by the successful percutaneous transluminal angioplasty of stenoses of both celiac and superior mesenteric artery in 1980\(^18\). In addition to this catheter-directed balloon dilatation, the first stent was placed in the superior mesenteric artery in 1996\(^19\), followed by combining these latter therapies in 1997\(^20\).
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Anatomy

The blood supply of the gastrointestinal tract consists of three main aortic branches: the celiac trunk, the superior mesenteric artery and the inferior mesenteric artery (Figure 1). The blood flow to the small intestine is predominantly supplied by the superior mesenteric artery. The superior mesenteric artery supplies the transverse and ascending duodenum, the jejunum and ileum, and the large bowel to the splenic flexure, however, great variability in the vascular anatomy has been described. From the superior mesenteric artery four major branches arise; the inferior pancreaticoduodenal artery, the middle colic artery, the right colic artery, and the ileocolic artery. These branches give rise to numerous jejunal and ileal branches and vascular circuits, and ultimately supply the straight end arteries of the terminal arcade. These arteries enter directly the layers of the intestinal wall.

The three main aortic branches are connected with each other, by means of arcades, through anastomoses and collateral pathways. The pancreaticoduodenal arcade anastomoses the celiac axis and the superior mesenteric artery by the superior and the
inferior pancreaticoduodenal branches. These branches originate from the common hepatic artery and superior mesenteric artery, respectively. The meandering mesenteric artery or the arc of Riolan connects the superior and the inferior mesenteric artery by the left branch of the middle colic artery and the ascending branch of the left colic artery. The marginal artery of Drummond, which also connects the superior and the inferior mesenteric artery, runs along the large intestine and may play a less important role in superior mesenteric artery occlusion.

Despite these collateral pathways the middle of the jejunum renders most vulnerable for developing intestinal ischemia from superior mesenteric artery occlusion, as this part of the small intestine is far away from collateral blood supply from celiac axis or inferior mesenteric artery.

**Etiology and pathogenesis**

Acute mesenteric ischemia can be grossly classified into ischemia of thrombotic or non-thrombotic origin (Figure 2). Non-occlusive mesenteric ischemia, the dominant non-thrombotic cause of acute mesenteric ischemia, results from low-flow states (e.g. cardiogenic shock, sepsis, hypovolemia), and is usually superimposed on already stenotic (e.g. atherosclerotic) mesenteric arteries. Thrombotic conditions include mesenteric arterial embolism, arterial thrombosis and venous thrombosis. This thesis focuses on superior mesenteric artery occlusion as the cause of acute mesenteric ischemia.

![Figure 2: Classification of mesenteric ischemia.](image)

Approximately 70% of acute mesenteric vasculopathy is caused by arterial occlusion, i.e. 30-50% by arterial embolism and 15-30% by thrombosis\(^{23,24}\). The superior mesenteric artery is susceptible to embolic occlusion because of its large diameter and its arising from the aorta at a narrow angle\(^ {22,25} \). Emboli usually originate from the left side of
the heart, less frequently from ulcerated atherosclerotic plaques or thrombosed aortic aneurysm. Cardiac arrhythmias, especially atrial fibrillation, are the main cause of thrombus dislodgement and embolization, in up to 80% of patients.

Acute thrombosis of the superior mesenteric artery is generally localized at a stenosis at the origin of the superior mesenteric artery (Figure 3), which is often a result of chronic atherosclerosis. These patients typically have extensive and diffuse atherosclerotic disease, with prior coronary, cerebrovascular, or peripheral arterial insufficiency.

**Clinical presentation**

Most patients with acute superior mesenteric artery occlusion present with severe abdominal pain, which persists for more than 2 to 3 hours and is classically more impressive than the physical findings. Acute mesenteric ischemia may be caused by an embolus if acute abdominal pain is followed by rapid and forceful bowel evacuation, whereas a thrombus may be suggested if a history of chronic abdominal pain for weeks or months is followed by an acute abdominal insult. Furthermore, the stools may contain occult blood in up to 75% of the patients. Diarrhea, nausea, and vomiting are common, but overall the clinical symptoms and signs are relatively non-specific for acute mesenteric ischemia and can be seen in a wide variety of gastrointestinal disorders. Patients older than 50 years with congestive heart failure, cardiac arrhythmias, recent myocardial infarction, arterial stenosis, hypovolemia, hypotension, or sepsis, have been identified as patients at risk in retrospective studies and should be evaluated. Immediate evaluation of a possible superior mesenteric artery occlusion is mandatory when prompt
acute abdominal pain occurs after a recent myocardial infarction, cardioconversion or cardiac catheterization. Cardiac surgery, aorta reconstruction and blood dialysis may also result in intestinal ischemia, whereas previous embolic or thrombotic events should raise clinical suspicion for superior mesenteric artery occlusion. Thromboembolism of the superior mesenteric artery does not always result in acute abdominal pain. Patients with atherosclerotic narrowing of the superior mesenteric artery trunk often stimulate the formation of collateral mesenteric circulation. Thrombotic obstruction of a pre-existing stenosis of the superior mesenteric artery may often sustain asymptomatic.

**Diagnosis**

The diagnosis of acute superior mesenteric artery occlusion in its early stages is important to improve survival. Serum markers to establish or exclude the diagnosis of superior mesenteric artery occlusion in its early phase are lacking. Elevations in the levels of serum markers most suggestive of intestinal ischemia (for example leucocytosis, metabolic acidosis, hyperamylasemia, elevated levels of lactate dehydrogenase, alkaline phosphatase, or intestinal fatty acid-binding protein) usually occur only after transmural bowel infarction has developed. A recent study, however, demonstrated potential use of D-dimers in detecting acute mesenteric ischemia; further studies are advocated to evaluate the sensitivity and specificity of this serum marker for detecting intestinal ischemia in its early phase.

![Figure 4](image-url)

**Figure 4:** (A) CT findings of a patient with atrial fibrillation and abdominal pain shows a large embolus lodged in the origin of the superior mesenteric artery (arrow), which has been surgically proven. (B) Transverse arterial phase CT image of a patient with atrial fibrillation and thrombus at echocardiography who presented with abdominal pain. Note relative lack of enhancement of the descending colon (arrowhead) when compared with the ascending colon (arrow). Ischemic segments of both small and large bowel were found at surgery.

Findings on plain X-ray films of the abdomen associated with acute mesenteric ischemia, such as pneumatosis, portal venous gas, or thumbprinting usually are nonspecific and occur late in the course of the disease and correlate with a high mortality rate. Abdominal plain X-ray films are useful in exclusion of other identifiable causes of abdominal pain, for example perforated gastro-duodenal ulcer, in a patient who is suspected of having acute mesenteric ischemia.
Duplex sonography, valuable in detection of peripheral vascular occlusion, is of no value in detecting emboli beyond the proximal superior mesenteric artery or in diagnosing non-occlusive mesenteric ischemia. Despite the high specificity of almost 100%, duplex sonography shows a sensitivity of only 70-89% for identification of proximal occlusions or severe stenoses of the mesenteric vessels. The paralytic ileus associated with mesenteric ischemia and the gaseous component of the abdominal distention make duplex sonography technically very difficult and unreliable. Furthermore, due to abundant collateral vessel formation a patient with superior mesenteric artery occlusion can be asymptomatic, which indicates that identification of significant arterial occlusion alone does not establish the diagnosis of intestinal ischemia.

Figure 5: (A) Selective angiography of the superior mesenteric artery without arterial obstruction or narrowing. (B) Selective mesenteric angiography of the superior mesenteric artery of a patient with surgically proven arterial embolism causing mesenteric ischemia.

Computed tomography (CT) in acute intestinal ischemia has recently been reviewed. Analysis of acute and exclusively arterio-occlusive transmural bowel infarction demonstrated that the necrotic small intestine may show dilated and fluid-filled or gas-and fluid-filled loops with a “paper thin wall” (Figure 4). Furthermore, CT has the ability to show a thrombus or embolus within the origin of the superior mesenteric artery or celiac trunk. The CT has emerged as the primary imaging test for acute abdominal disorders, supported by the rapid image acquisition time (less than 1 minute) and the comprehensive nature of an abdominal CT, which may diagnose other frequent mimics of acute mesenteric ischemia, including appendicitis, diverticulitis or acute abdominal aortic disorders. Despite the accurate demonstration of changes in ischemic intestine and the help in determining the primary cause and coexistent complications of acute mesenteric ischemia, most findings on CT associated with acute mesenteric ischemia are nonspecific and late in disease progression. It is to be suspected that the new multi detection-row CT-angiography becomes important in abdominal emergencies, because of its ability to
detect the causes of intestinal ischemia\textsuperscript{46,47}. However, future studies are advocated to demonstrate the additional value of this technique in diagnosing acute mesenteric thromboembolism in its early phase.

Figure 6: Intestinal ischemia that mandates resection

Magnetic Resonance (MR) imaging provides a noninvasive alternative for the initial evaluation of patients with suspected acute mesenteric ischemia. Gadolinium-enhanced MR angiography provides excellent morphologic information of the proximal mesenteric vasculature\textsuperscript{48}. However, impediments to more widespread use in the acute setting of superior mesenteric artery occlusion include a limited availability of MR imaging scanners, and the complexity, length and costs of MR imaging examinations. At present day, the additional value of MR imaging of acute superior mesenteric artery occlusions is lacking.

Selective mesenteric angiography with up to 100\% sensitivity and specificity is considered to be the golden standard for the diagnosis of arterial occlusions of the small intestine\textsuperscript{49}. Abrupt cutoff of the angiographic image of the superior mesenteric artery with the absence of collateral circulation is diagnostic of an acute thromboembolic occlusion (Figure 5)\textsuperscript{28}. Only angiography or explorative laparotomy (open or laparoscopic) enables early diagnosis which may convince the use of angiography in detecting acute mesenteric ischemia in suspected patients. Selective mesenteric angiography, which is described by Bakal\textit{et al.} in detail\textsuperscript{28}, provides an entrée for postoperative angiographic follow-up studies\textsuperscript{50} and inclines to initiate immediate treatment strategies, such as endovascular angioplasty or stent placement\textsuperscript{51}, catheter-directed vasodilator or thrombolytic therapy\textsuperscript{49}.

Therapy

Surgical therapy
The basis of treatment of patients with acute mesenteric ischemia traditionally emphasizes early diagnosis, resection of nonviable bowel, targeted surgical or non-surgical restoration of blood flow to the ischemic intestine, second-look procedures and supportive intensive care\textsuperscript{52-54}. Only surgery includes the assessment of intestinal viability, determination or confirmation of the underlying cause, revascularization, and resection of the nonviable
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The intestine (Figure 6 and 7). The most useful surgical revascularization techniques for superior mesenteric artery occlusions are the balloon catheter thromboembolectomy in embolism, with or without the patch angioplasty, and the aortomesenteric or iliomesenteric bypass grafting in atherosclerotic proximal occlusions or stenoses.

**Embolectomy** requires longitudinal or transverse arteriotomy after exposure of the superior mesenteric artery (Figure 8a). A 3-4 F Fogarty catheter is passed proximally or distally to extract clot and establish flow (Figure 8b and 8c). Distal thrombectomy may establish flow in smaller vessels (Figure 9). If recirculation is not established, bypass may bring solution after closing arteriotomy primarily or with a vein patch. Chronic mesenteric occlusive disease commonly becomes symptomatic when the celiac axis and the superior mesenteric artery inflow are significantly narrowed or suddenly occluded.

**Endarterectomy** can be carried out via the origin of the superior mesenteric artery, celiac artery or through the aorta (Figure 10). The origins of the arteries may be approached either via an anterior abdominal wall incision, followed by medial visceral rotation, or using a thoraco-abdominal approach from the eleventh rib, which gives retroperitoneal exposure. Multivessel occlusive disease associated with the clinical picture of chronic ischemia mandates revascularization of the celiac axis and the superior mesenteric artery.

For **bypass grafting** not only the superior mesenteric artery, but also the aorta and the iliac vessels should be exposed. A short antegrade reconstruction (Figure 11a and 11b) can provide better hemodynamic results than a long retrograde bypass (Figure 11c). But under certain circumstances, a retrograde bypass may be the procedure of choice, as for the most cases of acute mesenteric thromboses. For the retrograde superior mesenteric
Figure 8a: Exposure of the superior mesenteric artery in the root of the mesentery as it crosses over the junction of the third and fourth portions of the duodenum.

Figure 8b: A proximal thromboembolectomy, performed with a No. 4 balloon catheter.

Figure 8c: The propagated clot is extruded with a No. 3 catheter.

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artery revascularization the infrarenal aorta is used for inflow. The retrograde blood flow into the superior mesenteric artery may be a (theoretical) disadvantage. A major drawback, however, is kinking of the graft. After the viscera are returned to their normal locations, a saphenous vein or unsupported conduit may kink, resulting in immediate failure of the reconstruction. By using a long externally supported ePTFE graft, which makes a gentle loop as the viscera are returned to their normal conditions, kinking of the prosthesis is prevented. Similar patency rates are obtained compared to those for antegrade bypass.

Figure 9a: Distal thrombectomy of the superior mesenteric artery and its branches.

Figure 9b: Additional distal clot is milked proximally out of the arteriotomy.

When bowel resection may be necessary, it is advisable to refrain from the implantation of a prosthetic graft in patients with acute mesenteric ischemia. A single-vessel (i.e. superior mesenteric artery) is an acceptable option in this setting (Figure 12).

Once blood flow is restored, assessment of bowel viability should be performed, and non-viable bowel resected. The decision, whether viable bowel after resection should be primarily anastomosed or brought out as stomas, is based on the stability of the patient and the health of the bowel to be anastomosed.
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**Figure 11a:** Antegrade bypass to the celiac and superior mesenteric artery beds for proximal celiac and superior mesenteric disease.

**Figure 11b:** Grafting of the celiac orifice and superior mesenteric artery. Bifurcated prosthesis or straight grafts can be used as alternative antegrade celiac and superior mesenteric artery bypass.

**Figure 11c:** Retrograde grafting of the superior mesenteric artery.

Figure 12. Single-vessel implantation of the superior mesenteric artery directly into the aorta is advisory when bowel resection is mandatory, as prothetic material may increase the risk of infection.


Non-surgical therapy

Patients with acute mesenteric ischemia frequently present with established bowel infarction, which eliminates endovascular management as an emergency laparotomy because bowel resection is indicated. However, when transmural infarction and subsequent peritonitis has not occurred, endovascular treatment strategies may be an alternative or adjunctive to surgical therapy. The non-surgical treatment modalities for superior mesenteric occlusion are percutaneous transluminal angioplasty, endovascular stent placement, catheter-directed vasodilation or thrombolytic therapy. At present, limited studies are available in the literature and these procedures continue to be controversial, however, results are promising. Undoubtedly, as the average life expectancy increases and subsequently the number of elderly in our hospitals grows, the need for endovascular thrombolytic therapy, angioplasty, and stenting in either acute or chronic mesenteric ischemia will increase, especially when surgical therapy in some elderly is neither indicated nor safe.
Conclusion

The rapid onset of acute mesenteric ischemia and the potential rapidity with which bowel infarction may occur explain the lethality of this disease. The relative infrequency of acute mesenteric ischemia, the variable pathogenesis and the broad spectrum of ischemic injury of the small and large intestines make it almost impossible to study this disease and its diagnostic and therapeutic strategies in clinical randomized or case-controlled trials. Surgery is far the most favorable treatment, as it includes the assessment of intestinal viability, determination or confirmation of the underlying cause, revascularization, and resection of the nonviable intestine. However, in the last decades of the previous century, a number of new treatment modalities have been introduced, which may benefit a certain population of patients with acute mesenteric artery occlusion and may improve outcome of this lethal disease. In this thesis thrombolytic therapy of acute superior mesenteric artery occlusion as an adjunct to surgical therapy will be discussed. Furthermore, the ability to reduce ischemia and reperfusion injury by using drug therapies in experimental settings of acute mesenteric ischemia will be analyzed.
Chapter 1

References

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