On Acute Thrombo-Embolic Occlusion of the Superior Mesenteric Artery

BY

STEFAN ACOSTA
Dissertation presented at Uppsala University to be publicly examined in Auditorium Minus, Museum Gustavianum, Uppsala, Saturday, May 8, 2004 at 13:00 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

Abstract

Acute thrombo-embolic occlusion of the superior mesenteric artery (SMA) with intestinal infarction is a lethal disease, difficult to diagnose in time, with unknown incidence and cause-specific mortality. The aim of this thesis was to characterize the disease and to develop diagnostic methods.

Two laboratory studies were conducted on patients with suspected acute SMA occlusion. A pilot-study showed that the fibrinolytic marker D-dimer was elevated in six patients with the disease. In the subsequent study including 101 patients, D-dimer was the only elevated coagulation marker in nine patients with the disease. In a prospective study 24 patients (median age 84 years) were identified, of whom four were diagnosed at autopsy, despite an autopsy-rate of 10%. One-fourth were initially nursed in non-surgical wards. Length of the intestinal infarction was a predictor for death. An analysis of patients from the three studies showed that D-Dimer was elevated in all 16 tested patients with the disease.

Sixty patients with acute SMA occlusion underwent intestinal revascularisation and were registered in the Swedish Vascular Registry (SWEDVASC). One-year survival rate was 40%. Previous vascular surgery was a negative risk-factor.

A population-based study was conducted in Malmö, based on an autopsy-rate of 87%. Among 270 patients with the disease, 2/3 were diagnosed only at autopsy and 1/2 were managed in non-surgical wards. The incidence was 8.6 per 100000 person years. The age-standardized incidence increased exponentially without gender differences. The diagnosis was the cause of death in 1.2% among octogenarians and beyond. Thrombotic occlusions were located proximally within the SMA and associated with extensive intestinal infarctions. Synchronous embolism, often multiple, occurred in 2/3 of the patients with embolic occlusions.

Conclusions: A normal D-dimer at presentation most likely excludes the diagnosis. Acute SMA occlusion was more frequent than previously estimated from clinical series. The patients were often nursed in non-surgical wards.

Keywords: acute thrombo-embolic occlusion, superior mesenteric artery, intestinal infarction, D-Dimer, intestinal revascularisation, population-based study, incidence, autopsy

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Cover picture:
Schematic drawing of an embolic occlusion of the superior mesenteric artery.
LIST OF PAPERS

This thesis is based on the following studies which are referred to by their Roman numerals below:


VI. Acosta S, Ögren M, Sternby N-H, Bergqvist D, Björck M. Autopsy findings in 213 patients with fatal acute thrombo-embolic occlusion of the superior mesenteric artery. (submitted)
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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AAA</td>
<td>abdominal aortic aneurysm</td>
</tr>
<tr>
<td>Acute SMA occlusion</td>
<td>acute thrombo-embolic occlusion of the SMA</td>
</tr>
<tr>
<td>AMI</td>
<td>acute myocardial infarction</td>
</tr>
<tr>
<td>APTT</td>
<td>Activated Partial Thromboplastin Time</td>
</tr>
<tr>
<td>CA</td>
<td>celiac artery</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>ICU</td>
<td>intensive care unit</td>
</tr>
<tr>
<td>INR</td>
<td>international normalized ratio</td>
</tr>
<tr>
<td>IM</td>
<td>institutional mortality</td>
</tr>
<tr>
<td>IMA</td>
<td>inferior mesenteric artery</td>
</tr>
<tr>
<td>LR</td>
<td>likelihood ratio</td>
</tr>
<tr>
<td>LR+</td>
<td>positive likelihood ratio</td>
</tr>
<tr>
<td>LR-</td>
<td>negative likelihood ratio</td>
</tr>
<tr>
<td>MRT</td>
<td>magnetic resonance tomography</td>
</tr>
<tr>
<td>PT</td>
<td>Prothrombin Time</td>
</tr>
<tr>
<td>PTA</td>
<td>percutaneous transluminal angioplasty</td>
</tr>
<tr>
<td>SMA</td>
<td>superior mesenteric artery</td>
</tr>
<tr>
<td>SWEDVASC</td>
<td>The Swedish Vascular Registry</td>
</tr>
<tr>
<td>rtPA</td>
<td>recombinant tissue Plasminogen Activator</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell count</td>
</tr>
</tbody>
</table>
INTRODUCTION

Classification
Mesenteric ischaemia is defined as a state of perfusion that is insufficient to meet the ambient metabolic demands of any of the principal organs served by the mesenteric circulation including the small intestine, colon, stomach, liver, gallbladder and pancreas (Montgomery 1997). Traditionally, intestinal ischaemia is classified into four aetiologies: SMA embolus, SMA thrombosis, non-occlusive mesenteric ischaemia and mesenteric venous thrombosis (Fig. 1, Kaleya 1992). Colonic ischemia due to mesenteric artery insufficiency (ischaemic colitis) or bowel strangulation with secondary formation of predominantly mesenteric venous thrombosis, are in terms of aetiology both distinct clinical entities.

This thesis deals only with acute thrombo-embolic occlusion of the superior mesenteric artery (Fig 1)

![Figure 1](attachment:image.png) Classification of intestinal ischaemia. SMA = superior mesenteric artery
History

Acute thrombo-embolic occlusion of the SMA (Acute SMA occlusion) has been recognized as a cause of abdominal catastrophe and death since 1875, based on a classic experimental work on the effects of ligature of the mesenteric vessels (Litten). Recovery following resection of infarcted intestine secondary to mesenteric vessel occlusion was first reported in 1895 (Elliot). The total number of survivors from mesenteric vessel occlusion reported in the literature, increased from 24 in 1921 (Klein) to 217 in 1953 (Mersheimer).

The first acute SMA embolectomy was performed in 1951 (Klass): The intestinal revascularisation was successful, but the patient died from an acute myocardial infarction. The first survivor after an embolectomy, with resection of 50 cm of ileum, was reported from an operation performed in 1951 (Stewart 1960): “The embolus was exposed and removed in piecemeal fashion. Vigorous bleeding did not occur until the artery had been explored proximally with a small probe and with a catheter to which suction was applied to remove the entire embolus”. It was revealed that this patient had a two week old myocardial infarction, causing the embolic event. However, this 65-year old male lived for five more years. The first successful emergency thrombendarterectomy and aortomesenteric by-pass was performed in 1958 (Shaw) and 1973 (Ribet), respectively. Intra-arterial local lysis of an embolus, with a combination of streptokinase and heparin was first performed successfully in 1979 (Jamieson). This patient was discharged without laparotomy.

Incidence

Based on retrospective studies of clinical series it has been claimed that the disease is uncommon (Park 2002, Mamode 1999)(table 1). The mean age in the last published series was 67 – 68 years, and women were affected more frequently, 56 – 70 % (Endean 2001, Park 2002, Edwards 2003). To generate calculations of absolute risk, expressed as the incidence of a disease, studies based on the general population are needed. Consequently, the incidence related to age groups or gender is unknown, since such calculations need to adjust for distribution in age and gender in the general population. No population-based study has been published on the overall, age- and gender-specific incidence of acute SMA occlusion.
Table 1 Contemporary published series of patients with acute intestinal ischaemia

<table>
<thead>
<tr>
<th>First Author</th>
<th>Publication Year</th>
<th>Population</th>
<th>Mean age (years)</th>
<th>Number of patients</th>
<th>Study period</th>
<th>Frequency of acute SMA occlusion (%)</th>
<th>Freq of CMI (%)</th>
<th>30-day mortality rate (%)</th>
<th>Operation freq (%)</th>
<th>Autopsy freq (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edwards</td>
<td>2003</td>
<td>North Carolina*, USA</td>
<td>68</td>
<td>76</td>
<td>1990-2000</td>
<td>100</td>
<td>34</td>
<td>62</td>
<td>100</td>
<td>unknown</td>
</tr>
<tr>
<td>Park</td>
<td>2002</td>
<td>Minnesota*, USA</td>
<td>67</td>
<td>58</td>
<td>1990-1999</td>
<td>91</td>
<td>43</td>
<td>32</td>
<td>100</td>
<td>unknown</td>
</tr>
<tr>
<td>Endean</td>
<td>2001</td>
<td>Kentucky*, USA</td>
<td>67</td>
<td>43</td>
<td>1993-2000</td>
<td>100</td>
<td>9</td>
<td>60</td>
<td>98</td>
<td>unknown</td>
</tr>
<tr>
<td>Wadman</td>
<td>2000</td>
<td>Malm*, Sweden</td>
<td>75</td>
<td>74</td>
<td>1987-1996</td>
<td>&gt; 44</td>
<td>24</td>
<td>61</td>
<td>100</td>
<td>unknown</td>
</tr>
<tr>
<td>Wadman</td>
<td>2000</td>
<td>Scotland, Malm*, Sweden</td>
<td>75</td>
<td>74</td>
<td>1987-1996</td>
<td>&gt; 44</td>
<td>24</td>
<td>61</td>
<td>100</td>
<td>unknown</td>
</tr>
<tr>
<td>Mamode</td>
<td>1999</td>
<td>Glasgow, Scotland</td>
<td>68</td>
<td>57</td>
<td>1987-1993</td>
<td>&gt; 53</td>
<td>0</td>
<td>81</td>
<td>63</td>
<td>unknown</td>
</tr>
<tr>
<td>Järvinen</td>
<td>1994</td>
<td>Tampere, Finland</td>
<td>75*</td>
<td>214</td>
<td>1972-1990</td>
<td>&gt; 91</td>
<td>unknown</td>
<td>82</td>
<td>80</td>
<td>unknown</td>
</tr>
<tr>
<td>Batellier</td>
<td>1990</td>
<td>Strasbourg, France</td>
<td>67</td>
<td>82</td>
<td>1966-1988</td>
<td>100</td>
<td>0</td>
<td>43</td>
<td>100</td>
<td>unknown</td>
</tr>
<tr>
<td>Clavien</td>
<td>1987</td>
<td>Basle, Switzerland</td>
<td>71*</td>
<td>81</td>
<td>1968-1984</td>
<td>unknown</td>
<td>75</td>
<td>85</td>
<td>unknown</td>
<td></td>
</tr>
</tbody>
</table>

* State, * median age
**Intestinal blood supply**

Under fasting, basal conditions, approximately 20 - 25 % of the cardiac output is distributed to the splanchnic arteries; celiac artery (CA), superior mesenteric artery (SMA) and inferior mesenteric artery (IMA) (Haglund 1999, Kolkman 2003). The CA supplies the stomach, spleen, part of the liver and pancreas, and the proximal part of the duodenum. The SMA supplies the distal part of the duodenum, small bowel and large bowel up to the mid transverse colon. The IMA is a comparably small artery supplying the distal part of the colon and proximal part of the rectum. The CA receives 800 ml blood/minute and the SMA 500 ml/minute, increasing up to 1100 ml/minute and 1400 ml/minute after a meal, respectively (Moneta 1988, Kolkman 2003). The IMA receives 50 ml/minute under basal conditions (Kolkman 2003). Branches of these arteries enter the serosa of the gut on the mesenteric side to form a serosal vascular plexus around the gut. The blood is then directed to the submucosal plexus and finally to the mucosa. When intestinal blood perfusion pressure falls, local vasodilation (Bulkley 1987, Reilly 1997) ensures adequate blood supply within a wide pressure range. In addition, redistribution of blood flow within the intestine to the more metabolically demanding mucosa and increased oxygen extraction are other two important autoregulatory mechanisms (Haglund 1999). Experimental data have indicated that the splanchnic vasculature contains a large reservoir of blood. In conditions with circulatory stress, mesenteric vasoconstriction occurs as a physiological response and blood flow may be halved before signs of intestinal ischaemia develop (Bulkley 1985, Knichwitz 1998, Kolkman 2000, Dubin 2001),

**Patophysiology**

In acute mesenteric ischaemia, whatever the cause, the infarction starts from the mucosa outward (Haglund 1987). The technique of tonometry (Niinikoski 1972) was applied to evaluate intestinal perfusion (Fiddian-Green 1982). In an experimental model of peritonitis and haemorrhage, it was shown that at a pH of 7.1 in the intestinal mucosa, anaerobic metabolism prevails (Antonsson 1995). Colonic ischaemia after aortoiliac surgery at the same pH level was predictive of major complications (Björck 1994). In contrast to these reports on low flow states and distal colon ischaemia, respectively, acute SMA occlusion causes a more significant reduction in blood flow with rapid development of extensive intestinal infarction (Kolkman 2003). Tonometry of the small bowel mucosa is not feasible in the clinical situation.
Pathogenesis

Acute thrombotic occlusion of the SMA
Thrombosis occurs at areas of severe atherosclerotic narrowing, most often at the origin of the SMA. Many of these patients may have the pre-existing symptoms of chronic mesenteric ischaemia, including postprandial abdominal pain (abdominal angina), food fear, diarrhoea and weight loss. Most patients have also severe and diffuse atherosclerosis, with a prior history of coronary, cerebrovascular, or peripheral arterial insufficiency (Kaleya 1992). In a substantial proportion of these patients, atheroma at the origin of the SMA may have developed over a period of many years, resulting in collateral circulation to the SMA, mainly from the celiac and inferior mesenteric arteries. Dehydration, low cardiac output and hypercoagulable state are major contributing factors to thrombosis (Montgomery 1997). In the case of thrombosis at the origin of the SMA, ischaemia may have developed from the proximal jejunum to the mid transverse colon (Bergan 1967).

Embolic occlusion of the SMA
Like most peripheral arterial emboli, mesenteric emboli usually originates from the heart. Aortoarterial embolism has been described infrequently (Smith 1991, Sharifi 1994). Cardiac thrombi may be associated with valvular heart disease, dilated left atrium, recent myocardial infarction (4-6 weeks old), atrial arrhythmias and ventricular dilatation with mural thrombus. Iatrogenic embolisation has been reported after cardiac catheterisation, coronary arteriography and aortography (Batellier 1990). Patients with emboli would rarely be expected to have a previous history of intestinal ischaemia. A number of these patients have a history of prior arterial embolism (Eldrup-Jorgensen 1997). The embolus may occlude the arterial lumen completely or partially (Kaleya 1995). Emboli tend to lodge at points of normal anatomical narrowing, usually immediately distal to the origin of a major branch. Typically, the embolus lodge a few centimeters distal to the origin of the SMA, sparing the proximal jejunal branches, and allowing preservation of the proximal jejunum (Bergan 1967).

Diagnosis

Clinical diagnosis
The diagnosis must be considered when there is severe abdominal pain with initially minimal abdominal signs (pain out of proportion) in an elderly patient. Factors such as a history of generalised atherosclerosis and pre-existing symptoms of chronic mesenteric ischaemia are more commonly
associated with thrombotic occlusions. Pain out of proportion, accompanied by rapid and often forceful bowel evacuation, and a source of embolus/previous history of embolism is labelled the ‘clinical triad’ of early acute embolic occlusion (Kaleya 1992). The initial response of the bowel to the ischaemic attack is contractile. Abdominal tenderness and spasm may be lacking or unimpressive in early infarction. When present, tenderness is apt to be maximal in the right lower quadrant, where the terminal branches of the artery are localised. These symptoms sometimes fade, leaving the patient apparently improved or even asymptomatic until necrosis of the bowel develops. With progression to transmural bowel necrosis, peristalsis ceases and signs of generalised peritonitis, such as generalised rebound tenderness and fever, will occur (Shaw 1957).

**Laboratory tests**

Plasma lactate concentration has a high sensitivity, 91 – 100 %, (Park 2002, Lange 1994), but a low specificity, 42 % (Lange 1994). In the study by Lange, the mean lactate level was doubled from the upper reference limit late in the course, after a mean symptom duration of 43 hours, which probably explains the 90 % postoperative 30-day-mortality. It is well-known that metabolic acidosis occurs as a consequence of severe intestinal ischaemia and necrosis (Sitges-Serra 1988). In addition, pre-analytical factors such as venous stasis during sampling and erythrocyte production of lactate in vitro, may reduce the suitability of plasma lactate as a clinically useful test (Astles 1994). Elevated white cell blood count (WBC) has also a high sensitivity, 91 – 98%, (Potts 1999, Park 2002), but a low specificity, 36% (Potts 1999).

**Imaging techniques**

Plain radiography has both low specificity and sensitivity (Salzano 1999). Contrast-enhanced computed tomography (CT) angiography is neither specific (Wiesner 2003), nor sensitive (Kirkpatrick 2003). Selective angiography of the SMA is a specific, but invasive, diagnostic method, (Batellier 1990). Duplex sonography can be useful in detecting proximal SMA occlusion, particularly if it is performed early before a paralytic ileus is fully developed (Danse 1996). Duplex has been claimed to be almost as accurate as angiography in the diagnosis of high-grade stenosis or occlusion of the SMA (Zwolak 1998, Lim 1999), but this method is very operator dependent.

**Laparotomy**

Explorative laparotomy, to establish the diagnosis and estimate the extent of intestinal ischaemia, remains the gold standard. The intestines often show signs of extensive cyanosis and a reddish – black discoloration (Eldrup-Jørgensen 1997). It is very rare that the intestines appear entirely normal,
but if that is the situation, it is important to confirm the absence or presence of pulsations in the main trunk of the SMA at the root of the mesentery or its branches. The appearance of the intestines is dependent on the degree of collateral circulation and the duration of ischaemia (Shaw 1957). In contrast, cases with mesenteric venous thrombosis are characterised by a limited segment of intestinal ischaemia with oedema, swelling and discoloration of the affected small bowel and its adjacent mesentery, and a palpable pulsatile flow in the SMA and its branches (Rhee 1997).

**Treatment**

Explorative laparotomy and closure of the abdomen, followed by palliative care only, may be considered in cases with extensive intestinal infarction. The surgical treatment options are bowel resection, revascularisation of the SMA with or without bowel resection, and endovascular local intra-arterial thrombolysis. Second look laparotomy may be considered after primary intervention.

**Approach and vascular surgical technique**

*Embolic occlusion of the SMA*

After midline laparotomy, exposure of the SMA in the intestinal mesentery is the standard procedure to be able to perform an embolectomy (Valentine 2003). The transverse colon and omentum are lifted upwards and a horizontal incision is made in the peritoneum at the base of the transverse mesocolon. The middle colic artery can be identified in the transverse mesocolon and is traced proximally so that its origin from the SMA can be located. The SMA is isolated at the lower border of the pancreas. Embolectomy is performed with a balloon, *Fogarty* catheter (Fogarty 1965, Hill 1998), through a transverse arteriotomy in a proximal segment.

*Thrombotic occlusion of the SMA*

During laparotomy, it may be difficult to differentiate an embolic from a thrombotic occlusion, which may lead the surgeon to perform a thrombectomy with the balloon catheter technique described above. However, this technique is not recommended in cases with thrombotic occlusions due to the risk of rapid re-occlusion. In emergency situations, it may be advisable to reimplant the infrapancreatic part of the artery end to side in the aorta infrarenally (Kienny 1990) or to perform a short aorto-mesenteric (Bergan 1967) or iliaco-mesenteric by-pass (Ottinger 1978), rather than to try to perform a thrombectomy of the stenotic part near the aorta because of its difficult anatomic position (Stoney 1990). Autologous vein grafts should be avoided due to the risk of kinking because of the moveable mesentery and the weight of the intraperitoneal organs causing
compression (Haglund 1999). However, in patients with periitoneal contamination, a saphenous vein graft may be preferable to a synthetic graft. Antegrade supracoeliac aortomesenteric by-pass (Cormier 1979) is a time-consuming procedure more suitable for elective surgery on patients with chronic intestinal ischaemia. Endovascular treatment is technically feasible with low frequency of complications in patients with chronic mesenteric ischaemia (Sharafuddin 2003), but experience is very limited in emergency situations.

**Secondary prevention**

Patients should be anticoagulated immediately perioperatively with low-molecular weight heparin or unfractionated heparin (Levy 1990). Patients with embolic disease should remain anticoagulated at discharge and warfarin seems to offer the best protection from recurrent embolism (Connolly 2003). Secondary prevention of patients with thrombotic disease should be tailored to include maximum cholesterol reduction, blood pressure and glycaemic control, and single or combination antiplatelet therapy, equivalent to patients with a manifestation of a generalised atherosclerotic disease (Donnelly 2002).

**Prognosis**

The mortality is related to the extent of intestinal infarction (Ottinger 1978, Kieny 1990 and Järvinen 1994). Thrombotic occlusions occur often more proximally within the SMA than embolic occlusions and are commonly associated with more extensive intestinal infarction (Ottinger 1978). Studies on determinants on the extent of intestinal infarction, except the anatomical location of the occlusion, are lacking. The reported mortality of acute SMA occlusion varies, which likely reflects a heterogeneity of the studied populations (table 1). Patients with a thrombotic occlusion seem to have a poorer prognosis than those with an embolic occlusion (Schoots 2004). It can be assumed that the reported mortality rates in clinical series are underestimated and that the true mortality only can be assessed in population-based studies with a reasonably high autopsy rate.

**From a clinical observation to a thesis**

A 63-year old woman, with a history of chronic bronchitis, hypertonia, epilepsy, alcohol abuse and smoking, was admitted to the emergency department at Blekinge County Hospital of Karlskrona, with two hours history of severe abdominal pain. The pain was morphine-resistant. She underwent plain abdominal x-ray, ultrasound of the aorta and computerised tomography with intravenous contrast enhancement, without any
pathological findings. ECG showed sinus rhythm. Laboratory values including CRP, amylase and blood gas were normal, except WBC (14.9 x 10^9/L) and a very high D-dimer level of 6.9 mg/L (reference range < 0.3 mg/L). Explorative laparotomy verified an extensive intestinal ischaemia. The infarcted right colon was resected. The small bowel except the proximal jejunum, were moderately ischaemic. After thrombectomy of the proximal segment of the SMA, the proximal part of the small bowel seemed to recover. The patient was taken to the intensive care unit (ICU) and at second look 24 hours after the primary operation, three meters of infarcted small bowel had to be resected and diverting stomas constructed. Jejunoscopy at the ICU showed that there was necrosis in the distal 30 cm of the mucosa. The patient died three days after admission due to multiple organic failure. This observation of an elevated D-dimer in a patient with acute SMA occlusion initiated the research process, inspiring us to proceed with a pilot study (I) and to explore the following issues:
AIMS OF THE INVESTIGATION

- What is the overall, age- and gender-specific incidence of acute SMA occlusion in the general population? (Study V)

- Which are the characteristic findings in patients with thrombotic and embolic occlusion of the SMA? (Study VI)

- What is the frequency of synchronous emboli and which are the sources of emboli in patients with embolic occlusion of the SMA? (Study VI)

- Where are the patients with acute SMA occlusion hospitalised? (Studies III, VI)

- Can D-dimer be predictive in the early diagnosis of the disease? (Study I, II and III)

- Which are the risk factors for death in patients with acute SMA occlusion? (Study III)

- What is the prognosis after revascularisation for acute SMA occlusion, and are there risk factors for death? (Study IV)

- What is the cause-specific mortality from acute SMA occlusion? (Study V)
PATIENTS, METHODS AND RESULTS

This thesis is based on four clinical (PAPERS I – IV) and two epidemiological (PAPERS V – VI) studies.

![Diagram showing patient study summary]

*Partly calculated from a random clinical sample, see page 29.

The Blekinge studies – PAPERS I, II and III

Patients

Blekinge County is situated in the southern part of Sweden, and had a population of approximately 150 000 during the study period between 1999 and 2003. Three prospective studies were conducted with patients admitted to Blekinge County Hospital of Karlskrona. PAPER I reports an analysis of 14 patients with a strong suspicion of acute SMA occlusion, with respect to
clinical presentation and D-dimer levels. PAPER II reports an analysis of markers of fibrinolysis and coagulation in another 101 patients with a strong suspicion of acute SMA occlusion, with respect to clinical presentation, and where the diagnosis was confirmed in 9. PAPER III describes a clinical evaluation of 24 patients with acute SMA occlusion, of whom 6 each also were reported in the laboratory PAPERS I and II, respectively (fig. 3). In total, 27 patients were included prospectively in the Blekinge studies. These patients were diagnosed either at surgery (n=23) or autopsy (n=4).

Figure 3 Venn diagram showing the number of patients with acute SMA occlusion in PAPER I, II and III, and overall, in the Blekinge studies. There was no overlap of patients between the laboratory studies, PAPERS I and II.

Methods
The diagnosis of acute SMA occlusion was verified at operation or autopsy. The occlusions were defined as embolic in the presence of synchronous emboli, atrial fibrillation or acute myocardial infarction, and thrombotic in the absence of these signs.

In PAPER I and II, plasma D-dimer was analysed preoperatively in fourteen patients with strong suspicion of acute SMA occlusion. D-dimer was analysed with a quantitative method, Nycocard® immunofiltration assay, Nycomed (normal value < 0.3 mg/L).
In PAPER II, the 101 patients were selected only by specialists in surgery. Inclusion criteria were age ≥ 50 years, hospitalisation, maximum 24 hours of pain and Visual Analogue Scale (VAS) score ≥ 5. Coagulation markers (fibrinogen, activated partial thromboplastin time (APTT), prothrombin time (PT) and antithrombin), CRP and WBC were analysed.

In PAPER III, patients with chronic mesenteric ischaemia were excluded. The length of the ischaemic intestinal segment was estimated from the serosal side at operation. Autopsies performed during the study period were registered in a data base administered by the Department of Pathology. During the study period, the autopsy rate was 10.1 % in the county.

Results

PAPER I
Median (range) D-dimer values were 3.6 (1.3 – 10.1) mg/L in six patients with acute SMA occlusion.

PAPER II

D-dimer
All nine patients with acute SMA occlusion had an elevated D-dimer level. Median (range) D-dimer for these were 1.6 mg/L (0.4 – 5.6), compared to 0.5 (0.1 – 7.7) for patients without SMA occlusion (p= 0.009). There were 33 patients (36%) with D-dimer ≤ 0.3 mg/L among the 92 patients without acute SMA occlusion. There were statistically no significant differences in the levels of the coagulation markers, fibrinogen, APTT, PT or antithrombin, between the groups with or without acute SMA occlusion.

Comparison with three commonly used D-dimer assays
In 71 (70%) patients extra plasma samples were obtained, stored frozen and at the end of study delivered to the Dept of Clinical Chemistry, Örebro University Hospital, for analysis with three additional D-dimer assays from different manufacturers (Table 2). We found a highly significant correlation between the Nycomed Nycocard® D-dimer assay, utilized in the study, and the other assays at the group level. However, in two individual samples, our clinical suspicion of spurious D-dimer values in the primary study could be confirmed by the other assays: There was one patient with ureterolithiasis and a high D-dimer of 3.8 mg/L, but analysis of all the other tests showed very low values, within the normal range. There was also one patient with acute SMA occlusion and a D-dimer of only 0.4 mg/L, whose D-dimer level was found to be clearly elevated, 4–7 fold, in relation to the reference values, when tested with the additional tests.
Table 2  Comparison of D-dimer results obtained with the Nycomed Nyocard® D-dimer assay, utilized in PAPER II, with three different D-dimer assays. Plasma samples from 71 patients were available for analysis.

<table>
<thead>
<tr>
<th>Test principle</th>
<th>Manufacturer and assay</th>
<th>Mean (mg/L)</th>
<th>Median (mg/L)</th>
<th>Range (mg/L)</th>
<th>Pearson Correlation (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IF</td>
<td>Nycomed Nyocard® D-dimer ( &lt; 0.3 mg/L)</td>
<td>0.8</td>
<td>0.5</td>
<td>0.1 – 7.7</td>
<td>---</td>
</tr>
<tr>
<td>LIA</td>
<td>Stago STA-Liatest® D-Di ( &lt; 0.4 mg/L)</td>
<td>2.71</td>
<td>1.12</td>
<td>0.09 – 33.00</td>
<td>0.922*</td>
</tr>
<tr>
<td>LIA</td>
<td>Roche Diagnostics TINAcuant D-dimer ( &lt; 0.5 mg/L)</td>
<td>2.20</td>
<td>0.9</td>
<td>0.13 – 25.93</td>
<td>0.901*</td>
</tr>
<tr>
<td>LIA</td>
<td>Biopool AutoDimer® ( &lt; 0.4 mg/L)</td>
<td>0.92</td>
<td>0.38</td>
<td>0.05 – 13.62</td>
<td>0.929*</td>
</tr>
</tbody>
</table>

IF = Immunofiltration, LIA = Latex-enhanced immunoassay
Each LIA test was compared to the Nycocard® test. Reference values (suggested by the respective manufacturers) given within parentheses. *Correlation is significant at the 0.001 level (2-tailed).

Pancreatic amylase
Pancreatic amylase was measured with an enzymatic activity assay after inhibition of salivary amylase with specific inhibitory antibodies (COBAS INTEGRA alpha-amylase EPS Pancreatic AMY-P; Roche, Mannheim, FRG). In all, 94 (93.1%) patients had data available for analysis of this variable. Median pancreatic amylase was significantly higher among patients with acute SMA occlusion (n=8), compared to patients without acute SMA occlusion and without acute pancreatitis (n=82), 0.63 µkat/L (range: 0.05 – 2.52) vs 0.37 µkat/L (0.05 – 4.96), respectively (p =0.025, Mann-Whitney U-test).
Results – PAPER III

Median (range) age was 84 years (63 – 96) in the 24 patients with acute SMA occlusion. In the 16 women (67%), corresponding age distribution was 86 years (63 – 96), and in the eight men it was 76 years (70 – 88). The incidence of acute SMA occlusion in Blekinge County was 5.3 per 100 000 person years. Twenty patients were considered to have an embolic occlusion and four a thrombotic occlusion of the SMA.

Clinical presentation

Twelve patients (50 %) suffered from a sudden onset of pain (within minutes), seven (29 %) developed acute onset (within 1 h) and five (21 %) had an insidious onset of abdominal pain. On presentation, half of the patients had had symptoms for less than 4 h (range 0 – 168). Thirteen patients had morphine-resistant pain, whereas eleven had moderate intensity of pain at admission. Three patients had peritonitis at presentation.

Nineteen (95 %) of the 20 patients with embolic disease had atrial fibrillation, two (10 %) had acute myocardial infarction and in 16 (80 %) the clinical triad was present. Synchronous emboli occurred in six patients, of whom four were diagnosed peri-operatively (three cerebral, one femoral). Two patients were on anticoagulation treatment with warfarin, one of whom had sub-therapeutic INR on admission.

Occlusion of the SMA was suspected at first consultation in four patients, of whom two survived. It took a median of 5 hours (range 2 – 8) before these patients underwent laparotomy. The other 20 patients were evaluated by a total of 48 physicians at their first consultation; 23 were specialists in surgery. One-fourth of the patients were initially managed in non-surgery wards; equally distributed among the departments of internal medicine and infectious diseases. Sixteen of these patients waited a median of 33 hours (range 8-188) for the diagnostic laparotomy. Five cases were correctly diagnosed before surgery after diagnostic work-up. Four patients were diagnosed post-mortem.

Investigations

D-dimer was elevated in all 13 patients tested. Arterial blood gas was analysed in twelve patients, of whom five had alkalosis and three had acidosis. Four patients had a metabolic alkalosis, of whom three had been vomiting. None of the 34 radiological or seven endoscopical evaluations were diagnostic.
The surgical procedures
Twenty patients underwent surgery, of whom six were operated on with a thrombo-embolectomy of the SMA. The median length of the ischaemic bowel was 3.4 m (range 0.5 – 4.3 m). The median bowel resection length among patients undergoing curative surgery (n= 15) was 1.3 m (range 0 – 3.7 m) of the small intestine and 0.1 m (range 0 – 0.4 m) of the colon. The bowel resections were followed by primary anastomosis in eleven patients and by diverting stomas in four.

Outcome and prognostic factors
The 30-day mortality, institutional mortality and one-year-mortality were 58%, 62% and 79%, respectively. Age was not significantly associated with survival at the time of discharge or after one year (p= 0.056 and 0.064, respectively), whereas the length of the ischaemic bowel was negatively associated with survival at these two time-points (p= 0.004 and 0.005, respectively).

Comments – PAPER III
Acute intestinal revascularisation was undertaken in six out of 24 patients (25%) in PAPER III. We extracted data from SWEDVASC in February 2004, and found that five out of these six patients were reported. The patient who had not been reported was managed with an extensive bowel resection immediately after a failed intestinal revascularisation. The five patients were registered in spite of poor outcome and postoperative death in all. The Department of Surgery in Blekinge County has previously only registered one acute intestinal revascularisation procedure in SWEDVASC between 1987 and 1998. However, the patient file was missing and this patient could not be added to the analysis of the 60 patients in PAPER IV. Thus, the prospective design of PAPER III resulted in an increase of acute intestinal revascularisation procedures from one between 1987 and 1998, to six between 1999 and 2002.
Analysis of pooled data from the Blekinge studies

Patients with acute SMA occlusion
Median age was 84 years among the 27 patients, of whom 19 were women (70%). The correlation between patient age and the length of the ischaemic bowel segment was statistically significant (r= 0.44, p= 0.02).

The estimated pain intensity at presentation was related to the duration of symptoms (fig. 3). The pain intensity was assessed by physicians (n=20) or patients (n=7). In these seven patients, VAS scores of 5 – 6 were judged as moderate pain and VAS scores of 7 – 10 as severe/intolerable pain. Median (range) symptom duration in patients presenting themselves with severe (n=17) and moderate (n=10) pain was 2 hours (0 – 24) and 36 hours (2 – 168), respectively (p< 0.001).

D-dimer as an early marker was analysed in 16 patients (59%) (fig. 4). All 16 patients had an elevated D-dimer at presentation, but no correlation was found between D-dimer levels and symptom duration. There was no statistical correlation between D-dimer and CRP levels (fig. 5, p= 0.065). Considering the small sample size, and p-values close to 0.05, a type-II statistical error can be suspected. D-dimer was not significantly correlated to length of the ischaemic bowel (r = - 0.06, p= 0.82).

The median (range) pancreatic-amylase acitivity was 1.0 µkat/L (0.1 – 2.5) in the 23 tested patients (85.2 %) (reference values 0.2 – 0.8 µkat/L). There were 12 patients (52%) with values slightly above the upper limit.

In-hospital distribution of patients
Twenty patients were initially hospitalised in a surgical ward, whereas seven patients were not. The rationale to nurse four patients at the internal medicine wards were the following: One patient had a stroke, one patient had a recent AMI, a third had both and the fourth patient was referred to the heart unit after a negative CT evaluation of the abdomen. Three patients were nursed at the ward for infectious diseases; two patients had moderate abdominal pain, vomiting and diarrhoea, imitating gastroenteritis, and one patient had fever, elevated CRP and a suspected pneumonia.

Institutional mortality (IM)
Median (range) D-dimer was 2.0 (0.4 – 5.6) and 2.4 (0.4 – 10.1) among patients who were discharged alive (n=7) and who died during hospitalisation (n=9), respectively (p= 0.37). Length of the the ischaemic bowel segment (n=27) was not an age-independent predictor of IM (p= 0.19). Patients with severe abdominal pain (n=17) and moderate abdominal pain (n=10) at admission did not differ significantly in IM (p=0.95). Patients who were discharged alive and who died during hospitalisation had a median
(range) symptom duration at presentation of 7 hours (0 – 168) and 4 hours (0.5 – 120), respectively (p= 0.67). The IM was 59 % among the 27 patients.

Predicting the diagnosis

Methods
To characterize the diagnostic properties of the variables, the concept of likelihood ratio (LR) was introduced. The positive likelihood ratio (LR+) is the ratio of the frequency of a positive test among the diseased patients (true-positive rate) and among the non-diseased patients (false-positive rate), or the sensitivity/(1 – specificity). The negative likelihood ratio (LR-) is defined as (1 – sensitivity)/specificity. Different decision or cut-off levels may be used (Diamond 1979). A true diagnostic test has an LR > 10, and an exclusion test has an LR < 0.1 (Andersson 1999).

Results
In total, 127 patients from PAPER I (n=14), PAPER II (n=101) and PAPER III only (n =12), were analysed with regard to predicting the diagnosis in patients with suspicion of acute SMA occlusion (table 3).

For instance, the presence of atrial fibrillation in a patient above 50 years with acute abdominal pain results in an LR+ of 3.1. This means that atrial fibrillation is 3.1 times more likely to be present in a patient with acute SMA occlusion than in a patient with acute abdominal pain without acute SMA occlusion. On the other hand, the absence of atrial fibrillation results in an LR- of 0.3, which means that the absence of atrial fibrillation is 0.3 times less likely to be found in a patient with an acute SMA occlusion compared to a patient without acute SMA occlusion.

The variables “female sex” (LR+ 1.5) and “age ≥ 80 years” (LR+ 1.6) were weak individual predictors, whereas “atrial fibrillation” (LR+ 3.1) and “clinical triad” (LR+ 5.3), were better. WBC was a weak positive predictor at various cut off levels, but the LR+ ratios increased parallel to the WBC levels. No patient with acute occlusion of the SMA had a WBC below 8.0. D-dimer was a predictor with intermediate strength, when the cut-off level was raised > 1.5 mg/L (LR+ 4.2). A higher cumulative predictive power was obtained after combination of two variables.

Comments
The rationale for applying likelihood ratios (LR) were several: The LR summarize the information of both sensitivity and specificity and give the discriminative power of the test. Secondly, clinicians will start from a positive or a negative test, not from diseased or not diseased. Thirdly, the LR simplify the overall evaluation of sequential testing. Fourth and most importantly, the LR is independent of the prevalence of the disease among
the studied patients, unlike the “positive” and “negative predictive values”, and can therefore be generalized to other settings (Dujardin 1994).

In PAPER III, three patients with an acute onset of intestinal ischaemia superimposed on a previously known chronic mesenteric ischaemia were excluded from the study. This selection criterion should be taken into account when evaluating the LR+ values for “clinical triad” and “atrial fibrillation”. Nevertheless, clinicians who encounter a patient with suspected occlusion of the SMA should look for the presence or absence of the listed variables in table 3, particularly the combinations. D-dimer appears to be a far better test to rule out than to rule in the diagnosis of acute SMA occlusion.

Figure 3  Estimated pain intensity at presentation in relation to duration of symptoms in 27 patients with acute SMA occlusion (p< 0.001).
Figure 4  D-dimer levels in relation to duration of symptoms at presentation in 16 patients with acute SMA occlusion ($r = -0.18$, $p = 0.5$). The horizontal dashed line indicates the cut off value at 0.3 mg/L.
Figure 5  D-dimer in relation to CRP levels at presentation in 16 patients with acute SMA occlusion ($r = -0.47$, $p = 0.065$).
Table 3  Diagnostic predictors, expressed as likelihood ratios (LR), among patients with suspicion of acute SMA occlusion in the Blekinge studies.

<table>
<thead>
<tr>
<th>Variable(s)</th>
<th>LR+ (95 % C.I.)</th>
<th>LR- (95 % C.I.)</th>
<th>SMA occl/other disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combinations of two variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical triad + D-dimer &gt; 1.5</td>
<td>15.6 (3.3 – 73.8)</td>
<td>0.7 (0.5 – 1.0)</td>
<td>16/100</td>
</tr>
<tr>
<td>Clinical triad + female sex</td>
<td>11.1 (3.2 – 38.2)</td>
<td>0.7 (0.5 – 0.9)</td>
<td>27/100</td>
</tr>
<tr>
<td>Clinical triad + age ≥ 80 years</td>
<td>9.3 (3.1 – 27.2)</td>
<td>0.7 (0.5 – 0.9)</td>
<td>27/100</td>
</tr>
<tr>
<td>D-dimer &gt; 1.5 + age ≥ 80 years</td>
<td>7.1 (3.0 – 17.0)</td>
<td>0.5 (0.3 – 0.9)</td>
<td>16/100</td>
</tr>
<tr>
<td>D-dimer &gt; 1.5 + WBC &gt; 15</td>
<td>5.8 (1.5 – 22.8)</td>
<td>0.8 (0.7 – 1.0)</td>
<td>16/100</td>
</tr>
<tr>
<td>D-dimer &gt; 1.5 + Atrial fibrillation</td>
<td>5.4 (2.1 – 13.9)</td>
<td>0.7 (0.5 – 1.0)</td>
<td>16/100</td>
</tr>
<tr>
<td><strong>Single variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synchronous emboli</td>
<td>0.8 (0.6 – 1.0)</td>
<td>27/100</td>
<td></td>
</tr>
<tr>
<td>Clinical triad</td>
<td>5.3 (2.6 – 11.2)</td>
<td>0.6 (0.4 – 0.8)</td>
<td>27/100</td>
</tr>
<tr>
<td>D-dimer &gt; 1.5</td>
<td>4.2 (2.3 – 7.6)</td>
<td>0.4 (0.2 – 0.8)</td>
<td>16/100</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3.1 (2.1 – 4.6)</td>
<td>0.3 (0.2 – 0.6)</td>
<td>26/100</td>
</tr>
<tr>
<td>D-dimer &gt; 0.8</td>
<td>2.6 (1.8 – 3.8)</td>
<td>0.3 (0.1 – 0.8)</td>
<td>16/100</td>
</tr>
<tr>
<td>WBC &gt; 15</td>
<td>2.2 (1.4 – 3.5)</td>
<td>0.5 (0.3 – 0.9)</td>
<td>26/91</td>
</tr>
<tr>
<td>D-dimer &gt; 0.3</td>
<td>1.6 (1.3 – 1.8)</td>
<td>0.0 a</td>
<td>16/100</td>
</tr>
<tr>
<td>Age ≥ 80 years</td>
<td>1.6 (1.1 – 2.3)</td>
<td>0.6 (0.3 – 1.0)</td>
<td>27/100</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.5 (1.1 – 2.1)</td>
<td>0.5 (0.3 – 1.0)</td>
<td>27/100</td>
</tr>
<tr>
<td>WBC &gt; 10</td>
<td>1.4 (1.1 – 1.4)</td>
<td>0.5 (0.2 – 1.1)</td>
<td>26/91</td>
</tr>
<tr>
<td>WBC &gt; 8</td>
<td>1.3 (1.1 – 1.4)</td>
<td>0.0 a</td>
<td>26/91</td>
</tr>
</tbody>
</table>

D-dimer in mg/L, WBC = White cell blood count (x 10⁹/L). a C.I. cannot be calculated due to division with zero. b The existence of six true positive and no false positive cases, results in division with zero.
The SWEDVASC study – PAPER IV

SWEDVASC

The Swedish vascular registry (SWEDVASC) started in 1987 in the southern health care region of Sweden. Since 1994 the whole country is accounted for, which entails registration of 8000-9000 vascular procedures per year. Up to 2002, there were more than 100 000 registered procedures, with retrieval of clinical outcome after one month and one year. Long-term mortality data are obtained by record linkage with the national death registry. Repeated controls of SWEDVASC data have shown a validity of 90% compared with the in-patient registry, and a reproducibility of 90% measured by repeatedly filling out a random sample of protocols (Bergqvist 1998). A validation of acute intestinal revascularisation procedures registered in SWEDVASC had not been performed.

Patients

Based on SWEDVASC data, 84 patients with acute SMA occlusion were identified between 1987 and 1998, of whom 60 from 21 hospitals could be retrieved and analysed. Data on indications for surgery, preoperative risk factors, details regarding the operative procedure and outcome at 1 month and at 1 year were prospectively registered. Other data have been retrieved from patient records.

Results

Disease history

The median age of the 60 patients was 76 years for both female (35) and male (25) patients (range 35-90 years). Among preoperative risk factors 14 had previous vascular surgery, 10 had diabetes, 25 had hypertension, 14 had cerebrovascular disease, six had pulmonary disease, four had renal insufficiency and nine were smokers. Forty-four patients suffered from cardiac disease, but only two patients were on anticoagulation treatment. Both had interruption of warfarin treatment under protection of low molecular weight heparin when embolisation occurred. Eight of the patients reported previous symptoms compatible with intestinal ischaemia.

Symptoms and signs

Seventeen patients (30%) suffered from severe abdominal pain with sudden onset (within minutes), 19 (33%) patients from acute pain (onset within one
hour), whereas 21 (37%) patients had an insidious onset of pain and in three the pain characteristics were unknown. Sudden onset was not more frequent among patients with embolic disease compared to thrombotic disease. On presentation, thirteen patients had less than one hour’s duration of pain, in 22 it was less than two hours, in 42 the duration was less than 12 hours and 16 patients had more than 12 hours history of abdominal pain. In 27 (53%) pain out of proportion, i.e. no sign of peritonitis in spite of intense abdominal pain, was recorded. Fourteen patients (27%) had peritonitis at presentation.

The cause of acute occlusion was considered embolic in 40 patients and thrombotic in 20. The sources of emboli were atrial fibrillation (30), acute myocardial infarction (5), aortic thrombus (1), cardiomyopathy (1) or unknown (3). Two patients had simultaneous embolisation to the lower limb.

Diarrhoea was reported among 21 patients, in eleven the stools were bloody, and vomiting was reported in 33. The diagnosis of acute SMA-occlusion was suspected at the time of the first examination in 19 (32%) of the patients due to the presence of atrial fibrillation (11), recent cerebrovascular lesion (6) or embolectomy of the lower limb (2) and sudden onset of abdominal pain (8).

**Diagnosis**

The median WBC-count on admission was 16 200 per mm$^3$ (range 5 000 – 81 000). Only two patients had a normal WBC-count. Two computer tomography (CT) scans with contrast enhancement and one duplex ultrasonography were diagnostic, among 64 non-invasive radiological examinations. The diagnosis was verified by angiography in eleven patients and at laparotomy in 49 patients. One patient had angiography after laparotomy, followed by revascularisation. Among the twelve patients examined with angiography, five had a patent proximal segment of the SMA, with either a visible embolus or an occlusion distally. These lesions were interpreted as embolic. Seven patients had a thrombotic occlusion at the origin of the SMA.

After the diagnostic work-up, a median of 16 hrs (1.5-408 hrs) from presentation, 58 patients underwent exploratory laparotomy. At the time of surgery the diagnosis was suspected in 38 (66%) patients.

The median time from presentation to surgery or thrombolysis was significantly shorter ($p=0.01$) among the patients in whom the diagnosis was suspected at first examination (6h) than among those in whom it was not (24h).

**Treatment**

All 40 patients with embolism were treated with embolectomy, and in one of these an additional intraoperative thrombolysis was performed. Among the 20 patients treated for thrombosis ten had thrombectomy. Adjunct
procedures were patch angioplasty (2), percutaneous transluminal angioplasty (PTA) (2) and aortic thrombectomy (1). Eight patients were treated with by-pass from the aorta (7) or the common iliac artery (1) to the SMA (5) or to both the celiac artery and the SMA (3). Finally, two patients were treated with thrombolysis (fig. 6 a - c) without laparotomy, one of them also underwent PTA.

Ten patients with embolic disease (25%) and fourteen with thrombosis (70%) also required bowel resection at the primary procedure. A second look operation was performed in 41 patients and a third look in eight. Nineteen patients required additional resection at relaparotomy. In all, 43 patients underwent bowel resection, 42 had a median resection of the small intestine of 145 cm (range: 10-360) and 20 had a median colonic resection of 30 cm (15-120).

**Figure 6** SMA angiogram with subsequent local intra-arterial thrombolysis in an 87-year old male with history of peripheral vascular disease and six hours of severe abdominal pain. (With courtesy of Stefan Mellander, Rolf Hellberg, Per-Åke Karlqvist Dept of Surgery and Margit Svahn, Dept of Radiology, Eskilstuna County Hospital, Sweden. Case presented in Eur J Surg 2001; 167: 308 - 311)

**Figure 6a.** Arteriogram showing an occlusion of the SMA 4-5 cm from the origin of the aorta. Contrast filling of minor branches proximal to the occlusion can be seen.
Figure 6b. Partial thrombolysis of the thrombo-embolic occlusion was obtained after a two-hour infusion with 20 mg of rtPA. Note how the contrast (in black) surrounds the oval-shaped thrombus/embolus (appears in white).

Figure 6c. Restored blood flow in the SMA after 35 mg of rtPA at control angiography 14 hours after the start of thrombolysis.
Outcome
The 30-day, institutional and one-year mortalities were 43 %, 52 % and 60 %, respectively. Among the 24 patients who were alive one year after surgery none were dependent on intravenous nutrition, whereas six were on anti-diarrhoea treatment.

Prognostic factors
A history of previous vascular surgery was associated with a higher institutional mortality. Previous vascular surgical procedures had been performed for embolism (4), for chronic (4) or for acute (2) ischaemia of the lower extremity, for aortic aneurysm (3) and for thoracic aortic dissection. All procedures had been performed more than one year previously, except for two patients treated for embolism at the same admission.

The median time span from the first examination by a physician to laparotomy was shorter (p<0.05) among the patients in whom the diagnosis was suspected, either initially or after diagnostic work-up (13 h), than among those in whom the diagnosis was not suspected (24 h), but this did not affect outcome. The 15 patients with a sudden onset and who were not hospitalised had a better outcome.

The Malmö studies – PAPERS V and VI

Patients
Between 1970 and 1982 the population of Malmö declined from 264 000 to 230 000, but the elderly population, 80 years and above, increased from 6140 to 8890. During the study period 35 784 deaths occurred among the Malmö population. In all 23 446 clinical autopsies, and 7588 forensic autopsies were performed, resulting in an autopsy rate of 87 %.

Among 23 446 clinical autopsies, 997 cases were either coded for intestinal necrosis, thrombo-embolism in a visceral artery, or mesenteric vessel occlusion/bowel infarction was defined as the cause of death. The protocols from all these 997 cases were identified and analysed.

Among 7588 forensic autopsies, 7569 (99.8 %) cases were found and reviewed.

Among 56251 surgical procedures, 11985 (21.3%) operations performed during the years 1970, 1976 and 1982, at the Department of Surgery, Malmö General Hospital, were reviewed. This sample was chosen in order to capture trends of surgical activity during the study period. After screening of the registry of operative procedures, 525 (98%) out of 537 patient records were found and reviewed. Each of the number of cases retrieved after
operation only were divided by 0.213 in order to render the figures comparable with the number of cases retrieved after autopsies.

All patients where the acute SMA occlusion had resulted in a transmural infarction of the intestine were included.

Methods

The clinical autopsies
All clinical autopsies were performed at the Department of Pathology, Malmö General Hospital using a standardized protocol. Findings were coded according to the Systematized Nomenclature of Pathology (the SNOP code), as defined by the College of American Pathologists in 1965. There was a standardized intraluminal exposure of all major arteries originating from the aorta, including the carotid and subclavian arteries and down to the division of the common femoral arteries. During the standardized examination of the SMA, the bowel package was divided from the great mesenteric vessels at the mesenteric root, leaving the greater part of the mesentery attached to the bowels. SMA was then cut open from its aortic origin and checked for intraluminal thrombus or embolus. Distal branches in the mesentery were also examined, particularly if a short bowel segment showed signs of infarction.

Classification of thrombosis and embolism in the SMA – PAPER VI
In the differentiation between thrombotic and embolic occlusions, the pathologists descriptions and conclusions were of utmost importance. The presence of synchronous embolism was judged to be a clear-cut indication of embolic disease. The findings of heart thrombi strongly supported the interpretation of an embolic aetiology. The characteristics of SMA, such as extension and location of atherosclerotic lesions, the appearance of single or multiple occluding clots, the level of occlusion and the presence of clot adhesion to the intraluminal wall, gave supportive information.

In 31 out of 213 patients (15 %), the situation was less clear, and these autopsy protocols were validated separately by two experienced vascular surgeons to reach a consensus. In three cases it was not possible to elucidate the nature of the occluding lesion, and these cases were labelled as indeterminate.

The registry of surgical procedures – PAPER V
The registry of surgical procedures was cross-checked with the computerized in-patient registry, resulting in a validity of 100 % for the registry of operative procedures and 71 % for the in-patient registry. In the in-patient registry, nine patients had been incorrectly coded as having suffered from mesenteric vessel occlusion.
Results - PAPER V

Mortality from acute SMA occlusion

Between 1970 and 1982, 211 cases of acute SMA occlusion leading to transmural intestinal infarction were identified at clinical and two at forensic autopsies. This corresponds to a cause-specific mortality of 6.9/1000 autopsies. The mortality increased with increasing age: 11.8 /1000 autopsies occurring in octogenarians and beyond. Acute SMA occlusion accounted for 6.0 /1000 deaths. No deaths from this cause were encountered below the age of 35. The estimated overall mortality was 93 %.

Cases retrieved from the clinical sample

Sixteen patients with a median age of 75 years (range 64 – 94), and of whom nine were women, were diagnosed during an operative procedure in the years 1970 (n =2), 1976 (n=5) or 1982 (n=9). Four patients survived and twelve of the operated patients died, of whom eight did not undergo autopsy. Thus, twelve patients were not encountered at the autopsy registry in this sample, and the estimated total number of cases identified at operation only was calculated to 57 (12/0.21).

Incidence of acute SMA occlusion

The incidence of autopsy-verified acute SMA occlusion was 6.8 /100 000 person years (95% C.I. 5.9 – 7.7). The estimated overall incidence of fatal and non-fatal disease was 8.6 (95 % C.I. 7.6 – 9.7) per 100 000 person years. The incidence increased exponentially with age (p< 0.001) in both men and women, with approximately a doubling of the incidence per 5 year interval mounting up to a peak incidence of 217 (169 – 264) per 100 000 person years in the age category 85 and above (fig. 7).

The proportions of cases diagnosed at autopsy only, at operation and subsequent autopsy, and at operation only, were 65, 14 and 21 %, respectively.
Comments – PAPER V

It can be assumed that the choice to investigate only a sample of the surgical procedures will lead to less precision than in the autopsy material. However, in a 10-year period from 1975, Lindblad found 50 operated cases with acute SMA occlusion at Malmö General Hospital by screening the registry of surgical procedures (Lindblad 1987). The found rate of 5.0 operated cases/year was similar to the estimated 5.9 operated cases/year (16/0.21/13) in PAPER V.

Furthermore, the autopsy cohort has partly been investigated previously: In a 20-year period from 1968 – 1987, Wroblewski found 42 (20 %) cases with mesenteric infarction among 212 patients with peritonitis, confirmed at either autopsy (93%) or laparotomy (7%), at Värnhems Hospital, which is a large geriatric hospital in Malmö. Mesenteric infarction was the most common cause of peritonitis in these geriatric inpatients.
How does this incidence relate to other lethal conditions with diagnostic difficulties? Previous studies of the Malmö population provide a unique opportunity to compare incidences of lethal conditions (table 4). For instance, acute SMA occlusion was a more common condition than ruptured abdominal aortic aneurysm (AAA).

Table 4  Population-based studies on fatal diseases conducted in Malmö, Sweden

<table>
<thead>
<tr>
<th>First author</th>
<th>Disease studied</th>
<th>Study period</th>
<th>Autopsy Frequency (%)</th>
<th>Incidence / 100 000 person years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bengtsson</td>
<td>Ruptured abdominal aortic aneurysm</td>
<td>1971 - 86</td>
<td>85</td>
<td>5.6</td>
</tr>
<tr>
<td>Appelros</td>
<td>Acute pancreatitis, fatal</td>
<td>1985 - 94</td>
<td>42</td>
<td>1.3</td>
</tr>
<tr>
<td>Nordström</td>
<td>Pulmonary embolism, fatal</td>
<td>1987</td>
<td>79</td>
<td>77.4</td>
</tr>
<tr>
<td>Acosta (PAPER V)</td>
<td>Acute SMA occlusion</td>
<td>1970 - 82</td>
<td>87</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Results – PAPER VI

Patient characteristics

At clinical and forensic autopsies, 211 and two patients, respectively, were diagnosed with acute SMA occlusion and intestinal infarction. In the referral note for autopsy, a suspicion of intestinal ischaemia was noted in 39 (22 %) among the 176 patients managed non-operatively, and 30 (81 %) among the 37 patients who underwent abdominal surgery and subsequent autopsy. Thus, in total, there was a documented suspicion of intestinal ischaemia prior to death in 69 (32 %) of the 213 cases. Apart from laparotomy, ten limb embolectomies and seven lower limb amputations were undertaken within one week before death. The patients died in various ward units: Geriatric (77/213; 36 %), Surgery (74; 35 %), Internal medicine (47; 22 %), Infectious diseases (6; 3 %), Oncology (5; 2 %) and Orthopaedics (2; 1 %). Two patients (1 %) died outside of hospital. The patients at surgery wards had a mean age of 85 years, compared to 77 years in patients at both geriatric and internal medicine wards, respectively (p< 0.001). There was no difference in gender distribution between these wards (p = 0.11).
Thrombosis vs embolism in the SMA
The cause of occlusion was judged to be embolism in 122 (57.3 %), thrombosis in 88 (41.3 %) and indeterminate in 3 (1.4 %). Thrombotic occlusions were often located more proximally than embolic occlusions (p < 0.001). There were findings of cardiac thrombi in 58 patients with embolic occlusion (48%), compared to ten patients with thrombotic occlusion (11%). Atrial fibrillation was documented in 49 patients with embolism (40 %) and in 14 patients with thrombosis (16%). Adhesion of thrombus/embolus to the intraluminal wall was documented in 73 patients with thrombotic occlusion (83%) and in 47 patients with embolic occlusion (39%). The emboli were “slightly” or “partially” adhesive to the intraluminal wall in 15 out of these 47 cases with embolic occlusion (32%).

Determinants of extent of intestinal infarction
The intestinal infarction affected jejunum, ileum and colon in 158 (76%), 200 (96%) and 127 (61%) of the 208 classifiable cases, respectively (fig. 8). At least two of these intestinal segments were infarcted in 82% of the cases. All three intestinal segments were infarcted in 50%. The intestinal infarction was more extensive in patients with thrombotic, compared to embolic, occlusions (p= 0.025). The extent of the intestinal infarction, defined as the number of infarcted segments, was not correlated with age.

Figure 8  Extent of intestinal infarction in 208 patients with acute SMA occlusion.
Sources of emboli
Among the 122 patients with embolus to the SMA, 86 (70 %) had at least one of the following signs of a cardiac source: cardiac thrombi (n = 58), acute myocardial infarction (23) or documented atrial fibrillation (49) in the referral note. In six of these patients aortic thrombus was considered the probable source of embolus. In all, it was possible to identify a probable source of the embolus in 80 % of the patients with embolic occlusion.

Concurrent acute thrombo-embolic diseases
Apart from the SMA thrombo-embolism, there were 104 cases (49 %) with at least one additional acute thrombo-embolic disease, such as acute myocardial infarction, acute ischemic stroke and synchronous embolism.

Synchronous embolism
In 83 (68%) out of 122 patients, synchronous embolism was present, affecting a total of 273 arterial segments other than the SMA. Up to 14 synchronous emboli were found in one patient; 29, 20 and nine patients having synchronous emboli in one, two and three arteries, respectively (fig. 9).

In all, there were objective signs of embolic disease, i.e. source of emboli and/or synchronous embolism, in 115 (94 %) of the 122 patients with embolic occlusion of the SMA.

![Figure 9](image.png)

**Figure 9** Number of synchronous emboli among 122 patients with an embolus to the SMA
GENERAL DISCUSSION

Incidence

It is commonly stated in the literature that acute mesenteric ischaemia is uncommon, in spite of no supportive data from population-based studies. Up to 1950, there were published series on cases diagnosed at autopsy (Boley 1997). Later it became possible to save lives due to advances in surgery and reports have mainly focused on surgical outcome. Contemporary series deals with cases from specific hospitals or referral centres (Endean 2001, Park 2002, Edwards 2003), without being able to estimate the proportion of patients who were clinically undetected.

The necessary conditions to carry through a population-based study on such a highly lethal disease with diagnostic difficulties were found in Malmö in Sweden. Malmö General Hospital is the sole referral hospital for patients with somatic diseases for the city population. The Department of Pathology has been a central institute in epidemiological studies on atherosclerosis. The standardised autopsy technique and the exceptionally high autopsy-rate, were favourable factors in conducting an epidemiological study on acute SMA occlusion.

We estimated the overall incidence in Malmö between 1970 and 1982 to be 8.6/100 000/year. The incidence increased exponentially with age, equally in men and women, up to 217/100 000/year in the age category 85 and above. There were no cases in persons younger than 35 years. These incidence figures were very dependent on the number of cases found at autopsy, since 2/3 of the estimated 270 cases were detected at autopsy only. Women predominated among the elderly in the population of Malmö, and as in other studies (Mamode 1999, Endean 2001, Park 2002, Edwards 2003) on acute occlusion of the SMA, females were more affected than males, in terms of crude numbers. The gender-specific incidence rates, on the other hand, did not differ significantly when age-standardized incidences were compared. With sufficient sample-size, and with a high autopsy-rate even among the most elderly, it was possible to correct for the confounding factor of age, which hitherto has given the probably false impression that women predominated in this disease.
In the contemporary Blekinge study (PAPER III), the estimated overall incidence was lower, 5.3/100 000/year, in spite of the doubled proportion of octogenarians in the population. This difference can very well reflect the much lower autopsy rate.

It is unlikely that the contemporary incidence in Malmö can be assessed due to the presently low autopsy rate. Although diagnostic and surgical activities have increased since the 1970s, and in spite of the prospective study-design, the Blekinge studies have shown that the disease was frequently overlooked and diagnostic autopsies were not uncommon.

The proportion of octogenarians in Malmö has doubled up to 5.8 % of the population in 2002, compared to 3.0 % in 1976, and in absolute numbers there has been an increase of octogenarians with 8315 (116 %) persons (http://www.scb.se), suggesting that this condition may appear in larger number today than the about 21 annual cases who were diagnosed in the Malmö study. There was a trend towards an increase in patients diagnosed with acute SMA occlusion at laparotomy between 1970 and 1982, and in view of advances in radiological imaging and increased surgical activity, one might suggest that there has been a continuous increase in clinically detected cases. However, it is unclear if the proportion of cases diagnosed at laparotomy has increased since 1982 in Malmö. Future research on the relation between clinically detected and undetected cases can only be assessed in a population with a high autopsy rate.

It is likely that this suggested trend of increase in incidence of acute SMA occlusion will continue, since forecasts (Etzioni 2003) on population growth, clearly indicates that individuals aged 65 years or older are the fastest growing age category in the western world and in 2020 the number of individuals will have increased by 50 %, relative to 2001.

**Pathogenesis**

**The difficult distinction between occlusion of the SMA and non-occlusive mesenteric ischaemia**

The clinical studies, particularly PAPER III, were less accurate in determining the nature of the arterial ischaemia than the autopsy studies. Nevertheless, revascularisation procedures or autopsies verified the occlusion in ten cases (42%) in PAPER III. Since preoperative SMA angiography was not performed in the other 14 cases, it cannot be excluded that cases with systemic low flow states or non-occlusive mesenteric ischaemia (NOMI) were present (Montgomery 1997). In cases where revascularisation was not performed, clinical conditions such as synchronous embolus, atrial fibrillation, acute/recent myocardial infarction, and extension
of the infarction to the mid transverse colon, were interpreted as signs of occlusion of the SMA. However, we carefully excluded patients with probable NOMI due to cardiogenic, septic or hemorrhagic shock (Gottlieb 1986, Kolkman 2000) or who recently had undergone cardiac surgery (Huddy 1991, Sakorafas 1999,) in PAPER III. We were unable to identify any study reporting on the extent of visceral infarction, comparing patients with arterial occlusive mesenteric ischaemia and fatal NOMI.

The difficult distinction between embolic and thrombotic occlusion of the SMA

All patients in the SWEDVASC study had an occlusion, but the nature of occlusion is not always certain. The distinction between an embolus or thrombus may be difficult even for an experienced vascular surgeon, and only 12 out of 60 patients underwent angiography.

In the autopsy studies the presence of an occlusion was confirmed in all included patients. The occlusive mechanism was studied, and when there was any doubt about the aetiology, the entire autopsy protocol was assessed independently by two experienced vascular surgeons. In spite of a standardised autopsy technique and detailed description of the findings within the SMA, synchronous embolus was judged to be the most valid objective sign of an embolic occlusion. Cardiac thrombi and atrial fibrillation as such – providing the prerequisite for embolism but not giving the strengthening evidence of a synchronous embolism to another organ – were judged to be less valid findings of an embolic occlusion, and in fact occurred in ten and 14 patients with thrombotic occlusion, respectively. Thus, overestimation of cases with embolic occlusion may, in addition to the exclusion of patients with chronic mesenteric ischaemia, have contributed to the high embolus/thrombus ratio of 5 in PAPER III. Predominance of thrombotic occlusions has been reported in selected patient series in tertiary centres with a high frequency of chronic mesenteric ischaemia and subacute interventions (Park 2002, Edwards 2003). Objective signs of thrombotic occlusion were more difficult to find in PAPER VI, but firm adhesion of clot to the intraluminal wall occurred more frequently in thrombotic than in embolic occlusions. Thus, it is difficult to determine the occlusive aetiology of the SMA, even in PAPER VI, where the design allows an unprecedented accuracy in the assessment. In addition, the defined embolus/thrombus ratio of 1.4 in PAPER VI, may be valid only for the population and time-period studied.

Determinants of the extent of intestinal infarction

Thrombotic occlusions were located more proximal than embolic, rendering a more extensive intestinal infarction, a finding that is consistent with the
report by Ottinger. In the Blekinge studies, but not in PAPER VI, old age was associated with a more extensive infarction. The methodologies, however, were different in the two studies: In the Blekinge studies, length of the infarcted bowel was measured in decimetres from the serosal side at operation in 23 patients and at autopsy in four patients. In PAPER VI, the bowel from the 213 patients was evaluated post mortem, where the pathologists estimated the extension of the infarcted bowel semi-quantitatively, relating to segments, *i.e.* jejunum, ileum and colon, rather than in decimetres. Furthermore, macroscopic infarctions were assessed both from the mucosal and serosal side, and if there was suspicion of postmortem changes, *i.e.* autolysis, microscopy was undertaken to determine the nature of the changes.

**Co-morbidity**

The clinical and epidemiological studies each provide complementary information in describing the extent of comorbidity in these patients. The high frequency of coexistent conditions such as previous ischaemic stroke, ischaemic heart disease and hypertension in patients with acute SMA occlusion is well known (Endean 2001, Park 2002, Edwards 2003). The prevalence of atrial fibrillation in these patients has not received much attention and we found 95 % of the 20 patients with embolic occlusions to have atrial fibrillation in PAPER III. Treatment with and without warfarin occurred in two and eight patients, respectively, who had a history of coexistent atrial fibrillation and ischemic stroke, prior to the embolic occlusion of the SMA. It is well documented that warfarin is underprescribed as secondary antithrombotic prophylaxis in patients with atrial fibrillation and even in treated patients, about half the time they have subtherapeutic INR (Bungard 2000, Chiquette 1998, Evans 2000). Even if atrial fibrillation is recognised as a potential lethal disease, there is still a discrepancy between guideline recommendations, *i.e.* warfarin as primary prophylaxis to patients at risk for embolic complications, and actual practice (Frykman 2001, Connolly 2003).

Among the 213 autopsy cases, half had concurrent acute thromboembolic manifestations such as AMI, ischemic stroke or synchronous embolism. In embolic cases, the multiplicity of embolism, 273 synchronous emboli in 83 patients, was found to be unexpectedly high. Visceral embolism occurred frequently, a finding that has not been reported from previous studies. The impact of synchronous emboli on mortality has previously only been recognised by Batellier, who found 46 synchronous emboli in 36 patients in a selected series based on angiography.
Variability in abdominal pain expression

Onset of disease has often been thought to be dramatic and sudden in cases with embolic occlusion or insidious in cases with thrombotic occlusion (Bergan 1964, Eldrup-Jorgensen 1997). However, Endean reported that sudden onset of abdominal pain occurred in almost every patient in that study, regardless of aetiology, whereas the SWEDVASC study (PAPER IV) and the prospective Blekinge study (PAPER III) showed a spectrum of onsets of the disease. In the Swedvasc study, the onset was not reported to be more sudden among patients with embolic disease, but the history of sudden onset, in contrast to insidious onset, made the physician suspicious of the diagnosis in eight of 60 cases at first examination.

The pain intensity may vary in the course of the disease and sometimes three phases can be recognized (Shaw 1957): An initial phase with severe pain, that sometimes fades, followed by a third phase characterized by full wall bowel necrosis, peritonitis and increased pain. The pain analysis among the patients in the Blekinge studies showed that an early presentation was associated with a more severe pain than was a later presentation (fig. 3). However, the group of patients that presented themselves late with a moderate pain in some cases may had suffered from a more severe pain at onset. For different reasons these patients were admitted or examined late in the course of the disease. Thus, a detailed pain history may be of great importance at first examination.

Multi-disciplinary awareness

In order to increase the diagnostic accuracy, the use of terms such as ‘the clinical triad’ has developed. The Blekinge studies, however, suggested that this combination of severe abdominal pain in relation to minimal abdominal signs, bowel emptying and source of embolus, was not a strong predictor for acute SMA occlusion. In stead, it has to be recognized that this disease is variable in appearance and severity at presentation, and sometimes signs of extra-abdominal disease such as stroke, arterial embolism to the extremities or acute myocardial infarction, may predominate. In PAPER III, neither stroke nor leg ischaemia were helpful signs in the diagnostic work-up in the five patients with clinical synchronous emboli. Diagnostic delay in the three cases with acute ischemic stroke might have been caused by defective communication and unawareness of the possibility of a synchronous embolus to the SMA. Furthermore, elderly patients with stroke may not have sufficient priority compared to other emergency assignments. On the other hand, two patients in PAPER IV were diagnosed early due to synchronous leg ischaemia. Nevertheless, the surgeon should look for a source of emboli in cases with acute abdomen and suspected embolism, and include ECG in
the initial work-up to detect atrial fibrillation or signs of ischaemic heart disease.

Thus, it should be pointed out that there is an in-hospital mal-distribution of these patients after the first consultation at the emergency department, either because of misinterpretation of the disease or due to other more obvious concomitant manifestations, such as AMI or ischemic stroke. In a retrospective series of mixed cases of intestinal ischaemia, 19 (33%) out of 57 cases were initially managed in non-surgical wards (Mamode 1999). In the Blekinge studies, seven (26%) of the 27 patients were initially observed in non-surgical wards: four patients were nursed at internal medicine wards mainly due to concomitant cardiac and/or neurological manifestations, and three patients were nursed at the ward for infectious diseases due to suspected infections.

Investigations

D-dimer

D-dimer was elevated in all 16 tested patients with acute SMA occlusion, suggesting its utility as an exclusion test. A screening test to rule out a life-threatening condition must have a sensitivity very close to 100%, which of course cannot be established in a study of only 16 patients. Hence, larger patient studies are needed to obtain a more precise estimate and to narrow the confidence intervals. In the present Blekinge studies, we found that elevated D-dimer, the clinical triad, the presence of atrial fibrillation, old age and female sex, were rather weak individual predictors for acute SMA occlusion, but in combination they provided a higher predictive power.

D-dimer values are lowered by warfarin (Li-Saw-Hee 2000), even by subtherapeutic doses (Nozawa 2004), unfractionated heparin (Couturand 2002) and low-molecular heparin (Kraaijenhagen 2003). One should also be aware of the existence of various commercially available D-dimer assays and calibrators provided by the manufacturers and the variability in performance characteristics of these D-dimer tests (Dempfle 2001). Thus, our D-dimer results cannot directly be generalised to other hospital settings. However, we found a highly significant correlation at the group level between the immunofiltration assay used in the Blekinge studies (Nycocard®), and the three different quantitative latex-enhanced immunoassays.

There was no correlation between D-dimer levels and WBC, and a trend towards an inverse relation between D-dimer and CRP (fig. 4). This suggests that D-dimer is not an unspecific acute phase reactant or a marker for inflammation or necrosis, but rather an early marker of acute vascular
The rise in D-dimer in patients with acute SMA occlusion is consistent with previous reports on ruptured AAA (Adam 1999) and acute arterial thromboembolism in the lower limb (Peltonen 1995). In patients with aortic dissection, the highest D-dimer values were found early in the course, demonstrated by a significant negative correlation between the absolute D-dimer values and the time from the onset of symptoms (Weber 2003). This finding could not be verified among the 16 D-dimer tested patients with acute SMA occlusion in Blekinge (fig. 4).

In contrast to other markers of coagulation/fibrinolysis, D-dimer is a stable molecule and do not present large fluctuations in plasma (Amiral 1996), and the molecule has a sufficiently long half-life in vivo, 4 - 8 hours (Niewenhuizen 1982), to attain higher plasma levels in situations when the generation of D-dimer is accelerated. Hence, the D-dimer test may be less suitable in patients with symptoms exceeding one week, which may occur in cases with venous thromboembolism (Leroyer 1997, Oger 1998, Kraaijenhagen 2003). Nevertheless, the use of D-dimer as a test of exclusion in patients with a low clinical probability of venous thrombo-embolism is evidence-based (The Swedish Council on Technology assessment in Health Care 2002, Schutgens 2003, Wells 2003).

Hyperamylasaemia

It is important to note that a slightly elevated amylase activity is common, and has been reported to occur in 41 - 53 % of patients with acute SMA occlusion (Mamode 1999, Ottinger 1978, Clavien 1987). In PAPER II, when patients with acute pancreatitis had been excluded, patients with acute SMA occlusion had higher pancreatic amylase values at the group level, compared to those with other conditions. Theoretically some of the patients with acute SMA occlusion may have decreased pancreas perfusion due to obstructed flow in the inferior pancreaticoduodenal artery and/or due to a systemic low flow state, with subsequent leakage of pancreatic amylase to the circulation. However, this unclear mild hyperamylasaemia is also a common finding in patients with other causes of acute abdomen than acute pancreatitis (Lin 1989, Ventrucci 1992, Pezzilli 1997), and even in patients after cardiac surgery (Sakorafas 1999). In PAPER III, two patients (out of 24 patients) were initially misdiagnosed as acute pancreatitis due to a slightly elevated pancreatic amylase, resulting in diagnostic delay and death from acute SMA occlusion. It has been suggested that the cut-off value of total amylase should be raised in order to increase its positive predictive value as a specific marker for acute pancreatitis (Lin 1989).

Imaging techniques

Framing of specific questions such as occlusion of the SMA should be directed to the radiologist in order to be able to proceed with a technically optimized investigation concerning the SMA and its major branches. The
lack of specific questions resulted in negative CT examinations without contrast-enhancement in both PAPERS III and PAPER IV. Distal occlusions of the SMA were also missed, in spite of contrast-enhancement. The role of high resolution multiple detector-row CT-angiography (Fleischmann 2003, Wiesner. 2003, Kirkpatrick 2003) and contrast-enhanced 3-D MRT (Goyen 2002, Laissy 2002) may become increasingly important in the future. In addition, CT and MRT images may be shared by clinicians as they are more easily demonstrated, compared to duplex examinations. Furthermore, they are less operator dependant, and therefore more feasible in the emergency situation. Duplex may also be unreliable when the disease has turned into the paralytic phase with intestinal gas distension. One must be aware of, though, that a proportion of the patients will have distal occlusions, difficult to diagnose with these imaging techniques.

**Time window to operation**

Prompt recognition and timely intestinal revascularisation is crucial to avoid extensive bowel resections in order to reduce mortality and to avoid short bowel syndrome. The degree of intestinal ischaemia caused by the occluding thrombus/embolus can not be predicted. In case of rapidly developing extensive intestinal ischaemia, only vigorous action can rescue the patient from death. However, the clinical studies have suggested that intestinal ischaemia may be a dynamic process in some patients, probably due to factors such as degree and location of the occlusion, collateral circulation and systemic blood pressure. In PAPER IV, nine patients had duration of symptoms between 1 – 7 days, but were alive without dependency of intravenous fluid support one year after the intestinal revascularization. Thus, a few patients with acute SMA occlusion can be revascularised late in the course with successful outcome. However, it is likely that these patients may suffer from a more extensive bowel loss and other morbidities than if treated earlier. In the Blekinge studies, five patients with symptom duration between 1 – 8 days were alive at one year after resection of the infarcted bowel. In addition, there was one patient who sustained intestinal ischaemia for nine days, due to an initially false negative explorative laparotomy, followed by a bowel resection at re-laparotomy, and survived four months postoperatively. Thus, only laparotomy can estimate the extent of intestinal infarction and patients with a limited bowel infarction can sometimes be saved late in the course by a bowel resection. Hence, patients with suspicion of acute SMA occlusion should not be refused therapy merely based on time limits.
Diagnosis

Laparotomy
At laparotomy, in rare cases the intestines may seem normal in colour and peristaltic motion, despite acute occlusion of the SMA. In such a situation, it is essential to isolate the main SMA and note the presence or absence of pulsations (Shaw 1957). This was not performed in one out of the twenty operated cases in PAPER III, which resulted in a severe diagnostic delay. Other causes, particularly intestinal ischaemia secondary to adhesive bowel strangulation can in most cases be excluded at laparotomy.

It must be recognised that mortality is high among elderly patients with acute abdominal complaints who are admitted through the emergency department, particularly those who are misdiagnosed (van Geloven 2000). The spectrum of diseases among the elderly with acute abdomen frequently requires surgery (Potts IV 1999). Laparoscopy might be a feasible and an underused alternative to laparotomy for an early diagnostic approach of intestinal ischaemia (Leister 2003). This minimal invasive strategy has the advantage of being quick, and can guide the surgeon to make a more limited abdominal wall incision (Riemann 2003). The method also has the advantage of preventing unnecessary laparotomies, which are associated with a higher morbidity and longer hospital stay (Karnam 2002). Through laparoscopy three patients with intestinal ischaemia were correctly diagnosed in the Blekinge studies, of whom two could be discharged. In PAPER II, one negative laparoscopy was performed in an un-communicable patient, who later on improved after antibiotic treatment and could be sent back to the nursing home.

Angiography
Selective angiography is a specific method to diagnose acute SMA occlusion (Batellier 1990). There are major drawbacks with this invasive technique: Acute angiography is not feasible in all hospitals, or may not be feasible throughout the twenty-four hours. An aggressive diagnostic policy will lead to a large number of negative examinations and is considered by some to be a poor use of resources. Angiography must be utilised early in the course, since the procedure further delays surgical intervention (Bradbury 1995). The use of angiography in eleven patients in PAPER IV was not associated with an increased survival-rate.
Treatment

**Assessment of intestinal viability**

Late diagnosis and transmural extensive necrosis at laparotomy are seen all too often (Eldrup-Jorgensen 1997, Järvinen 1994), leaving the surgeon with no surgical option. In many cases there are multiple segments of questionable viability. Determination of intestinal viability then becomes a matter of great importance: Clinical judgement, *i.e.* assessment of visible pulsations in the mesenteric arcade vessels, bleeding from cut surfaces, colour and peristaltic motion, were used in our clinical studies. In two prospective studies clinical judgment proved accurate, compared to Doppler ultrasound and flourescein injection (Bulkley 1981), and Laser Doppler flowmetry (Redaelli 1998), respectively. Re-evaluation of intestinal viability should be postponed until at the earliest 30 minutes after revascularization.

**Bowel resection**

It can be questioned if an elderly patient with full wall intestinal infarction from near ligamentum Treitz to the mid-transverse colon can be saved to a meaningful life by a bowel resection. Some researchers advocate bowel resection of extensive transmural necrosis in the presence of spared jejunal arcades, as long-term survival has been reported with and without long-term parenteral nutrition (Bradbury *et al.* 1995). At laparotomy, we did not have a clear policy at Blekinge hospital, whether to perform an extensive resection or not. There were a total of eight patients with an extensive intestinal infarction of the small bowel up to the mid-transverse colon: Six cases were considered untreatable and two were treated with bowel resection, of whom one died two days postoperatively and the other had a miserable life due to a short bowel syndrome until he died six months postoperatively.

The issue of anastomosis or diverting stomas following bowel resection is controversial. Bowel resection with an end to end anastomosis at primary operation can be performed in patients with a short infarcted segment with a clear bowel margin viability (Järvinen 1994). In contrast, bowel resection followed by double stomata, may be considered a treatment option in patients with extensive ischaemia or necrosis with an unclear demarcation zone (Levy 1990). In the Blekinge series, we found disadvantages with both methods, such as late anastomotic leakage in one patient and persistence of bowel discontinuity with short bowel syndrome in two patients, respectively.

A third alternative would be to staple off the infarcted intestine and to leave the reconstruction of bowel continuity until second look laparotomy, in line with the concept of abbreviated laparotomy (McPartland 2003).
Revascularisation of the SMA

Surgeons deal with conditions referred to as ‘acute abdomen’, but may have limited experience of cases with intestinal ischaemia and may not have the expertise required to perform an intestinal revascularisation. Timely intestinal revascularisation seems to be a prerequisite for survival in many patients with acute SMA occlusion, since it was shown that a high proportion of the patients had proximal thrombo-embolic occlusions with extensive intestinal infarction at autopsy. In view of these findings, general surgeons need to collaborate with vascular surgeons.

It is not unusual to find mixed segments of transmural intestinal necrosis and other segments with less severe ischaemia, at laparotomy. Brittain advocates that revascularisation attempts should be used liberally, preceding bowel resection, since restoration of pulsatile flow to the SMA may produce remarkable change to the dark appearance of the intestines. However, rapid bowel resection of the full wall necrotic intestinal segment prior to revascularisation is suggested by Weixong, to avoid reperfusion of irreversible infarcted intestines and flushing of toxic metabolites, activated leucocytes and platelets into the systemic circulation. This may lead to ‘splanchnic shock’, where patients may progress rapidly to death from cardiac arrest or multiorgan failure (Wang 1990 and Fullerton 1993). In PAPER III, bowel resection prior to revascularisation was performed in only one case, due to a leaking perforation in a necrotic intestinal segment.

Second look

Second look laparotomy is recommended in cases after revascularisation procedures, regardless of the condition of the patient, at 12 – 36 hours after primary surgery (Levy 1990). The rationale for this is that although the main stem of the SMA seems to be cleared from thromboembolism, occluded peripheral branch with a short segment of intestinal infarction, may be apparent at second look (Klass 1951). It aims also at reducing unnecessary bowel resections at primary exploration and to detect insufficient bowel anastomoses (Lindblad 1987). It must be remembered that severe intestinal ischaemia causes bowel destruction from the mucosa outward (Marston 1963, Haglund 1987). Second looks were frequently performed in the SWEDVASC study (PAPER IV), and in half of these cases additional life-saving bowel resections were performed. The second look rate was lower among the revascularised patients in PAPER III, probably inflicted by ethical considerations and by the fact that the median age of these six patients was ten years higher.
Thrombolysis

There are sparse case reports of successful early mesenteric angiography with subsequent local thrombolysis without laparotomy (Kwauk 1996, Sternbergh 2000). Mellander reported two successful cases from Eskilstuna Hospital, both presenting themselves early in the course, and were included in PAPER IV (the first case is illustrated in fig 6a – c). Despite this success and awareness of the disease, not a single patient with this condition has been treated with local thrombolysis the last five years at this county hospital. Thrombolysis may have the potential to lyse an embolus and its fragments more completely than an embolectomy. If early diagnosis becomes more feasible, local thrombolysis may be optimal in these elderly patients with concurrent cardio-vascular disease. The need for a subsequent laparotomy to assess intestinal viability after local thrombolysis is unclear, but conservative treatment can be successful in the absence of peritoneal signs or persistent pain (Mellander 2001). However, thrombolysis is contraindicated if intestinal infarction is suspected, since there is a risk of fatal bleeding from the mucosa (Bradbury 1995).

Prognosis

Prognostic factors

The impact of the extent of intestinal infarction on mortality is well-known (Ottinger 1978, Kieny 1990 and Järvinen 1994). Also in the Blekinge studies an association between the length of the ischaemic bowel and mortality was found, but this association disappeared after adjusting for patient age. In PAPER IV, sudden onset of pain was a predictor of survival only when the patient fell ill outside of hospital. This might be explained by the fact that hospitalised patients already suffered from serious co-morbid conditions when they fell ill in acute occlusion of the SMA. However, neither pain intensity at presentation, nor symptom duration, predicted survival in the Blekinge studies. Furthermore, previous vascular surgery, mainly due to lower limb ischaemia, was related to higher IM in PAPER IV. This may be attributed to the fact that these patients, apart from the occlusive event of the SMA, often have a generalised atherosclerotic disease and an increased risk of premature death (Ögren 1993).

The revascularised patients in PAPER III had a less favourable outcome in comparison to the patients in PAPER IV. This may be explained by the fact that the patients were a decade older in Blekinge, that in some cases a late revascularization was performed and that second look laparotomy was not as frequent. Furthermore, two thrombectomies were performed with the
Fogarty balloon catheter, which is not considered to be an optimal revascularization technique in patients suffering from thrombosis.

The prospective setting of the Blekinge studies contributed to a more active approach to the elderly with acute abdomen. This might have rescued some patients with acute SMA occlusion, probably due to a timely performed bowel resection. On the other hand, it is also likely that advanced surgery and intensive care was initiated in patients who were beyond therapy already at onset of disease.

We were not able to show that second look laparotomy was associated with lower IM in PAPER IV, but the groups were not comparable. The patients who had not undergone a second look laparotomy had either a favourable prognosis due to no signs of peritonitis nor of sepsis, or they had a dismal prognosis due to the fact that further treatment was withheld. However, two-thirds of the patients underwent second look, and half of these patients needed additional bowel resections.

**Mortality**

The cause-specific overall mortality was 6.9/1000 autopsies, increasing up to 11.8/1000 autopsies among octogenarians. Relating to the 270 cases found in Malmö 1970-82, there was a 93% IM. Here, one must consider the potential underestimation of mortality due to lack of precision or systematic bias owing to the fact that whereas the autopsy study covered the entire time-period, the clinical sample only represented a 21% sample. Survival may be higher today, due to increased diagnostic and surgical activity. However, whether this is the case or not is difficult to study in light of the dramatic decrease of the autopsy frequency. We found the IM to be 59% among the 27 patients in Blekinge. This is a favourable outcome compared to other series (table 1), especially when considering the very high median age and the inclusion of four cases detected at autopsy. The prospective setting might explain this result.

**Ethical aspects**

It is important to gather as much background information as possible about each patient, *i.e.* disease history and physical abilities, to be supportive in the decision-making process, particularly when there is a suspicion of a lethal condition such as acute SMA occlusion. In these emergent situations available information may be scarce. When can you hope to enhance life expectations by operating and when does an operation only extend the suffering? The right decision in these emergent situations reflects high
surgical competence, whereas technical operating skills are of secondary importance (Spencer 1983).

Among the four patients who were diagnosed at autopsy in PAPER III, two were never considered for a laparotomy due to age above 90 years and aversion to any investigation, respectively. In the two other elderly patients a less active approach may have been inflicted by factors such as blindness and previous operation for breast cancer with unknown metastatic status, respectively. In addition, there were three non-operatively managed patients with suspected acute SMA occlusion who had to be excluded from the Blekinge studies, since the diagnosis could not be confirmed by autopsy. In these cases, the surgeons firmly refrained from exploratory laparotomy due to dementia and/or age above 90 years. Such decisions may be hazardous, since only laparotomy can confirm the diagnosis. It is strongly advised that surgeons refer an unclear fatal case to autopsy, since feedback to clinical practice will help doctors make better decisions for their future patients (de Dombal 1986). Furthermore, as observed in PAPER III, ethical considerations may cause the surgeon to abstain from performing an extensive bowel resection (Sitges-Serra 1988) or not to proceed with a second look after primary surgery. However, uneventful recoveries after operation among the most elderly patients were also observed. For instance, one alert 92-year old woman could be discharged to her home ten days after a bowel resection, and at four month follow-up, she had no complaints. Thus, it may be important to differentiate chronological from biological age.
Clinical implications – the route to an early diagnosis

The accumulated knowledge based on the clinical and epidemiological studies enabled us to formulate a management algorithm for the early diagnosis of acute SMA occlusion. Ethical aspects were not included in this algorithm.

![Management Algorithm Diagram]

Figure 10 Suggested management algorithm for the early diagnosis of acute SMA occlusion

Experience is still limited in the evaluation of acute SMA occlusion with the most recent development of CT (Kirkpatrick 2003) and MR-angiography (Laissy 2002), and these diagnostic modalities were not included in the algorithm.
CONCLUSIONS

The estimated incidence of acute SMA occlusion was 8.6 per 100 000 person years in Malmö 1970 – 1982. The age-standardized incidence increased exponentially with age and did not differ between men and women.

Thrombotic occlusions were generally located more proximally within the SMA and were associated with a more extensive intestinal infarction, whereas embolic occlusions were associated with a higher frequency of acute myocardial infarction.

Synchronous embolism, often multiple, occurred in 2/3 of the patients with an embolic occlusion of the SMA. A source of emboli and remaining cardiac thrombi could be identified in 4/5 and 1/2, respectively, of the patients with embolic occlusion.

The patients were managed in non-surgical wards in up to one half of the cases. This frequency varied depending on the studied population.

A normal D-dimer at presentation most likely excludes the diagnosis.

The length of the ischaemic bowel segment at operation was a risk factor for death.

In the selected series of patients who were revascularised and reported to the SWEDVASC-registry, the one-year survival rate was 40 %. A history of previous vascular surgery was a risk factor for death.

The diagnosis constituted the cause of death in 1.2% among octogenarians and beyond.
Akut blodpropp i övre tarmkäxpulsådern

Övre tarmkäxpulsådern utgår från stora kroppspulsådern i buken strax ovanför pulsådorna till njurarna. Akut blodpropp i övre tarmkäxpulsådern kan antingen uppstå genom att en propp (trombos) bildas på en lokalt sjuklig förändring (åderförkalkning) i pulsådern eller genom att en blodpropp som bildats i hjärtat slungas iväg och fastnar i pulsådern (emboli). Patienten är oftast en äldre kvinna med långvarig rytmrubbning på hjärtat (förmaksflimmer) eller åderförkalkningssjukdom. Akut blodpropp i övre tarmkäxpulsådern leder oftast snabbt till att större delen av tunntarmen och en del av tjocktarmen inte får någon blodförsörjning med utbredd tarminfarkt som följd.

dödlighet på 90 %, vilket bland annat beror på att det saknas precisa diagnostiska metoder.


**Blekingestudierna: Delarbete I, II och III**

I delarbete I studerades 14 patienter med misstänkt propp i övre tarmkäxpulsådern. Alla sex patienter som hade sjukdomen hade förhöjda D-dimer värdet, median värdet var 3.6 mg/L.

I delarbete II studerades 101 äldre patienter med misstänkt propp i övre tarmkäxpulsådern som alla inlades för vård på sjukhuset. Prover för att studera blodlevringsystemet, inklusive D-dimer, togs hos alla patienter. Alla nio patienter som hade sjukdomen hade förhöjda D-dimer värdet, median värdet var 1.6 mg/L, vilket var högre än för alla andra diagnosgrupper, förutom de med häl på tarmen och bukhinneinflammation.

I delarbete III, som innefattade en studieperiod på tre år diagnostiserades 24 patienter med konstaterad propp i övre tarmkäxpulsådern. Medianåldern var mycket hög, 84 år. Fyra patienter diagnostiserades först vid obduktion trots den låga obduktionsfrekvensen på 10 %. Av de 20 patienterna som hade emboli i övre tarmkäxpulsådern, hade 95 % förmaksflimmer och 30 % embolier till andra pulsådor i kroppen. Få patienter med sjukdomen diagnostiserades direkt vid första doktorskontakten och ¼ av patienterna vårdades vid medicin eller infektionskliniken. Långden av tarminfarkten var mer avgörande för prognosen än hög ålder.

Genom att analysera alla patienter med propp i övre tarmkäxpulsådern i delarbetena så kan man konkludera att D-dimer kan användas som ett exklusionstest vid misstänkt sjukdom. D-dimer och inflammationsmarkören CRP tenderar att ha en invers korrelation, d v s att D-dimer stegningen kommer tidigt i sjukdomsförlöpnet, medan CRP stiger senare, vilket gör D-
dimer testet lämpligt för att diagnostisera tidigt. Dödligheten på sjukhuset i sjukdomen var 59 %.

**SWEDVASC-studien – delarbete IV**


**Malmöstudierna – delarbete V och VI**

I delarbete V och VI studerades hela Malmöbefolkningen mellan 1970 – 1982. Anledningen till detta var att Malmöborna under denna period obducerades i 87 % av alla dödsfall, gentemot dagens 15 % i riksgenomsnitt, vilket möjliggjorde att man kunde kartlägga sjukdomens förekomst och dödlighet. I delarbete V, diagnostiserades totalt 270 patienter med akut propp i övre tarmkäxpulsådern, varav 2/3 först vid obduktion. Av de 174 patienter som inte opererades, fanns det misstanke om diagnosen före döden hos 1/5. Totalt insjuknade 8,6 fall per 100 000 invånare och år, vilket var fler fall än efter brustet pulsåderbråck på den stora kroppspulsådern (aortaaneurysm) under samma tidsperiod i Malmö. Sjukdomen var lika vanlig hos män och kvinnor relaterat till åldersgrupper, men eftersom kvinnorna levde längre var sjukdomen vanligare bland kvinnor. Insjuknande i sjukdomen ökade markant i takt med stigande ålder, 217 fall per 100 000 invånare och år. Vid obduktion fann man att 1.2 % av alla över 80 år dog av denna sjukdom. Dödligheten bland de 270 patienterna var 93 %.

Denna avhandling har främst bidragit med att visa att D-dimer är en tidig känslig blodmarkör för akut propp i övre tarmkäxpulsådern och kan användas för att utesluta diagnosen. Sjukdomen är vanligare än vad som tidigare rapporterats från kliniska studier och en väsentlig andel av patienterna vårdas på icke-kirurgiska kliniker.
Trombo-embolia aguda en la arteria mesentérica superior

La arteria mesentérica superior parte de la gran aorta abdominal, justo por encima de las arterias que van a los riñones. Un coágulo agudo en la arteria mesentérica superior puede surgir bien sea por la producción de un trombo (trombosis) a raíz de un cambio morboso local (arteriosclerosis) de la arteria, o bien porque un coágulo formado en el corazón sea arrastrado por la corriente sanguínea y obturaya la arteria (embolia). Lo más frecuente es que el paciente sea una mujer mayor con disritmia (fibrilación auricular) de larga duración o con enfermedad arteriosclerótica. Un coágulo agudo en la arteria mesentérica superior suele conducir rápidamente a que gran parte del intestino delgado y parte del grueso se queden sin riego sanguíneo, con infarto intestinal generalizado como consecuencia.

Los síntomas clásicos en una fase temprana del proceso son fuertes dolores abdominales, con hallazgos insignificantes en la exploración del abdomen, vómitos y diarreas, a veces manchados de sangre, así como la presencia de disritmia en el corazón. Hasta ahora, ninguna prueba de laboratorio ni ningún método radiológico, aparte de la radiografía vascular (arteriografía), han podido servir de ayuda en el diagnóstico. Sin embargo, la arteriografía resulta costosa y de difícil acceso las 24 horas del día en muchos hospitales. La enfermedad se suele descubrir en relación con una operación (laparotomía exploradora), al empeorar el paciente con signos de peritonitis. El tratamiento es quirúrgico y en él se extirpa la parte del intestino considerada como muerta (infarto intestinal) o, si se considera que el intestino aún es viable, se intenta restablecer la circulación en la arteria mesentérica superior. Esas intervenciones se pueden combinar y, la mayoría de las veces, se controla la viabilidad del intestino mediante una nueva operación al cabo de un día (second look). Una vez extirpada una parte del intestino, se puede elegir el empalme de los extremos del mismo o bien dejar que ambos extremos terminen en la piel (estomas). No obstante, a veces hay que renunciar a todas las medidas imaginables, una vez que se ha constatado que el infarto intestinal es demasiado amplio, lo que conduce a la muerte del paciente en unas horas o días. Si, en lugar de ello, se hubiera elegido la
extirpación de todo el intestino muerto, y si el paciente hubiera sobrevivido, habría quedado con un intestino corto y se habría convertido en uno de los llamados inválidos intestinales a una edad mayor. Esa enfermedad sigue teniendo una tasa muy elevada de mortalidad, el 90%, lo que, en parte, se debe a la falta de métodos precisos de diagnóstico.

El origen de la tesis fue el caso de una paciente. Se trataba de una mujer de 63 años de edad que tomaba medicamentos contra la tensión arterial alta y una enfermedad pulmonar obstructiva crónica relacionada con el tabaquismo. Al ingresar en el hospital de Blekinge en Karlskrona, tenía fuertes dolores abdominales desde hacía dos horas. A pesar de repetidas inyecciones de morfina, no remitía el dolor. Rápidamente se le hicieron ecografías, revisión abdominal y tomografía axial computadorizada con medio de contraste, y todas fueron normales. El ECG fue normal. Lo único de la lista del laboratorio que resultaba notable, era el valor muy elevado del D-Dimer, 6,9 mg/L (el valor de referencia es < 0,3 mg/l). (D-Dimer es un producto de descomposición de un coágulo.) La paciente fue operada, y se encontró precisamente un coágulo en la arteria mesentérica superior, así como una alteración de la circulación en el intestino. Una vez extirpada parte del intestino grueso y restablecido el flujo sanguíneo en la arteria, la paciente fue trasladada a la unidad de cuidados intensivos. Un día después se hizo un control de la viabilidad de los intestinos, momento en que hubo que extirpar gran parte del intestino delgado debido a infarto intestinal. La paciente murió al cabo de otros tres días de cuidados intensivos. El valor del D-Dimer, fuertemente elevado, sirvió de estímulo para hacer un estudio piloto, el trabajo parcial I.

Estudios de Blekinge: trabajos parciales I, II y III

En el trabajo parcial I se estudiaron 14 pacientes con presuntos coágulos en la arteria mesentérica superior. Los seis pacientes que tenían la enfermedad, mostraban valores elevados del D-Dimer, con una media de 3,6 mg/L.

En el trabajo parcial II se estudiaron 101 pacientes mayores con presuntos coágulos en la arteria mesentérica superior. Todos ellos fueron ingresados en el hospital para su asistencia. A todos se les hicieron pruebas para estudiar el sistema de coagulación de la sangre, incluido el D-Dimer. Los nueve pacientes que tenían la enfermedad, mostraron valores elevados del D-Dimer, con un valor de la media de 1,6 mg/L, que era mayor que en todos los demás grupos de diagnóstico, excepto los que tenían perforación del intestino y peritonitis.

En el trabajo parcial III, que comprendió un período de estudio de tres años, se diagnosticó a 24 pacientes con coágulo comprobado en la arteria mesentérica superior. La edad media era muy alta: 84 años. Cuatro pacientes fueron diagnosticados sólo en la obducción, a pesar de la baja frecuencia de las autopsias, un 10%. De los 20 pacientes con embolia en la
arteria mesentérica superior, un 95% tenían fibrilación auricular y un 30%, embolias a otras arterias del cuerpo. Pocos pacientes con la enfermedad fueron diagnosticados directamente en su primer contacto con el médico, y una cuarta parte de los pacientes fueron cuidados en la clínica de medicina general o en la de enfermedades infecciosas. La extensión del infarto intestinal fue más decisiva para el pronóstico que la edad avanzada.

Del análisis de todos los pacientes con coágulo en la arteria mesentérica superior incluidos en los trabajos parciales, se puede sacar la conclusión de que el D-Dimer puede utilizarse como prueba de exclusión en caso de presunta enfermedad. El D-Dimer y el marcador de inflamación CRP tienden a mostrar una correlación inversa, es decir que el aumento del D-Dimer se produce en una fase temprana del proceso morboso, mientras que el CRP sube después. Eso hace que la prueba del D-Dimer sea idónea para diagnosticar en una fase temprana. La mortalidad en el hospital debido a la enfermedad fue del 59%.

Estudio SWEDVASC: trabajo parcial IV

En el registro sueco SWEDVASC se inscriben las operaciones vasculares realizadas desde 1987. Según un control realizado en 1993 contrastado con el registro de asistencia en régimen de ingresados, ya entonces se registraban el 90% de todas las operaciones vasculares en el SWEDVASC. Entre 1987-1998 se vio que 60 pacientes habían sido intervenidos en la arteria mesentérica, con o sin operación intestinal, con objeto de restablecer la circulación intestinal. Se consideró que todos tenían una amplia alteración circulatoria, y únicamente una operación destinada a restablecer la circulación intestinal podía salvar la vida de los pacientes. En un porcentaje bastante elevado, una tercera parte de ellos, se sospechó la presencia de coágulos en la arteria mesentérica superior ya en el primer contacto con el médico. Se vio que 40 pacientes tenían embolias, todas operadas con embolectomía de la arteria, y que 20 pacientes tenían trombosis, que requerían reconstrucciones más avanzadas de la arteria. La enfermedad no se presentó más repentinamente en los que tenían embolia. La supervivencia de un año fue relativamente buena, un 40%. Ninguno de los supervivientes dependió del gotero.

Estudios de Malmö: trabajos parciales V y VI

En los trabajos parciales V y VI se estudió a toda la población de la ciudad de Malmö entre 1970 y 1982. El motivo fue que, en aquel periodo, los fallecidos en la ciudad eran sometidos a la autopsia en un 87% de los casos, mientras que, en la actualidad, la media nacional es de un 15%. Ese hecho posibilitó el estudio sobre la existencia de la enfermedad y la mortalidad. En el trabajo parcial V se diagnosticó de coágulo agudo en la arteria
mesentérica superior a un total de 270 pacientes, de ellos dos terceras partes sólo en la obducción. De los 174 pacientes que no fueron operados, la sospecha del diagnóstico se dio antes de la muerte en una quinta parte de los casos. En total, hubo 8,6 casos de enfermedad por cada 100.000 habitantes y año, es decir más casos que a raíz de de la ruptura de un aneurisma en la aorta (aneurisma aórtico) en aquel mismo periodo en Malmö. La enfermedad era igual de corriente entre los hombres que entre las mujeres por categorías de edades, pero como las mujeres vivían más tiempo, se daba más en las mujeres. La enfermedad aumentaba de forma marcada con la edad, y entre las personas mayores de 85 años habían 217 casos por cada 100.000 habitantes y año. En casos de obducción entre personas mayores de 80 años, se vio que un 1,2% habían muerto debido a esa enfermedad. La mortalidad entre los 270 pacientes fue del 93%.

En el trabajo parcial VI se analizaron los resultados de la obducción. Hubo más embolias que trombosis. Las trombosis en la arteria mesentérica superior se daban a menudo en una fase temprana en la salida de la arteria, cerca de la aorta, lo que producía grandes infartos intestinales. Los pacientes con embolias en la aorta, por el contrario, tenían infarto de miocardio agudo en mayor medida. En la mitad de los casos de embolia se encontraron otros coágulos en las cavidades cardiacas. En dos terceras partes de los casos de embolia, se encontraron una o varias embolias a otras arterias del cuerpo. En la mitad de los casos, el paciente fue asistido en una clínica no quirúrgica antes del fallecimiento.

Esta tesis doctoral ha contribuido sobre todo a mostrar que el D-Dimer es un marcador sanguíneo temprano sensible a coágulos agudos en la arteria mesentérica superior, y que puede utilizarse para excluir el diagnóstico. La enfermedad es más corriente de lo que se ha desprendido anteriormente de estudios clínicos, y una proporción importante de los pacientes son asistidos en clínicas no quirúrgicas.
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A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series *Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine*. (Prior to October, 1985, the series was published under the title “Abstracts of Uppsala Dissertations from the Faculty of Medicine”.)