Clinical and experimental studies on treatment of acute mesenteric ischemia
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(Figure on previous page) Tabula I of Adriaan van der Spiegel’s (Adrianus Spigelius) anatomy book *De humani corporis fabrica*, 1627, showing the greater omentum, the colon and mesocolon.
"The results of diagnosis and management of mesenteric ischemia have improved significantly over the past 100 years but remain poor. The best part of the history of mesenteric ischemia remains to be written."

Scott J. Boley
Acute mesenteric ischemia represents a major clinical problem, not only because it is associated with a poor prognosis with mortality rates up to 93%, but also because this vascular disorder may progressively increase in time. As the average life expectancy increases and subsequently the number of elderly in our hospitals grows, the vasculopathy of acute or chronic mesenteric ischemia will rise. Unfortunately, despite the progress in our understanding of the pathophysiology, diagnosis and treatment of acute mesenteric ischemia, mortality rates in clinical series in the last 15 years remain as high as they did a century ago. The aim of this thesis is to provide better insight into the complex syndrome of intestinal ischemia and reperfusion. Acute mesenteric ischemia will be addressed from a clinical and a experimental point of view.

In the first part of this thesis clinical articles review acute mesenteric ischemia and surgical as well as new treatment strategies.

In chapter 1 we introduce the clinical syndrome of acute mesenteric ischemia and summarize the different surgical treatment modalities. At present-day, surgical therapy is still the far most favorable treatment modality as it includes the assessment of intestinal viability, determination or conformation of the underlying cause, revascularization, and resection of the nonviable intestine. However, relatively new treatment modalities may serve as an adjunct to surgical intervention in some cases.

In chapter 2 we discuss the difficulties of analyzing the diversity of the clinical syndrome of acute mesenteric ischemia. We attempted to subdivide this condition according to disease etiology. The etiology of acute mesenteric ischemia remains often undefined in reported studies, as the correct diagnosis can usually only be confirmed at autopsy. Furthermore, the relative infrequency of acute mesenteric ischemia and the varied clinical presentation constitute an obstacle to analyze each etiological subset individually and to undertake randomized or case–control trials. Most of the previous retrospective studies assessed, calculated a mortality rate based on data compiled from all etiological subsets taken together. This has the drawback of obscuring differences in clinical presentation and characteristics, diagnostic investigation, disease progression, mortality and response to therapeutic modalities that are specific to disease etiology. Systematic evaluation of research results, even if only observational data and small case series are available, is necessary to move forward, certainly in view of improved imaging and current thrombolytic strategies. The aim of this systematic analysis of the literature on acute mesenteric ischemia was to investigate the relationships between disease etiology (arterial embolism, arterial thrombosis, venous thrombosis and non-occlusive mesenteric ischemia), mode of treatment and mortality.

In chapter 3 we evaluate thrombolytic therapy for acute superior mesenteric artery occlusion as an alternative or adjunctive treatment modality to surgical therapy in order to provide current knowledge for timely and informed decisions regarding treatment of acute mesenteric ischemia. Therefore, we performed a systematic analysis of the available literature from 1966 to 2003 regarding thrombolytic therapy for superior mesenteric artery thromboembolism.

In the second part of the thesis we discuss the eponym Riolan’s anastomosis (chapter 4). Riolan’s anastomosis or arc is eponymously used to indicate the arterial anastomosis between the superior and inferior mesenteric arteries. Vascular as well as gastro-intestinal
surgeons are well-acquainted with this collateral mesenteric pathway for retrograde perfusion of the superior mesenteric artery when the origin of the latter is occluded. The eponym suggests that Jean Riolan (1580-1657), a famous 17th century French anatomist, was the first to describe this arterial anastomosis. Riolan was a strong defender of traditional Galenic doctrine in medicine and therefore, proved a vigorous opponent of the new concept of the circulation of the blood as exposed by William Harvey (1578-1657). This makes it unlikely that Riolan would have conceived an arterial collateral pathway in the mesocolon, a notion confirmed by examining his anatomy book published in 1649.

In the third part of this thesis experimental studies of acute mesenteric ischemia in rats are described, regarding different mechanisms that may play a role in the induction of ischemia and reperfusion injury.

In chapter 5 we briefly review these different mechanisms as addressed in the following chapters relating to intestinal ischemia. First we focused on the coagulation cascade that may lead to the formation and deposition of fibrin, consequently occluding the microvasculature which is crucial in the oxygenation of the intestinal epithelium. We discuss the anticoagulant mechanisms and fibrinolysis system that may be insufficient to inhibit microvascular occlusion or to restore blood flow in the occluded microvasculature, respectively. Furthermore, we describe the potential crosstalk of coagulation and inflammation in the ischemia and reperfusion syndrome. In addition to these different mechanisms, we address the role of drug-intervention in ischemia and reperfusion syndrome, with the aim of restoring the imbalance within these mechanisms and attenuating the ischemia and reperfusion injury.

In chapter 6 we investigate intravascular coagulation and thrombotic obstruction in the splanchnic vasculature after intestinal ischemia and reperfusion in relation to epithelial integrity and function. Ischemia and reperfusion-induced endothelial cell injury results in a procoagulant and fibrinolysis-suppressing environment giving rise to intravascular fibrin deposition which may further compromise the (micro)circulation of for example the intestine and promote necrosis in distal tissue. Moderate and more severe intestinal ischemia was induced in rats by superior mesenteric artery occlusion. Intestinal injury was assessed by histological analysis, biochemical markers and functional studies. During reperfusion, portal and systemic blood samples were collected to analyze activation of coagulation and fibrinolysis.

In chapter 7 we review situations of ischemia and reperfusion in which activated protein C might be effective. The efficacy of activated protein C in sepsis may rely on the fact that it can modulate both coagulation and inflammation. Therefore, a potential beneficial effect of activated protein C may be present in disease states that are also characterized by simultaneous activation of these systems. Ischemia and reperfusion injury of various organs may represent such a state. Published articles on experimental and clinical studies of activation of both coagulation and inflammation in various disease states (including intestinal ischemia) were analyzed.

In chapter 8 we examine whether administration of activated protein C or antithrombin reduce local splanchnic derangement of coagulation and inflammation and attenuate intestinal dysfunction and injury following intestinal ischemia/reperfusion. Mechanisms that have been incriminated to play a role in the procoagulant response following ischemia and reperfusion are the upregulation of tissue factor in combination
with dysfunctional anticoagulant pathways, along with suppression of fibrinolysis mainly due to increased levels of the inhibitor of fibrinolysis: plasminogen activator inhibitor-1. Regulatory anticoagulant pathways, in particular the antithrombin system and the protein C system, appear to be ineffective in inhibiting thrombin generation following ischemia and reperfusion. Physiological anticoagulants such as antithrombin and activated protein C, in addition to reducing thrombin generation, may exert anti-inflammatory properties including modulation of cytokine expression, regulation of cell migration and promotion of apoptosis. Restoration of these defective, physiological anticoagulant mechanisms form a logical approach to the treatment of local or remote post-ischemic reperfusion injury. Rats were subjected to superior mesenteric artery occlusion and a randomized intravenous administration of vehicle, heparin, antithrombin, or activated protein C was performed during ischemia, briefly before reperfusion. Coagulation and fibrinolysis parameters obtained from portal blood, were correlated with mucosal fibrin deposition (determined by anti-rat fibrin antibody staining), intestinal function (glucose/water clearance) and intestinal injury (histological evaluation by Park/Chiu score).

In chapter 9 we analyze the effect of enhanced fibrinolysis in the same rat model of intestinal ischemia and reperfusion that results in local activation of coagulation, suppression of endogenous fibrinolysis and mucosal fibrin deposition. Intestinal ischemia and reperfusion causes local inhibition of endogenous fibrinolysis in combination with activation of coagulation. This may lead to thrombotic obstructions that compromise microcirculation and promote intestinal injury. This led to the hypothesis that "recanalization" of the thrombotic microvasculature by fibrinolysis may attenuate the sequelae of intestinal post-ischemic, reperfusion injury. Inhibited fibrinolysis following intestinal ischemia and reperfusion is related to increased plasminogen activator inhibitor-1. Therefore, fibrinolysis was enhanced by intravenous administration of recombinant tissue plasminogen activator (rt-PA) or by inhibition of PAI-1 by administration of monoclonal antibody MA-33H1F7. Again, coagulation and fibrinolysis parameters obtained from portal blood, were correlated to mucosal fibrin deposition, intestinal function and intestinal injury.

Intestinal ischemia and reperfusion may lead to profuse secretion of water and electrolytes. The underlying mechanisms have been related to increased hydrostatic pressure, to denudation of intestinal villi and recently, to adenosine-mediated enhancement of chloride secretion. Considering the complex interplay between vascular, subepithelial and epithelial factors in in vivo models of ischemia and reperfusion, and taking into account that compared to in vivo studies, monolayers of intestinal cell-lines show a notably different response to hypoxia, it is of interest to study the effects of hypoxia and reoxygenation in in vitro small intestinal preparations. In chapter 10 we report the determination of baseline electrophysiological parameters, glucose absorption, glutamine absorption, cAMP-mediated secretion induced by forskolin, Ca^{2+}/PKC-mediated secretion induced by carbachol or histamine, and epithelial barrier function using disodium-fluorescein and horseradish peroxidase as permeability probes, during varying periods of hypoxia and reoxygenation in rat ileum mounted in Ussing chambers.

In the fourth part of this thesis we analyze the role of reactive oxygen species in intracellular mechanisms of the endothelial cell in response to vascular endothelial growth factor (VEGF). An important goal in vascular biology is to understand the molecular
mechanisms underlying the modulation of endothelial cell phenotypes in health and disease. Reactive oxygen species (ROS) have traditionally been viewed as cytotoxic molecules, predominantly generated in pathological conditions such as ischemia and reperfusion syndromes, but they are now recognized to play a critical role in signal transduction and transcriptional regulation within the vascular tree. VEGF is important for the growth of new blood vessels (vasculogenesis and angiogenesis) and the maintenance of vascular integrity.

In chapter 11 we investigate the hypothesis that NADPH oxidase-derived ROS serve to modulate selective VEGF-dependent signaling pathways, transcriptional profiles and biological functions in endothelial cells. VEGF signaling in the endothelium involves a number of different pathways, including PI3-kinase/Akt, MAPK, and PKC. It has recently been shown that VEGF-induced proliferation, migration, and downstream expression of some but not all genes in endothelial cells are dependent upon a Rac1-regulated NADPH oxidase-derived ROS, suggesting that VEGF signaling in the endothelium is tightly coupled to NADPH oxidase activity.