

**Microcirculatory derangements in acute pancreatitis**

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Ethanol consumption2 and gallstones3 are thought to be the major causes of pancreatitis. Apart from these, a variety of other factors, such as drugs, trauma, metabolic disorders, and infection, have been recognized as capable of inducing acute pancreatitis.3 Finally, pancreatitis has also been reported as a consequence of specific vascular disorders, including vasculitis and atherosclerotic embolization.3

The development of microcirculatory derangements in acute pancreatitis, however, does not necessarily depend on a specific pathogenic cause of the disease or on the characteristic process of autodigestion. The significance of disorders of the microcirculation, with the consequence of tissue hypoxia and/or anoxia, has been under consideration as a determining factor in the pathogenesis of acute pancreatitis for several decades.4–7 Organ alterations following primary or secondary disturbances of pancreatic blood flow have been of substantial interest, in particular since the reports of Warshaw and coworkers,8–10 demonstrating clinical evidence of the high susceptibility of the pancreas to hypoperfusion and ischemic injury. Meanwhile, there is a considerable body of evidence that both the initiation and the progression of pancreatitis are characteristically associated with alterations in the gland’s microcirculation.

**Abstract** During the past decade, a considerable number of experimental studies have confirmed the hypothesis that microcirculatory derangements play a pivotal role in the pathogenesis of acute pancreatitis, including the process of conversion from edematous to necrotizing injury. Predominant microcirculatory disorders are nutritive capillary perfusion failure, with the consequence of prolonged focal hypoxia or anoxia, and inflammation-associated microvascular leukocyte recruitment, CD11b- and intercellular adhesion molecule (ICAM)-1-mediated leukocyte-endothelial cell interaction and loss of endothelial integrity, which may result in both edema formation and necrosis. A variety of proinflammatory mediators, such as oxygen radicals, leukotrienes, platelet-activating factor, and interleukins, but also bradykinin and endothelins, seem to be involved in triggering the manifestations of these microcirculatory disorders. In contrast, the anti-inflammatory interleukin-10, as well as nitric oxide, are thought to be capable of protecting from these pancreatitis-associated microvascular injuries. This knowledge may be encouraging for the development of novel therapeutic strategies, aiming at the attenuation of microcirculatory disorders, and, thus, preventing tissue injury in acute pancreatitis.

**Key words** Microcirculation · Pancreas · Pancreatitis · Transplantation · Capillary no-reflow · Leukocyte-endothelial cell interaction · Inflammation · Endothelins · Nitric oxide · Oxygen radicals · Ischemia/reperfusion

**Introduction**

Acute pancreatitis continues to represent a vexing clinical disorder associated with high morbidity and mortality in severe disease states. Although a variety of pathophysiologic concepts have been proposed,1,2 the complex sequence of events in the evolution of this disease is still far from being completely understood.

**Deterioration of microvascular perfusion in acute pancreatitis**

Some 30 years ago, a variety of experimental studies focussed on analysis of the characteristics of the pancreatic microcirculation in acute pancreatitis. By intraarterial injection of methylene blue,11 india ink,12,13 or polymerizing agents,13,14 vasoconstriction of intralobular arterioles was demonstrated in severely injured tissue regions, while vessel dilation was found in less affected areas, indicating the spatial heterogeneity of the pathological processes, with both focal ischemia and hyper-
emeric response. Light and electron microscopic analysis revealed distortion of the pancreatic microvasculature, with a marked reduction in the number of filled capillaries. In line with this, a decrease of pancreatic blood perfusion in pancreatitis was demonstrated, using the 86 rubidium-clearance technique. Subsequent experimental investigations with electromagnetic flowmeters and radioactive microspheres have confirmed that pancreatic blood perfusion is, indeed, impaired in acute pancreatitis.

Other studies, however, analyzing blood flow during acute pancreatitis, have yielded conflicting results, by reporting unchanged or even increased total blood perfusion of the gland. In fact, analysis of the overall pancreatic blood flow may not be appropriate for elucidating the pathogenesis of acute pancreatitis, because it may not reflect the tremendous disturbances in blood flow distribution, i.e., the heterogeneity, within the pancreas, and may not detect the potential function of arteriovenous shunts bypassing the nutritive capillary bed.

To overcome these limitations, recent studies have used high-resolution in-vivo fluorescence microscopy to study the nutritive microcirculation in acute pancreatitis. Detailed quantitative analysis confirmed a marked reduction in the number of perfused capillaries and microvascular hemoglobin saturation, both significantly correlating with the severity of the disease.

Moreover, the microvascular perfusion pattern within the pancreatic gland has been shown to be characterized by local heterogeneity due to focal necrosis, with pronounced impairment of nutritive perfusion in perinecrotic, but less impeded capillary blood flow in nonnecrotic areas.

Several mechanisms seem to be involved in mediating pancreatitis-associated microvascular perfusion failure. One of these mechanisms is the deterioration of the balance between nitric oxide (NO) and endothelins. Shibuya and coworkers demonstrated a decline in pancreatic tissue NO levels during pancreatitis, while others have shown that endothelin-1 is capable of inducing pancreatitis-like microvascular deterioration and acinar cell injury, and aggravating cerulein-induced edematous disease to hemorrhagic pancreatitis by causing pronounced microcirculatory disturbances. The view that endothelins, in fact, play a major role in triggering the manifestation of disease is further supported by experiments that demonstrated decreased capillary leakage, as well as improved fluid sequestration, capillary blood flow, and survival by endothelin receptor blockade. In line with this, the increase in NO levels by the administration of NO donors has been shown to effectively attenuate pancreatitis-associated microcirculatory failure, while the inhibition of NO-synthase further aggravates nutritive perfusion deficits. Thus, the deterioration of the endothelin-NO system may represent a convincing concept in the pathogenesis of pancreatitis, and may allow specific pharmaceutical targeting of these mediators to improve therapeutic outcome.

Apart from the imbalance between NO and endothelins, intravascular thrombosis has been suggested as a mechanism of pancreatitis-associated impairment of the microcirculation. Indeed, hemoconcentration caused by increased microvascular permeability, as well as intravascular coagulation, have to be considered relevant for the development of microcirculatory disorders. The pancreatitis-associated intravascular hemoconcentration may be counteracted by isovolemic hemodilution, which results in significant improvement of the gland’s microcirculation. Also, anti-coagulative treatment with heparin has been shown to ameliorate microvascular perfusion deficits, indicating that these factors may play, at least in part, a causative role in the deterioration of microvascular perfusion in acute pancreatitis.

Finally, there is major evidence that a variety of biologically active peptides, such as bradykinin, trypsin, kallikrein, and others, are involved in the pathogenesis of acute pancreatitis. The question whether these mediators contribute to the manifestation of disease by compromising the gland’s nutritive microcirculation has been addressed by a number of recent experimental studies. Using bradykinin B$_2$ receptor antagonists or gabexate mesilate, which exerts inhibitory action on trypsin, kallikrein, thrombin, plasmin, C1-esterase, and phospholipase A$_2$, these studies showed remarkable improvement in the pancreatic microcirculation, and thus confirmed that bradykinin, as well as different proteolytic enzymes, are involved in the development of pancreatitis-associated microcirculatory disorders.

**Inflammatory microvascular response in acute pancreatitis**

Acute pancreatitis is characterized by a local and a systemic inflammatory response, which results not only in pancreatic microvascular and parenchymal tissue injury but also provokes alterations in remote organs, including, primarily, the liver and the lung. This inflammatory response involves the activation of both mononuclear phagocytes and leukocytes, as well as the release of various cytotoxic and inflammatory substances, such as proteolytic enzymes, reactive oxygen species, cytokines, and lipid mediators, resulting in the manifestation of systemic inflammatory response syndrome (SIRS) and, finally, multiple organ dysfunction syndrome (MODS). The activation of leukocytes is followed by enhanced interactions with the microvascular endothelium, as