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Coagulation Abnormalities in Acute Pancreatitis

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1. Introduction

Acute pancreatitis (AP) is a potentially lethal disorder with no specific medical treatment. AP is characterized by a spectrum of symptoms, ranging from a local inflammatory process to the more severe form (acute necrotizing pancreatitis) which is associated with a systemic inflammatory response and a mortality rate of 27-45%. A number of risk factors have been identified for AP including alcohol abuse, gallstones, abdominal surgery/injury, cigarette smoking, cystic fibrosis, endoscopic retrograde cholangiopancreatography, hypercalcemia, hyperparathyroidism, hypertriglyceridemia, infection, pancreatic cancer, and injury to the abdomen (Pandol et al., 2007). Alcohol abuse and the development of gallstones account for the majority of AP cases. In AP, inappropriate intracellular activation of digestive enzymes within the pancreas (e.g. trypsin, chymotrypsin, elastase) is the main initiating event. The development of acute necrotizing pancreatitis is usually associated with pancreatic glandular necrosis. Acinar cell apoptosis, the release of cytokines, activation of coagulation, tissue ischemia, and tissue necrosis are key factors in the progression of the condition, as well as in the development of associated extrapancreatic complications (Steinberg & Tenner, 1994; McKay & Buter, 2003; Pandol et al., 2007).

AP induces a strong inflammatory response in experimental animal models and in humans, and is independent of the initiating factor for acinar cell damage (Granger & Remick, 2005). The major inflammatory mediators in AP include tumor necrosis factor (TNF), interleukins 1, 6, and 8, chemokines, and platelet activation factor (Makhija & Kingsnorth, 2002). Release of proinflammatory mediators into the circulation results in a systemic inflammatory response syndrome (Granger & Remick, 2005).

Inflammatory mediators in turn can influence hemostasis. Indeed, the pathways of inflammation and coagulation are intimately linked. For example, pro-inflammatory cytokines (e.g. TNF, IL-1β) act in autocrine and paracrine loops to activate neutrophils and monocytes. These cytokines also activate endothelial cells by upregulating adhesion molecules (e.g. P- and E-selectins) and chemokines. This results in leukocyte recruitment to the site of injury. Activated monocytes and endothelial cells express tissue factor (TF), the "spark" that initiates the coagulation cascade. TF can also be expressed by cells in the injured pancreas. The TF/VIIa complex activates factor X to Xa (or factor XI to XIa), and the

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factor Xa/factor Va complex converts prothrombin to thrombin. Thrombin not only forms the fibrin clot but is also a potent activator of protease activated receptor-1 (PAR-1). PAR-1 activation triggers pro-inflammatory responses including secretion of cytokines and growth factors, and upregulation of adhesion molecules.

In AP, coagulation abnormalities range from localized intravascular thrombosis to disseminated intravascular coagulation (DIC). Ultrastructural changes in the pancreas that accompany human AP include the infiltration of polymorphonuclear leukocytes into the stroma and parenchyma, intra- and extravascular accumulation of platelets, and microthrombi in blood vessels (Bockman et al., 1986). This chapter will provide an overview of the pathophysiology of acute pancreatitis with emphasis on coagulation abnormalities. The topics covered include dysregulation of coagulation and anticoagulant pathways, animal studies of AP, and the therapeutic potential of experimental interventions.

2. Overview of hemostasis

Hemostasis is a delicate balance between procoagulant (including platelets and clotting factors) and anticoagulant mechanisms (including blood flow and the production of anticoagulant proteins). It encompasses the vessel wall and endothelial cells, cellular constituents within the vessel (such as red blood cells, leukocytes, and platelets), soluble plasma proteins (coagulatory proteins and their moderators), as well as microparticles derived from leukocytes and platelets (Hoffman & Monroe, III, 2001). It is a physiologic process which modulates blood fluidity while also retaining the capacity to produce a hemostatic plug outside a damaged blood vessel. Thrombosis is a pathologic event inside the vessel lumen, consisting of platelet accumulation, adhesion, activation and aggregation, as well as tissue-factor-initiated thrombin generation and fibrin formation (Furie & Furie, 2007). The hemostatic process is tightly regulated in a healthy individual by a system of anticoagulant mechanisms (Dahlback, 2000; Esmon, 2000b; Esmon, 2009). Through these mechanisms, the transformation of blood from a liquid to a solid state (and vice versa) is tightly regulated by the multiple participants of the coagulation, anticoagulation, and fibrinolytic pathways. The following sections describe the key components of the hemostatic system and their relevance to AP. Biomarkers of hemostasis in acute human pancreatitis are summarized in Table 1.

3. Platelet activation in AP

Platelet adhesion at sites of vessel injury is a multistep process involving interactions between various platelet receptors and subendothelial adhesive ligands (Furie & Furie, 2007). The initial tethering of platelets to exposed subendothelial collagen is mediated by von Willebrand factor (VWF), a large multimeric protein secreted by endothelial cells and activated platelets (Furie & Furie, 2007; Lippi et al., 2009). Adherent platelets become activated and undergo a shape change, becoming spherical and extruding long filopodia that enhance platelet-platelet interactions. Activated platelets secrete ADP from their dense granules and synthesize and release thromboxane A_2. Released ADP and thromboxane A_2 bind to distinct receptors on nearby platelets and activate them, thereby recruiting additional platelets to the sites of injury. Activated platelets also secrete the contents of their alpha granules (e.g. VWF, platelet-derived growth factor, and coagulation cofactors V and

VIII) (Wagner & Burger, 2003). Finally, activated platelets promote blood coagulation via the expression of phosphatidylserine, a negatively charged phospholipid that is normally found on the inside of the platelet cell membrane. Assembly of coagulation factors on the activated platelet surface results in an explosive generation of thrombin (described in more detail below).

Evidence of increased platelet activation associated with pancreatitis has long been established in experimental animal models. In rabbits, administration of pancreatic fluid from patients with chronic pancreatitis induced platelet aggregation and activation (Prinz et al., 1984). In cases of acute pancreatitis, platelets have been shown to be activated, and their indices (mean platelet volume, platelet large cell ratio, and platelet distribution width) have also been shown to be elevated between onset and remission of AP (Mimidis et al., 2004). While a heightened platelet response is typical of patients with mild AP, a decreased platelet count (due to increased consumption of platelets) is observed in cases of severe AP. Low plasma levels of platelets in patients with AP are also associated with poor clinical outcome (Maeda et al., 2006).

4. Coagulation and fibrinolysis abnormalities in AP

Simultaneous to platelet activation, coagulation occurs in three overlapping stages: initiation, amplification, and propagation (Hoffman & Monroe, III, 2001). Tissue factor (TF) is the "spark" that initiates blood coagulation. Under normal conditions, TF is not expressed by cells that are in direct contact with blood (Butenas & Mann, 2004). After damage to the endothelial wall, however, TF is exposed to blood where it is free to bind plasma factor VIIa, forming TF-factor VIIa complex. TF is also expressed by macrophages and monocytes after stimulation by inflammatory mediators (Esmon, 1999; Nijziel et al., 2001; Bouchard & Tracy, 2003)

Tissue factor (TF) forms a complex with a small amount of circulating activated factor VII (FVIIa) and acts as a cofactor for increasing the ability of FVIIa to convert FX to FXa and FIX to FIXa at the cell surface (Osterud et al., 1978). FXa activates FV and together they convert a small amount of prothrombin to thrombin (Monroe et al., 1996). This is known as the initiation phase of coagulation. During the amplification phase, the small amount of thrombin generated initiates a positive feedback loop upon itself through further activation of FV, and thus, increased thrombin generation (Monroe et al., 1996). The initiation of large-scale thrombin generation begins with the formation of the tenase complex (which consists of FVIIIa and FIXa) and the prothrombinase complex (consisting of FVa and FXa) on an anionic surface such as activated endothelial cells or platelets (Hoffman & Monroe, III, 2001). This causes a thrombin burst, which further generates fibrin from fibrinogen. This rapid formation of thrombin also activates factor XIII and thrombin-activatable fibrinolysis inhibitor (TAFI). Factor XIIIa is then able to cross-link with fibrin strands to support and stabilize a fibrin meshwork, while TAFI protects the forming clot from plasmin-mediated fibrinolysis (Dahlback, 2000; Butenas & Mann, 2002).

Plasma levels of TF in AP patients have been shown to be higher than those of healthy volunteers, though there is no statistically significant difference in the TF levels between the severity groups of AP (Sawa et al., 2006). Plasma levels of TF in alcoholic severe AP with pancreatic necrosis was significantly higher than that in alcoholic severe AP without

pancreatic necrosis or that in nonalcoholic severe AP with pancreatic necrosis. These findings suggest that an increase in plasma TF may be related to the development of pancreatic necrosis in alcoholic severe AP.

Other measurements of blood coagulation are the prothrombin time (PT) and the activated partial thromboplastin time (APTT) which measure the extrinsic and intrinsic coagulation pathways, respectively. Clinical studies have shown an elevated prothrombin time in patients with AP (Radenkovic et al., 2009). However, there have been no reports of significant deviations in partial thromboplastin time (APTT) or in F1+2 levels in patients with AP. While these measurements suggest early hemostatic disturbances of AP, their usefulness in predicting patient outcome is limited. Clinical studies which measure other parameters (most notably d-dimer and antithrombin) have demonstrated an improved specificity and sensitivity in predicting outcome for these parameters, when compared to the utility of either PT or APTT.

AP is also characterized by abnormalities in fibrinolysis. The fibrinolytic system counteracts fibrin deposition, thereby preventing excessive fibrin accumulation at sites of vascular injury and restoring blood flow. Plasmin, the enzyme that dissolves fibrin clots, is formed from plasminogen in the presence of tissue plasminogen activator (tPA) or urokinase plasminogen activator (uPA). Plasmin cleaves fibrin, resulting in the production of fibrin degradation products (e.g. D-dimer) (Adams & Bird, 2009).

The levels of DIC parameters (low levels of platelets and AT, and high levels of D-dimer) and thrombin-antithrombin complex upon admission have been found to be associated with increased severity and poor prognosis of AP (Maeda et al., 2006). A four-fold increase in D-dimer levels has been shown to be a marker of complicated AP (Salomone et al., 2003). In patients with severe AP, non-survivors have significantly higher levels of D-dimer and plasminogen activator inhibitor (PAI)-1 than survivors (Radenkovic et al., 2004). The high concentrations of D-dimer and PAI-1 in AP patients are indicative of a hypercoagulable state and microvascular coagulopathy which may lead to the formation of microthrombi and, ultimately, facilitate the progression of organ failure.

4.1 Anticoagulant abnormalities in AP

The potentially explosive nature of the coagulation cascade is tightly regulated by three natural anticoagulant systems: antithrombin (AT), the protein C (PC) pathway, and tissue factor pathway inhibitor (TFPI).

4.2 Antithrombin in AP

AT, a plasma serine protease inhibitor (serpin) synthesized and secreted by the liver, demonstrates broad inhibitory activity for enzymes of the coagulation cascade, particularly thrombin and factor Xa (Lippi et al., 2009). The rate of enzyme inhibition by AT is slow but is accelerated approximately 1000-fold in the presence of negatively charged polysaccharides such as pharmacologic heparin as well as heparan sulfate found on the endothelial cell surface (Bjork et al., 1992). The stimulatory effect of heparin and heparan sulfate is mediated by a unique pentasaccharide sequence which binds AT with high affinity. Binding of this pentasaccharide sequence evokes a conformational change in AT

that facilitates its interaction with FXa but not with thrombin. To accelerate thrombin inhibition by AT, heparin must bind simultaneously to AT and thrombin, a process that bridges the enzyme and the inhibitor together in a ternary complex (Bjork et al., 1992). AT also demonstrates anti-inflammatory properties through the induction of prostacyclin release from endothelial cells, the inhibition of leukocyte-endothelium interactions (e.g. rolling and adhesion), the inhibition of procoagulant cellular signaling pathways, and the alteration of cellular receptor expression which modulate lysosomal proteinases, interleukin release, and soluble intercellular adhesion molecules (Mammen, 1998; Esmon, 2005).

In patients with AP, low levels of AT (< 69%) at admission were found to be associated with a poor prognosis (Maeda et al., 2006). In taurocholate-induced experimental pancreatitis in rats, high dose AT treatment was shown to improve survival (Bleeker et al, 1992). In cerulein-induced AP, AT supplementation inhibited the release of high mobility group box 1 protein (HMGB1) as well as other proinflammatory cytokines in rats (Hagiwara et al., 2009). However, in a systematic review of randomized trials, AT seems ineffective in improving overall mortality in critically ill patients (Afshari et al., 2007).

4.3 The protein C pathway in AP

The second natural anticoagulant is PC, a vitamin-K dependent glycoprotein synthesized by the liver. The PC pathway provides an "on site" and "on demand" anticoagulant response whenever thrombin is generated (Esmon, 2000c; Esmon, 2000a). Briefly, vascular injury initiates the coagulation cascade, ultimately resulting in thrombin generation and blood clot formation. Excess thrombin then binds to thrombomodulin (TM), a receptor found on the surface of vascular endothelial cells. The binding of thrombin to TM is critical for efficient protein C activation because this interaction induces a major specificity change in thrombin that increases its rate of protein C cleavage (ie. activation) by ~1000-fold. The conversion of PC to APC is augmented approximately 20-fold *in vivo* by the endothelial cell protein C receptor (EPCR). EPCR binds circulating protein C and presents it to the thrombin-TM complex. Activated protein C (APC), in conjunction with its cofactor protein S (PS), degrades coagulation cofactors Va and VIIIa on the surface of negatively-charged phospholipids (e.g. activated platelets).

Significant changes in protein C levels were observed in both experimental and clinical AP. In rabbits, a rapid decrease in PC levels was found after the induction of acute necrotizing pancreatitis (Ottesen et al., 1999). Serial measurements of PC in AP patients have shown a difference between surviving and non-surviving patients. Survivors exhibited a progressive normalization of PC levels in plasma, while patients who died exhibited no increase in PC levels (Radenkovic et al., 2004). Decreased PC levels may reflect an increased consumption of PC, vascular leakage, or impaired PC synthesis by the liver in the diseased state (Levi & ten Cate, 1999). Upregulated but insufficient generation of APC was shown to be associated with the development of multiorgan failure in severe AP (Lindstrom et al., 2006).

Plasma levels of soluble TM (important for PC activation) increase throughout the course of AP (Ida et al., 2009). Soluble TM levels were also significantly higher in non-surviving patient subgroups when compared with survivors. Exhibiting a specificity of 91% in predicting the prognosis of AP, sTM levels may be a useful prognostic marker for early mortality predictions.

4.4 Tissue Factor Pathway Inhibitor (TFPI) in AP

The third natural anticoagulant is tissue factor pathway inhibitor (TFPI), a Kunitz-type serine protease inhibitor that is produced by monocytes, macrophages, the liver, as well as endothelial cells (Lwaleed & Bass, 2006). It is stored mainly in three different regions of the body: in circulation, in the cytoplasm of platelets, and bound to the endothelium (DelGiudice & White, 2009). TFPI forms a quaternary complex with TF, factor FVIIa, and factor Xa, thereby preventing further production of factor Xa and factor IXa by the TF:VIIa complex and blocking additional generation of thrombin by factor Xa.

Yasuda et al. examined the levels of TFPI in patients with AP (Yasuda et al., 2009). Plasma TFPI levels in patients with AP were significantly higher than those in healthy volunteers, and plasma TFPI levels in severe AP were greater than those in mild AP. The elevation of TFPI appeared to be positively correlated with the severity, degree of necrosis, as well as incidence of organ dysfunction.

5. Therapeutic strategies in AP

Modulation of hemostasis may be an attractive strategy to treat AP. Experimental animal models include administration of activated protein C (APC) to improve microvascular coagulation and inflammation. Other strategies target procoagulant factors such as platelet activating factor (PAF), platelets, and factor VIIa.

5.1 Activated protein C in AP

Recombinant human APC (rAPC; Drotrecogin alpha activated; Xigris®) is the first biological agent to improve survival in patients with severe sepsis , a common co-morbidity associated with AP (Bernard et al., 2001; Bernard et al., 2004). Studies investigating the protective properties associated with APC treatment in vivo and in vitro have shown that APC functions not only as an anticoagulant, but also as a cytoprotective signaling molecule involved in inflammation, apoptosis, and vascular permeability. The protective effect of rAPC therapy in patients with severe sepsis likely reflects its ability to modulate the complex changes associated with sepsis pathophysiology.

The importance of the protein C anticoagulant pathway in AP was first studied in a rabbit model. Induction of severe AP caused a marked decrease in protein C activity compared to rabbits subjected to sham surgery (Ottesen et al., 1999), an effect that is also observed in non-surviving patients with AP. More recently, Chen et al. elucidated the effects of APC treatment on coagulation mechanisms in AP. In a 5% retrograde sodium taurocholate infusion rat model, pretreatment with 50 ug/kg of APC versus untreated rats with AP resulted in significant decreases in serum TNF, serum IL-8, and pancreatic matrix metalloproteinase 9 (MMP-9), an enzyme which degrades a wide range of extracellular matrix components (e.g. collagen, fibronectin, and gelatin). Moreover, APC-treated rats had significantly higher levels of pancreatic EPCR and TM, receptors critical for protein C activation. It has been shown that endotoxins increase shedding of membrane EPCR to produce soluble EPCR via MMP-9 (Gu et al., 2000) which respond to an increase in inflammatory cytokines (Wright & Friedland, 2004). It is proposed that APC treatment downregulates MMP-9 expression, thus reducing the shedding of EPCR to enhance endothelial EPCR cell expression in the pancreas. Following this study, the therapeutic

effects of rAPC in AP have been demonstrated in various models of AP by different groups (Yamanel et al., 2005; Alsfasser et al., 2006; Chen et al., 2007) while others have shown no survival benefit attributed to treatment with APC (Akay et al., 2008).

The anti-inflammatory and protective functions of APC have been documented in severity-graded models of AP. In a 5% sodium taurocholate infusion model (via the common biliopancreatic duct) of acute necrotizing pancreatitis, it was found that treatment with recombinant human APC (bolus injection of 100 μg/kg) 6 hours following AP induction was associated with a decrease in pancreatic bacterial contamination as well as fewer mesenteric lymph nodes (Yamanel et al., 2005). APC-treated animals with AP also had significantly decreased amylase levels, plasma IL-6, and TNF-α by decreasing NF-κβ activation. Moreover, APC treatment resulted in improvements in pancreatic histology as reflected by the resolution of pancreatic edema, perivascular inflammation, acinar cell necrosis, and fat necrosis. This study found that APC neither worsened nor improved the hemorrhagic state of the pancreas in the experimental condition suggesting that the coagulation system remains intact despite significant pancreatic tissue injury in the early pathophysiology of acute necrotizing pancreatitis (Yamanel et al., 2005).

In a rat model of mild (cerulein injection) and severe AP (intravenous cerulein injection with intraductal glycodeoxycholic acid infusion), treatment with recombinant human APC at 100 ug/kg per hour for 6 hours significantly reduced inflammation in the lungs and pancreas and furthermore improved survival from 38%-86% (p = 0.05) (Alsfasser et al., 2006). Inflammation was characterized by the presence of myeloperoxidase (MPO) in the pancreas and lungs of rats with severe AP, which decreased significantly with APC treatment for 6 hours following induction of AP. MPO levels in the lungs were reduced to levels even lower than those in sham-operated rats, similar to levels observed in healthy mice, while MPO levels in the pancreas were reduced to those observed in sham-operated and healthy control animals, demonstrating the anti-inflammatory effect of APC (Alsfasser et al., 2006). In contrast, no significant changes in coagulopathy were observed in untreated rats with severe AP versus APC-treated rats. Coagulopathy associated with severe AP was characterized by significantly prolonged prothrombin and partial thromboplastin times, decreased fibrinogen, marked leukocytosis, and thrombocytopenia, which were not significant in untreated versus APC-treated rats. APC appears to offer a survival benefit by suppressing inflammation in the pancreas and lungs without concomitant reversal of the pancreatic tissue damage and coagulopathy observed in experimental severe AP (Satake et al., 1981; Alsfasser et al., 2006).

Further studies aimed at elucidating the mechanism by which APC treatment improves outcome in AP demonstrated the involvement of mitogen-activated protein kinases (MAPKs) (Chen et al., 2007). MAPKs are mammalian serine/threonine protein kinases known to amplify signals involved in differentiation, inflammation, and apoptosis (Robinson & Cobb, 1997). P38 MAPK and JNK/SAPK (c-Jun N-terminal kinase/stress-activated protein kinase) are stress-responding MAPKs which induce inflammatory pathways in the early pathogenesis of severe AP (Dabrowski et al., 2000; Samuel et al., 2003). In this study, severe AP was induced through retrograde infusion of a 5% sodium taurocholate solution via the pancreatic duct at 100 uL/min. Rats were pretreated before AP induction with a 50 ug/kg dose of APC, 10 ug/kg dose of APC, or CNI1493 (a synthetic molecule which significantly reduces AP severity by inhibiting MAPK phosphorylation thus

attenuating inflammatory pathways (Lowenberg et al., 2004; Denham et al., 2000). In rats with severe AP, p38 MAPK and JNK2 proteins as well as inflammatory mediators TNF and IL-1β were significantly elevated. These effects were reversed in rats treated with the higher APC dose and CNI1493 (Chen et al., 2007). Decreases in the protein expression of MAPKs and cytokines in both treatments were comparable to levels in the healthy control group (Lowenberg et al., 2004; Wang et al., 2005; Chen et al., 2007). Moreover, APC treatment at 50 ug/kg and not CNI1493 significantly increased expression of ERK1/2 protein (Chen et al., 2007), the activation of which is known to protect against cell injury by promoting cellular regeneration (Sapieha et al., 2006).

These studies demonstrated that APC at a dose of 50 ug/kg inhibits p36 MAPK and JNK expression, thus reducing levels of proinflammatory cytokines like TNF and IL-1β in the pancreas. Additional protective effects of APC include the upregulation of ERK1/2 which promotes pancreatic cell regeneration and diminishes the severity of AP.

While some studies demonstrated the therapeutic potential of APC with high bolus APC injections (Yamanel et al., 2005; Chen et al., 2007) and hourly infusion (Alsfasser et al., 2006) treatments, others have suggested that APC offers no survival benefit in early phase AP (Akay et al., 2008). In a 5% sodium taurocholate rat AP model, APC was given hourly at the same dose given in the PROWESS study which tested the therapeutic effects of APC in sepsis patients (Bernard et al., 2001). Akay et al. found that APC treatment at 24 ug/kg per hour given 4 hours after AP induction resulted in significantly reduced serum IL-6 and amylase levels compared to untreated rats with AP (Akay et al., 2008). However, no significant improvements in pancreatic histology, pancreas oxidative stress, pancreas MPO, or renal function were observed. It is possible that that differences observed regarding the therapeutic benefit of APC may be due to dosage effects and differences in experimental design. The use of a lower dose of APC (24 ug/kg) may have been insufficient to offer any therapeutic benefit compared to the previous studies using 100 ug/kg of APC bolus or hourly (Yamanel et al, 2005; Alsfasser et al, 2006). Furthermore, the PROWESS trials used the 24 ug/kg per hour dose over 96 hours versus 5 hours in the experimental AP study (Akay et al., 2008). As such, studies testing the therapeutic effects of APC treatment in animal models of AP have yielded varying results.

5.2 Targeting Platelet Activating Factor (PAF) and platelets in AP

Modulation of platelet activating factor (PAF) has also been studied in experimental AP. PAF is a receptor-binding lipid and vasodilator that activates basophils, endothelial cells, platelets, and neutrophils. It is the most extensively studied experimental therapy in clinical trials of AP. In sodium taurodeoxycholate and trypsin injection models (via the biliopancreatic duct), PAF is released into the peritoneal fluid, bloodstream, and lung of rats (Kald et al., 1993). Furthermore, inhibition of PAF via an antagonist or an enzyme accelerating its degradation (acetylhydrolase) decreased inflammation characterized by marked reductions in pro-inflammatory cytokines (Lane et al., 2001; Hofbauer et al., 1998), pancreatic enzyme activation (Fujimura et al., 1992), and improved survival (Leonhardt et al., 1992; Dabrowski et al., 1995), hemodynamics (Ais et al., 1992), and histology (Dabrowski et al., 1995) in caerulein- (Fujimura et al., 1992; Lane et al., 2001; Hofbauer et al., 1998), deoxycholate- (Ais et al., 1992), taurocholate-infusion (Leonhardt et al., 1992; Dabrowski et al., 1995) and murine bile duct ligation models (Hofbauer et al., 1998).

The therapeutic effects of reducing pro-inflammatory platelet activity while maintaining its hemostatic abilities have also been studied. The inflammatory role of platelets was demonstrated in a study where platelet supernatant administered to platelet-depleted mice restored normal leukocyte recruitment (Tamagawa-Mineoka et al., 2007). In a cerulein model of AP, platelet depletion via an antibody (anti-GP1bα) reduced many markers of severe AP including serum amylase levels, acinar cell necrosis, interstitial pancreatic hemorrhage, inflammatory infiltration by neutrophils, pancreatic MPO, pancreatic macrophage inflammatory protein-2 (MIP-2), and circulating leukocytes and neutrophils (Abdulla et al., 2011a). This study along with others showed that platelets exert a pro-inflammatory response by invoking MIP-2 chemokine synthesis in pancreatic cells (macrophage and acinar cells) (Ramnath & Bhatia, 2006; Sun & Bhatia, 2007), a major signal for neutrophil infiltration and chemotaxis (Bhatia & Hegde, 2007; Li et al., 2004). Therefore targeting the inflammatory nature of platelets may have therapeutic potential in reducing pancreatic tissue injury and the severity of acute pancreatitis (Abdulla et al., 2011).

Measurement	Biomarker	Effect	Normal Value	AP Admission Value		References
Global Coagulation	PT (sec.)	Increased	9.8-12.7	13.46-13.92		1,2
	APTT (sec.)	NS†	21-39	32.99-33.22		1,2,3,4,5
	Platelet Count (10^4/μl)	NS†	9.2	Survivor	Non-Survivor	1,6
				16.2	6.8	
	Fibrinogen (g/L)	Increased	1.8-3.5	3.7-5.39		1,2
Procoagulant Activity	D-dimer (ng/mL)	Increased	0-0.39	5.5-903.50		1,3,4,7,8
	TAT (μg/L)	Increased	1-16.1	11.8-25.3		3,4,6
	TF antigen (pg/ml)	Increased	120-140	363-721		7,9,10
	sP-selectin (ng/mL)	Increased	82-181	150-215		11,12,13
Fibrinolysis Pathway	Alpha-2-Antiplasmin (%)	Decreased	80-120	73.22-105.28		1,2
	PAI-1 (U/mL)	Increased	0.3-3.5	4.39-4.56		1,2,4
	Plasminogen (μg/mL)	Decreased	150 - 200	70.11-103.94		1,2,17
Anticoagulant Activity	AT (%)	Decreased	80-120	63.47- 81.47		1,2,4,5
	PC (%)	Decreased	81-173	52-84.75		1,2,4,5,8
	APC (%)	Decreased	100%	76-102		2
	Protein S (μg/mL)	Decreased	23.8-30.6	17.3-26.9		16
	sTM (ng/mL)	Increased	10.3-54	23.48-153.9		4,14,18
	TFPI (ng/mL)	Increased	26.4-28.6	34.6-40.4		15

[1]Radenkovic et al. 2009; [2]Radenkovic et al. 2004; [3]Mavrommatis et al. 2000; [4]Kinasewitz et al. 2004; [5]Collins et al. 2006; [6]Maeda et al. 2006; [7]Stief et al. 2007; [8]Lindstrom et al. 2006; [9]Sawa et al. 2006; [10]Gando et al. 1998; [11]Powell et al. 2001; [12]Ogura et al. 2001; [13]Osmanovic et al. 2000; [14]Lu et al. 2007; [15]Yasuda et al. 2009; [16]Uehara et al. 2009; [17]Vinazzer et al. 1988; [18]Ida et al. 2009;
†Denotes a non-significant value compared with normal controls.

Table 1. Biomarkers of hemostasis in human acute pancreatitis.

5.3 Inhibition of factor VIIa in AP

The effect of inhibiting FVIIa on experimental AP was investigated in an intraductal taurodeoxycholate infusion model of AP (Andersson et al., 2007). Administration of active-site inactivated FVII (FVIIai) and N-acetylcysteine (NAC, an anti-inflammatory antioxidant) 90 minutes prior to AP induction caused a significant reduction of MPO levels in distant organs like the lungs and ileum and reductions in plasma IL-6 and MIP-2 compared to saline controls 6 hours following AP induction (Andersson et al., 2007). This study suggests that coagulant mediators may potentially be therapeutic targets to decrease AP severity.

6. Conclusions

Coagulation abnormalities are a hallmark of AP and are related to disease severity. Results from experimental animal studies and human studies suggest that modulation of hemostasis may provide a therapeutic target for the treatment of AP. Inhibition of the coagulation cascade may prevent intravascular coagulation and inflammation in the pancreas and distant organs, thereby reducing systemic complications in patients with acute pancreatitis.

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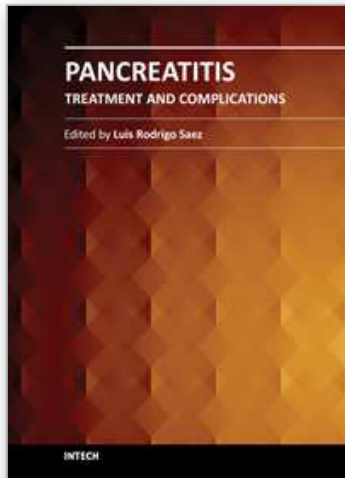
Pancreatitis - Treatment and Complications

Edited by Prof. Luis Rodrigo

Pancreatitis may be acute or chronic. Although they can be caused by similar aetiologies, they tend to follow distinct natural histories. Around 80% of acute pancreatitis (AP) diagnoses occur as secondary to gallstone disease and alcohol misuse. This disease is commonly associated with the sudden onset of upper abdominal that is usually severe enough to warrant the patient seeking urgent medical attention. Overall, 10 to 25% of AP episodes are classified as severe, leading to an associated mortality rate of 7 to 30%. Treatment is conservative and consists of general medical support performed by experienced teams, sometimes in ICUs. Although most cases of acute pancreatitis are uncomplicated and resolve spontaneously, the presence of complications has significant prognostic importance. Necrosis, hemorrhage, and infection convey rates of up to 25%, 50%, and 80% mortality, respectively. Other complications such as pseudocyst formation, pseudoaneurysm formation, or venous thrombosis increase morbidity and mortality to a lesser degree. The presence of pancreatic infection must be avoided.

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