JOP. J Pancreas (Online) 2002; 3(6):162-168.

Mechanisms Involved in the Onset of Post-ERCP Pancreatitis

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Summary

In various prospective studies, the frequency of post-ERCP pancreatitis ranges from 1 to 14%. After exposure to trigger events, injury to the gland occurs extremely rapidly. In experimental models of acute pancreatitis, it has been suggested that digestive enzyme activation might occur within acinar cells and it has been shown that in the early stages of acute pancreatitis induced by secretagogues or by diet, there is a co-localization of digestive enzymes and lysosomal hydrolases within large cytoplasm vacuoles; this co-localization mechanism might result in activation of the digestive enzyme. In this article, we will review the trigger events which may determine the final effect of acute pancreatitis during ERCP and endoscopic sphincterotomy: mechanical, chemical, enzymatic and microbiological. Nonetheless, factors related to the patient and the physician will be considered. Finally, the hypothesis of activation of chemokines by endoscopic maneuvers as a cause of acute pancreatitis will be described.

The Pathogenesis

In various prospective studies, the frequency of post-ERCP pancreatitis ranges from 1% to 14% [1, 2, 3, 4, 5]. After exposure to trigger events, injury to the gland occurs extremely rapidly [6]. In normal condition, intrapancreatic digestive enzyme activation occurs within the pancreatic ductal space or in the duodenum. In experimental models of acute pancreatitis, it has been suggested that digestive enzyme activation might occur within acinar cells and it has been shown that in the early stages of acute pancreatitis induced by secretagogues or by diet, there is a co-localization of digestive enzymes and lysosomal hydrolases within large cytoplasm vacuoles [7, 8, 9, 10] (Figure 1). In the diet model, the vacuoles arise from the fusion between zymogen granules and lysosomes, a

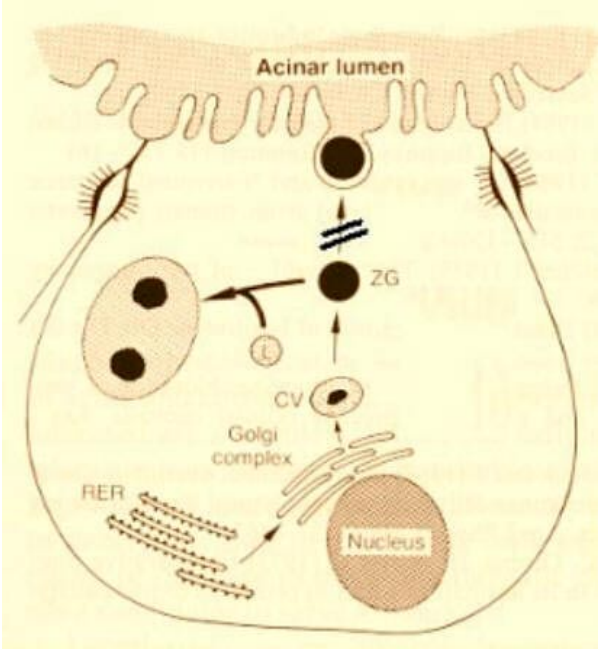

Figure 1. Mechanism of acute pancreatitis. The initiating event is the blockage of secretion, leading to the accumulation of zymogen granules within the acinar cells. After this event, there is a fusion of lysosomes and zymogens within large vacuoles and, finally, there is an activation of enzymes and acute intracellular injury.
L= lysosome; ZG = zymogens; CV = condensing vacuole; RER = rough endoplasmatic reticulum.

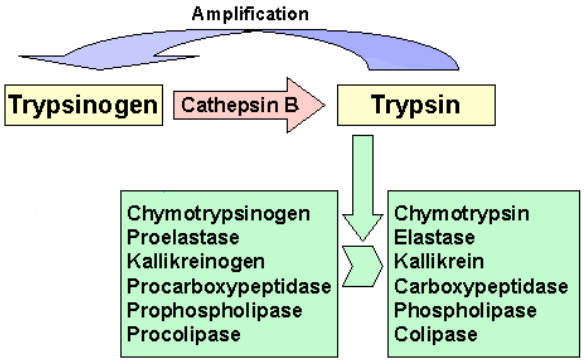

Figure 2. Cathepsin B mediates trypsinogen activation in experimental pancreatitis. Once trypsin is activated, it can catalyze the activation of other digestive proenzymes as well as trypsinogen itself, initiating the autodigestion of the gland.

mechanism called crinophagy; on the other hand, in cerulein induced acute pancreatitis, the vacuoles appeared to develop as a result of both crinophagy and a defect in the normal sorting mechanisms which segregate lysosomal hydrolases from digestive zymogens during intracellular transport [7, 8, 9, 10]: this co-localization mechanism might result in activation of the digestive enzyme (Figure 1). As the lysosomal enzyme cathepsin B is known to be capable of activating trypsinogen [11] and trypsin can activate the remaining digestive enzyme zymogens, the co-localization phenomenon could result in intravacuolar digestive enzyme activation (Figure 2). The trigger events which may determine the final effect of acute pancreatitis during ERCP and endoscopic sphincterotomy (ES) are mainly mechanical, chemical, enzymatic, and microbiological. Nonetheless, factors related to the patient and the physician will be considered. Finally, the hypothesis of the activation of chemokines by endoscopic maneuvers as a cause of acute pancreatitis will be described.

Mechanical Factors

Direct trauma from endoscopy rarely causes pancreatitis [12]; cannulation trauma to the papilla is the most common cause of sphincter of Oddi spasm [13] and/or an edema of the papilla, thus creating an obstacle to the flow of pancreatic juice, and subsequently determines an acute pancreatic inflammation [14]. Moderate-to-difficult cannulation was an independent risk factor in the prospective, multicenter study of Freeman *et al.* [15]. The importance of this mechanism in the development of acute pancreatitis is also highlighted by a Japanese group [16]. In their study, the authors showed that, although the frequency of ES-induced pancreatitis is significantly higher than that of post-ERCP pancreatitis, the frequency of severe pancreatitis within 48 hours, and the worsening of pancreatitis after 48 hours is significantly lower within the group of patients who contracted ES-induced pancreatitis; thus, the lowering of intraductal pressure after ES mitigates the severity of post-procedural pancreatitis. Deep cannulation into the pancreatic duct increases the chances of duct or ampullary perforation with an associated intraparenchymal or submucosal injection, even if submucosal injections rarely lead to pancreatitis [17]; duct perforation more commonly causes acute pancreatic inflammation [17]. Visualization of the main pancreatic duct alone is associated with a 31% incidence of hyperamylasemia; this figure is similar to the 24% incidence of hyperamylasemia which occurs after cholangiography alone [18]. This suggests that mechanical entry into the duct is a less important cause of hyperamylasemia than other potential factors. On the other hand, multiple pancreatic duct injections have been demonstrated by Freeman *et al.* to be an independent risk factor in the etiology of acute pancreatitis following ERCP [15]. During difficult cannulation, the endoscopist must balance the need for specific duct visualization or deep cannulation against the possible provocation of complications. During ES and stone removal, the ampullary area may be traumatized by the various devices used: stone or basket entrapment at the biliary-duodenal junction may obstruct the pancreatic duct. Patients with a patent minor papilla and an accessory pancreatic duct are reported to have a lower incidence of pancreatitis after ERCP [19]; it is possible that a pathological route permits a better flow

of pancreatic juice, despite transient major papilla trauma/edema, or protects the ductal system from overinjection. Injection pressure, during contrast media or other fluid injection into the pancreatic duct contributes to ductal epithelial or acinar injury. This injury probably occurs from the disruption of cellular membranes or tight junctions between the cells and the backflow of the intraductal contents, especially into the interstitial space [20]. Contrast medium combined with a marker substance injected into the pancreatic duct of experimental animals caused acinarization and the marker substances were observed to be localized mainly in the interstitial spaces between acinar cells, perivascular spaces and epithelial cells, as well in the capillary lumen below the basement membrane of the acinar cells [21]. These findings support the existence of a pancreatic ductal-interstitial-venous pathway [22]. Acinarization occurs when the volume injected into the pancreatic duct exceeds the ductal capacity. However, it seems that the elevation of the pancreatic enzyme level depends on the volume of the contrast medium injected [23]. Several studies have demonstrated a correlation between the elevation of serum pancreatic enzyme levels and the degree of duct opacification [18, 24, 25]. A rapid rate and high-pressure injection contributes to the development of acinarization [25, 26]; this phenomenon is associated with an increased incidence of post-ERCP pancreatic enzyme level elevation and pancreatitis [27, 28]. Reducing the injection pressure can minimize acinarization; however, in the study of Freeman *et al.* [29], even if the acinarization of the pancreas was significantly higher in patients who developed pancreatitis at univariate analysis, thus confirming a previous study of the same author, this risk disappeared at multivariate analysis when ES is performed. Another cause of post-procedural acute pancreatitis is the edema of the surrounding tissue produced by electrocautery [30]. It is thought that cautery in the vicinity of the pancreatic orifice may produce edema of that orifice and obstruction to the flow of pancreatic juice.

Chemical Factors

The contrast media used for pancreatography can provoke pancreatitis. Contrast media are differentially visualized from the surrounding tissue because of their iodine content. The osmolarity and ionic nature of the contrast media are believed to be the major factors responsible for many of the adverse effects that occur after intravascular administration [31]. Investigators have used low-osmolarity agents, usually non-ionic, to reduce the rate of this complication. Results of previous studies comparing different contrast media have been inconclusive; of the several prospective randomized studies which have attempted to compare the frequency of pancreatic enzyme level elevation, clinical pancreatitis and the quality of pancreatograms with the low- and high-osmolarity agents, some [32, 33] have suggested that low-osmolarity media were safer, whereas others [28, 34, 35] have shown no difference between the media used.

Enzymatic Factors

According to the reflux pathogenesis of acute pancreatitis [36, 37], the amount of activated intestinal enzymes carried into the pancreatic ductal system by ERCP maneuvers is unknown. It is possible that contrast agents, not used in clinical practice at present, may activate trypsinogen in pancreatic juice [38]. If enzyme activation at ERCP is a major cause of acute pancreatitis, enzyme inhibitors might have a therapeutic role. Previous studies using old protease inhibitors failed to demonstrate any beneficial effects in preventing acute pancreatitis [39, 40]. More recently, gabexate mesilate, a low molecular weight protease inhibitor, has been shown to have a prophylactic effect on ERCP-induced pancreatitis [41].

Microbiological Factors

It has been suggested that bacteria may play a role in the induction of post-ERCP pancreatitis; however, bacterial-specific enzymes, toxins or activators of bacterial

origin may release cytokines from monocytes and result in pancreatitis [42]. However, at present, according to the guidelines of the European Society of Gastrointestinal Endoscopy [43], antibiotic prophylaxis is recommended even in average risk patients in the case of therapeutic retrograde cholangiopancreatography.

Patient and Physician Factors

Patient-related factors are as important as procedure-related factors in determining risk for both post-ERCP and post-ES pancreatitis. In the study of Freeman *et al.* [15], history of post-ERCP pancreatitis, suspected sphincter of Oddi dysfunction, female gender, and absence of chronic pancreatitis were predictors of post-procedural pancreatitis at multivariate analysis. In the subsequent study of Freeman *et al.* [29], in which only risk factors for pancreatitis after ES were considered, only younger age resulted as a risk factor; it is reasonable to think that ES may prevent post-ERCP pancreatitis. Finally, it is important to use caution when performing pancreatography in patients with homozygous alpha-1-anti trypsin deficiency [44]; two cases of hemorrhagic pancreatitis with one death following ERCP have been reported in patients with this genetic abnormality. ERCP contrast media reactions are believed to be rare [45, 46]. The low frequency of allergic reactions is probably based on the slow absorption of the contrast media and also on the low dose of the agent administered. A multicenter study by Lasser *et al.* [47] showed that the administration of methylprednisolone before the contrast injection lowered the incidence of adverse reactions from ionic agents to a level similar to that reported from other series with nonionic media. However, whether or not allergic reactions may cause pancreatitis is presently unknown.

Univariate analysis showed that higher case volume per endoscopist was unexpectedly associated with a higher rather than a lower rate of pancreatitis. However, in the multivariate model, after adjustment for case mix, endoscopist case volume showed no effect on the rate of pancreatitis [15]. Previous multicenter studies have also failed to show a significant correlation between ERCP case volumes and pancreatitis rates, although they have shown a consistent correlation with bleeding rates, overall complication rates and rates of severe complications [29, 48]. It is possible that none of the participating endoscopists in the study of Freeman *et al.* [15] reached the threshold volume of ERCPs above which pancreatitis rates would diminish. However, endoscopists with low volumes of ERCPs account for most of these procedures in the United States, as reflected by the fact that about 33% of all ERCPs in this multicenter study were contributed by endoscopists who performed on average not more than two ERCPs per week. Furthermore, the reported rates of pancreatitis from the tertiary referral centers with the highest volumes of ERCPs in the United States are generally as high as or higher than those seen in the study of Freeman [49, 50, 51, 52].

Chemokines

Recent studies [53, 54, 55, 56] have indicated the usefulness of ERCP as a model for studying the early inflammatory response in acute pancreatitis. In their study, Kiviniemi *et al.* [54] found that, in uncomplicated cases, acute phase response determined by serum C-reactive protein levels was rare and did not parallel the serum amylase or lipase levels. However, Blanchard *et al.* [57] hypothesized that cytokines may be produced primarily by pancreatic parenchymal cells. Reasoning that ductal epithelium is the cell type most likely to be exposed to noxious stimuli in common causes of pancreatitis, such as ERCP and passage of a gallstone, they examined the response of well-differentiated pancreatic ductal adenocarcinoma cell lines to stimuli known to stimulate cytokine production in other cells. CAPAN-1 and CAPAN-2 cells were incubated with endotoxins or TNF-alpha and the supernatant was assayed for production of IL-1, IL-6, and IL-8 by ELISA. The cells were assayed for activation of the

transcription factor NF-kappa B by electrophoretic mobility shift assay. These authors found no detectable production of IL-1 by either cell line. CAPAN-1 cells had a concentration-dependent production of IL-6 and IL-8 in response to both endotoxins and TNF-alpha. CAPAN-2 cells had a concentration-dependent production of IL-6 and IL-8 in response to TNF-alpha. They had low level expression of IL-8 which was unaffected by any concentration of lipopolysaccharide (LPS) and no detectable production of IL-6 in response to LPS. On the basis of these findings the authors concluded that pancreatic duct cells may play an active part in the pathogenesis of acute pancreatitis through the production of cytokines. More recently, we found [58] that ERCP maneuvers significantly increase serum levels of C-reactive protein, amyloid A and IL-6 also in patients who did not develop acute pancreatitis, thus confirming the data of Blanchard *et al.* [57]. In view of the possibility that IL-10 administration reduces the incidence of pancreatitis after therapeutic endoscopic retrograde cholangiopancreatography in humans [59], this topic should receive more attention in the near future.

Key words Acute Disease; Cholangiopancreatography, Endoscopic Retrograde; Sphincterotomy, Endoscopic; Pancreatitis, Acute Necrotizing; Risk Factors

Abbreviations ES: endoscopic sphincterotomy; LPS: lipopolysaccharide

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