Heart in acute pancreatitis: facts and fictions

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Abstract

Pain is the hallmark of acute pancreatitis and it is localized in the epigastrium in more than 60% of patients having mild or severe disease. Acute pancreatitis may mimic other diseases such as acute coronary syndrome. In addition, the acute illness of the pancreas is associated with a number of metabolic abnormalities, such as hypocalcemia and hypophosphatemia, which may cause hemodynamic changes and variations in the concentration of ionized calcium. In turn, these have been directly correlated to changes in myocardial contractility. The aim of this paper is to review the current literature on the involvement of heart during the course of acute pancreatitis and also to evaluate experimental and clinical data on this topic.

Introduction

Pain is the hallmark of acute pancreatitis and it is localized in the epigastrium in more than 60% of patients having mild or severe disease.[1] Sometimes acute pancreatitis may mimic other diseases and, in particular, acute coronary syndrome.[2] In addition, the acute illness of the pancreas is associated with a number of metabolic abnormalities, such as hypocalcemia and hypophosphatemia which may cause hemodynamic changes and variations in the concentration of ionized calcium have been directly correlated to changes in myocardial contractility.[3] Our aim is to review the current literature on the involvement of heart during the course of acute pancreatitis and to evaluate experimental and clinical data on this topic.

Pathogenesis of acute pancreatitis

The main etiology of acute pancreatitis, at least in Western countries remains that of bil-iary origin. In fact, biliary forms represented the most frequent etiological category (69.3%), while alcoholic forms occurred in only 6.6%; all together the remaining etiologies (post-surgery, post-endoscopic cholangiopancreatography, traumatic, hyperlipemic, drug-induced and pancreas divisum) accounted for 7.1% of cases and 17.1% remained without a definite etiological factor.[4] The current theory of acute biliary pancreatitis is the common bile duct obstruction, which increases pancreatic duct pressure that led to trypsin activation and pancreatic auto-digestion.[5] Although pancreatic duct obstruction may play an important role in the pathogenesis of gallstone pancreatitis, it is not sufficient to cause the morphological changes of acute pancreatitis,[6] indicating that other events must occur if the changes induced by pancreatic duct obstruction lead to acute pancreatitis. ossible that pancreatic acinar hyperstimulation, in the presence of duct obstruction, triggers and exacerbates acute pancreatitis.[7] Probably a common pathogenic pathway that triggers various forms of acute pancreatitis may involve exocrine increased pancreatic hyperstimulation, pancreatic duct pressure, active trypsin reflux, and unregulated activation of trypsin within pancreatic acinar cells. When intracellular protective mechanisms aimed to prevent trypsinogen activation or reduce trypsin activity are overwhelmed, acute pancreatitis occurs.

Pathophysiology of acute pancreatitis

From experimental studies it has been postulated that acute pancreatitis evolves in 3 phases:[7] in the first phase, there are intrapancreatic trypsinogen activation and acinar cell injury as a result of release of trypsin; subsequently, there is an intrapancreatic inflammatory reaction that leads to the third phase characterized by development of system inflammatory response syndrome and multiple organ system dysfunction.[8] Proteolytic enzymes such as trypsin, lipase and phospholipase A, kinins such as bradykinin, cytokines, and other active peptides such as trypsinogen activation peptide and carboxypeptidase activation peptide are liberated from the inflamed pancreas and they transform a single-organ disease into a multisystem disease.[8] As shown in Figure 1 the pathogenesis and evolution of acute pancreatitis correlate with the clinical phases of the disease.[8]

The experimental evidence

In experimental animals, myocardium produces cytokines locally under stress events and IL-6 production is an early event. In addition other cytokines are also produced by the heart and could be correlated with the echocardiographic left ventricular change; for example the production of TNF-alpha occurs in the same period of histological findings as acute myocardial damage, whereas TGF-beta is released in the subsequent period.[9] In addition, there is experimental evidence in support of the existence of an intrinsic renin-angiotensin system in the pancreas. The pancreatic renin-angiotensin system is activated in experimental acute pancreatitis and may cause cardiac and alterations[10] in humans as well.[11]

The clinical evidence

Drummond first reported electrocardiographic changes in patients with abdominal pain.[12] The causes of these alterations were hypothesized due to sympathetic adrenergic activation from a parasympathetic reflex, reduction of intra-cellular potassium, activation of enzymatic systems, reabsorption of toxic substances.[13] Clinical studies have identified electrocardiographic changes and pericardium alterations due to hemodynamic status.[14,15] Experimental studies have also reported that in acute pancreatitis there are myocardial ultrastructural disturbances, including interstitial edema and cardiomyocyte hypoxia,[16] myofiber overcontractility, intercellular edema between the cardiomyocytes, and cardiomyocyte hypertrophy with

collagenization of myocardial stroma.[17] The electrocardiographic alterations in acute pancreatitis are various, say tachyarrhythmia or bradyarrhythmias, atrial flutter and atrial fibrillation, supraventricular premature contractions, short PR interval, QRS prolongation, various bundle-branch blocks (such as left and right bundle-branch block, and left anterior hemiblock), non-specific changes in depolarization, decreased T-wave voltage, T-wave changes, and ST-segment abnormalities. These alterations are often seen in approximately 50% of patients.[18,19] Evaluation of left ventricular function in the early phases of acute pancreatitis has also been investigated, showing an impairment of contractility in a significant portion of patients with acute pancreatitis.[20] Echocardiographic assessment based on clinical parameters of severity may help to select those patients who merit highly intensive treatment.[20]

The laboratory evidence

Easy and largely available serum markers are required to rapidly identify those patients having a cardiac involvement during the course of acute pancreatitis.[21] In a recent study, we evaluated the presence of elevated levels of high-sensitivity cardiac Troponin (hs-TnT) in patients with acute pancreatitis,[22] and we found that more than 35% of them had high serum levels of this cardiac marker. The time course of serum troponin T in the early phases of acute pancreatitis is reported in Figure 2.[22] However, the absence of any clinical and electrocardiographic features of acute coronary syndrome in our patients suggests that abnormally high results should be interpreted as of non-ischemic origin.[23,24] In conclusion, we believe that troponin I should be used in assessing cardiac damage in acute pancreatitis patients, but additional studies exploring this possibility are needed.

The future way

Other markers of cardiac damage should be evaluated in clinical practice for a more in-depth evaluation of cardiac involvement in acute pancreatitis of different severity. For example, arginine vasopressin (AVP) also known as antidiuretic hormone (ADH) is one of the key hormones for cardiovascular homeostasis. Despite its pivotal role in cardiovascular diseases, both the measurement and the diagnostic use of AVP have never reached clinical practicability due to the technical problems related mainly to three

reasons: its short plasma half-life, its interaction with platelets in the serum, and its small circulating quantity. Another interesting molecule to test in clinical practice is copeptin, a glycosylated 39-amino acid long peptide with a leucine-rich core segment.[25] Copeptin and AVP share the same precursor peptide, the 164-amino acid long preprovasopressin and copeptin is the C-terminal part of pro-AVP (CT-pro-AVP) and it is released together with

AVP during precursor processing. In contrast to AVP, copeptin is very stable in serum or plasma at room temperature, and is easy to measure. In contrast to many other biomarkers, the copeptin plasma concentration was similar in different age groups and showed no correlation with age. A particularly interesting observation was the response of circulating copeptin levels as a result of an acute myocardial infarction[26] since these protein

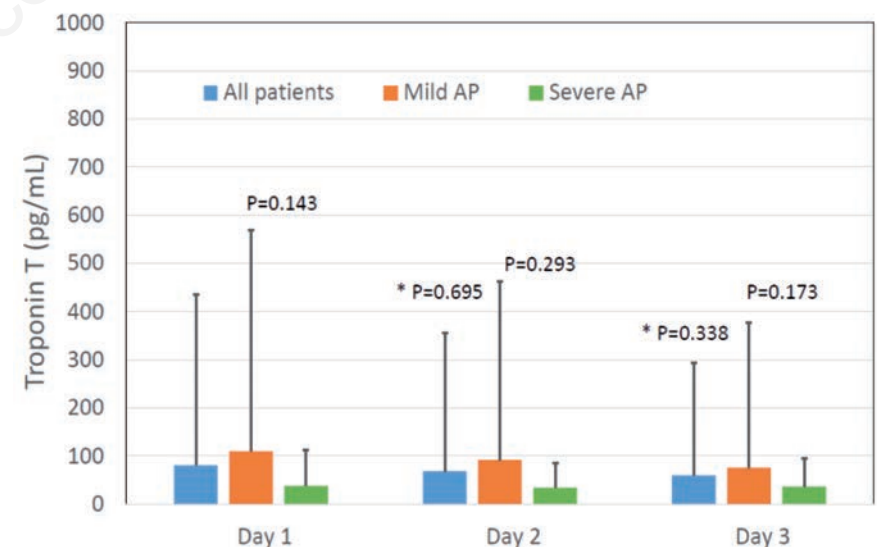Figure 1. Pathophysiology of acute pancreatitis.

Figure 2. Mean and standard deviation of troponin T in 37 patients with acute pancreatitis (22 with mild acute pancreatitis and 15 with severe acute pancreatitis). *Indicates P values of serum concentrations of troponin T at days 2 and 3 compared to day 1. The other P values refer to the comparison of serum concentrations of troponin T between mild and severe acute pancreatitis during the three days of the study.

levels were higher in patients who died or were readmitted with heart failure as compared to event-free survivors. Thus, the measurement of plasma copeptin should be investigated in acute pancreatitis patients in order to select those who require more intensive support.

Finally, adrenomedullin (ADM), a 52-amino-acid peptide elevated in plasma of patients having heart failure and/or post-acute coronary syndrome, has been isolated in human pheochromocytoma and it is also present in the heart, brain, lung, kidney and gastrointestinal organs; it has a potent vasodilator activity due to an increase in cyclic adenosine monophosphate levels.[27] It should be underlined that the quantification of ADM is quite difficult due to a short half-life and the lack of the reliable laboratory techniques. The identification of mid-regional pro-adrenomedullin (MR-proADM)[28,29] has overcome these problems, because it is a stable peptide possibly reflecting the concentration of ADM. MR-proADM is probably secreted in equimolar amounts to those of ADM, and it does not have any physiological effects which might explain its apparent stability. Plasma MR-proADM concentrations predict an adverse outcome in patients in the recovery phase of myocardial infarction and appear to add information beyond the strong predictor N-Terminal pro-B-Type natriuretic peptide (NT-proBNP). There are no studies on the ADM circulating concentration in

acute pancreatitis patients and this topic should be explored in order to obtain more accurate information regarding cardiac involvement in acute pancreatitis. In any way, it has been recently reported that MR-proADM is a strong predictor of rehospitalization and mortality in patients with septic shock[28,30] and we believe that this molecule may have a practical role in patients with infected pancreatic necrosis. Regarding NT-proBNP, we have found that this molecule is abnormally elevated in acute pancreatitis and its elevation persists for at least 72 hours (Figure 3). In addition, similar high levels of serum NT-proBNP are present in patients with mild acute pancreatitis as well as in those with severe disease.[22] Thus, we should be aware that elevated values of NT-proBNP in patients with acute pancreatitis cannot be useful to detect hearth failure.

Conclusions

The exact mechanism of myocardial injury during the course of acute pancreatitis still remains unclear. In clinical practice, laboratory examinations are needed to distinguish in the emergency room patients with epigastric pain having acute pancreatitis from those with acute myocardial infarction because the treatment strategy of the two diseases differs markedly. In addition, further efforts should be

made to identify acute pancreatitis patients at high risk of cardiovascular disease and the new above-mentioned markers need to be explored for their possible use in clinical practice.

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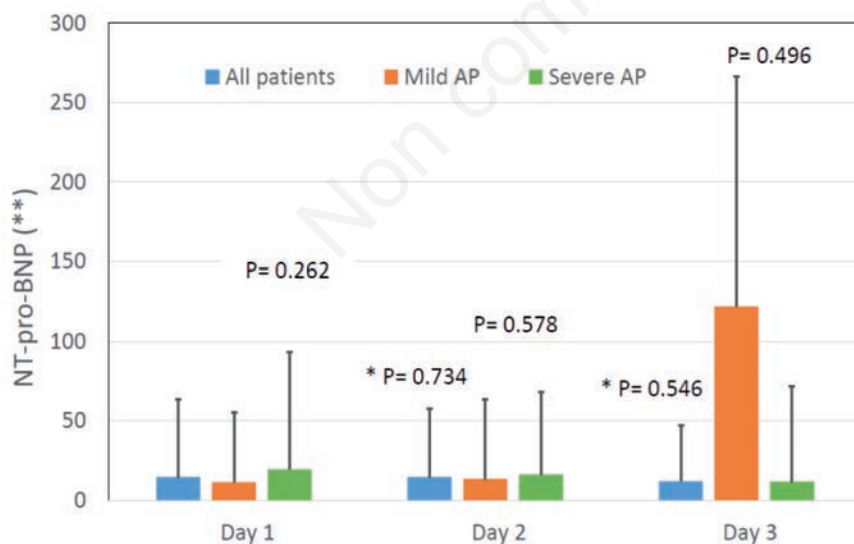
Figure 3. Mean and standard deviation of NT-pro-BNP in 37 patients with acute pancreatitis (22 with mild acute pancreatitis and 15 with severe acute pancreatitis). **Indicates normalized values of NT-pro-BNP: values from 0 to 1 represent values within the reference range, and values greater than 1 represent values above the upper reference limit. *Indicates P values of serum concentrations of troponin T at days 2 and 3 compared to day 1. The other P values refer to the comparison of serum concentrations of troponin T between mild and severe acute pancreatitis during the three days of the study.

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