Dig Dis Sci (2008) 53:297–306
DOI 10.1007/s10620-007-9866-5

REVIEW ARTICLE

The Pathogenic Mechanism of Severe Acute Pancreatitis Complicated with Renal Injury: A Review of Current Knowledge

Xi Ping Zhang · Lei Wang · Yi Feng Zhou

Received: 11 April 2006 / Accepted: 4 June 2006 / Published online: 28 June 2007

Abstract The onset of severe acute pancreatitis (SAP) is clinically harmful as it may rapidly progress from a local pancreatic inflammation into proemial systemic inflammatory reactions. Patients with SAP have a high mortality, with most cases of death resulting from complications involving the failure of organs other than the pancreas. The distinctive feature of SAP is that once it starts, it may aggrevate the clinical condition of the patient continuously, so that the levels of injury to the other organs surpass the severity of the pancreatic lesion, even causing multiple organ failure and, ulitmately, death. In clinical practice, the main complications in terms of organ dysfunctions are shock, acute respiratory failure, acute renal failure, among others. The acute renal injury caused by SAP is not only able to aggravate the state of pancreatitis, but it also develops into renal failure and elevates patients' mortality. Studies have found that the injury due to massive inflammatory mediators, microcirculation changes and apoptosis, among others, may play important roles in the pathogenic mechanism of acute renal injury.

Keywords Acute pancreatitis/severe · Renal injury

X. P. Zhang (✉)
Department of General Surgery, Hangzhou First People's Hospital, Hangzhou, Zhejiang Province 310006, China
e-mail: zxp99688@vip.163.com

L. Wang
Zhejiang University of Traditional Chinese Medical, Hangzhou, Zhejiang Province 310053, China

Y. F. Zhou
Department of Digest, Hangzhou First People's Hospital, Hangzhou, Zhejiang Province 310006, China

Introductions

Acute pancreatitis (AP) is an acute abdominal disease commonly encountered by surgeons. The courses of most AP cases are auto-restricted, but the conditions of about 15–20% of all patients may become worse,with progression to multiple organ dysfunction or local complications (including necrosis, pseudocyst and abscess) and, eventually, severe acute pancreatitis (SAP) [1]. The onset process of SAP is hazardous, with a relatively high mortality [2–5], but despite the rapid advances in modern medicine and the many extensive studies that have focused on SAP, its pathogenic mechanism has yet to be completely elucidated [6–10], and the pathological process, prevention and treatment of SAP are not yet completely understood. Consequently, the morbidity and incidence of serious complications of SAP have not been substantially reduced to date. The main cause of early death is multiple organ failure, and available data indicate that the mortality of SAP patients with the complication of acute renal failure has reached 45–50% [11]. Pathogenic mechanism studies are of high clinical value. The aim of this article is to summarize current knowledge on the main pathogenic mechanism of SAP when complicated with renal injury, based on published research material.

Participation of inflammatory mediators

Recent studies haves found that some inflammatory mediators play important roles in SAP complicated with multiple organ injury [12, 13]. Due to the co-action of manifold inflammation transmitters, AP changes from local pathological changes and rapidly develops into SAP. Systemic multiple organ dysfunction occurs together with

massive necrosis of pancreatic tissues [14–17]. The main inflammatory mediators participating in SAP renal failure are cytokine [18], phospholipase A_2 [19], arachidonic acid metabolite [20] and platelet activating factor, among others.

Cytokine

During AP, especially SAP, some inflammatory cells and pancreatic tissues release inflammatory mediators and cytokine, which influence the whole process of pancreatitis. The most important cytokines are tumor necrosis factor-α (TNF-α), interleukin (IL) and transforming growth factor (TGF).

TNF-α

Lipsett [21] and Hirota et al. [22] independently proved that the levels of inflammatory cytokines always increase during AP and that the degree of the increase is closely linked to the severity of the disease. Many other studies have reported that self-tissue injured with over-activated neutrophil leucocytes is an important causal factor of AP systemic complications [23–36]. One proposal is that the neutrophilic granulocyte may generate and release inflammatory cytokines such as TNF-α following AP inflammatory stimulation [37–39]. TNF-α is an important species of inflammatory cytokines that participates in the SAP pathomechanism. Christoph et al. [40] found that injecting TNF-α antibody into SAP rats can markedly improve the state and survival of rats with SAP, thereby indicating the important role of TNF-α in the onset and progression of SAP. A number of mechanisms have been proposed for TNF-α-induced pancreatic and renal injury. (1) TNF-α can directly injure pancreatic duct cells and cause microthrombus, pancreatic acinus ischemia, hemorrhage, necrosis, inflammation and edema [41]; it also can directly act on glomeruli and the renal tubule capillary, causing ischemia and necrosis of the renal tubular epithelial cell [42]. (2) When the quantity of produced TNF-α exceeds that of the tissue TNF receptor, the excessive free TNF-α will enter the blood circulation, activate neutrophilic granulocytes and cause the aggregation of neutrophilic granulocyte. It then stimulates the release of cytokines, such as IL-1β, IL-8 and IL-6 [43], causing a cytokine cascade reaction that promotes the systemic inflammatory reaction syndrome (SIRS) and aggravates pancreatic and renal injury. (3) The continuous existence of TNF-α may enhance the expression of endothelium adhesion molecule, which is necessary for the aggregation of inflammatory cells. Numerous granulocytes invade the pancreatic and renal tissues, increase granulocyte phagocytosis and degranulation, generate oxygen-derived free radicals (OFR), lysosomes, elastin enzyme, among others, and cause cell metabolic disturbances and renal failure [44].

Interleukin (IL)

IL-1 is a pre-inflammation cytokine generated by the pancreas that plays an important role in the early stage of SAP. In a SAP animal model, the IL-1 receptor antagonist (IL-1r) has been found to decrease case fatality by 30% [45]; in addition, the IL-1 receptor can markedly lower the concentrations of IL-6 and TNF-α [46]. Fink et al. [47] administered the IL-1 receptor antagonist before inducing the pancreatitis model and found that the IL-1 receptor block markedly lowered the release of amylopsin and pancreatic necrosis in a dose-dependent manner.

The generation of IL-1β formed from IL-1 through the mediation of IL-1 convertase (ICE). IL-1β and TNF-α have many of the same biological activities, including pyrogen functions, the promotion of cell catabolism, the production of protein in the acute reaction period, effecting the secretion of PGI_2 by epithelial cells and platelet activating factor, among others, that will cause the expansion of the inflammation area and increase the levels of inflammatory mediators, destructive enzymes and OFR secretion. IL-1β can interact with TNF-α to induce or aggravate organ injury. It also has chemotaxis and activating effects on granulocyte and can stimulate the production of other inflammatory mediators, such as IL-8, IL-6 and other inflammatory cytokines, through autocrine or paracrine mechanisms.

IL-6 is mainly generated by mononuclear macrophages, which have extensive inflammation-promoting effects, such as promoting the activation and proliferation of B cells and their final differentiation into plasmocytes, increasing immunoglobulin synthesis, promoting T cell differentiation and proliferation, promoting the acute period reaction and injuring tissue. The level of IL-6 in the serum can reflect the state of SAP. There are marked differences between AP patients without complications and SAP patients with complications in terms of IL-6 levels. When present at levels of over 40 μl, IL-6 is considered to be an indication index of SAP [48]. Relevant data show that IL-1 and IL-6 can act on endothelial cells, causing them to lower their thrombomodulin activity, aggravate renal ischemia, form thrombus [49] and activate inflammatory cells to release NO and OFR to directly cause renal injury.

IL-8 is a potent neutrophilic granulocyte chemotatic factor and activating factor that is mainly generated by neutrophilic granulocytes. Generated by mononuclear/macrophages and endothelial cells, it can activate and induce T and B cell differentiation, enhance NK cells for killing target cells, promote phagocytosis and play an important role in tissue injury mediated by neutrophilic

granulocytes. It is currently believed that most inflammatory reactions induced by TNF-α, IL-1 and IL-6 are realized by inducing the generation of chemotatic factors, mainly IL-8. Studies have shown that during SAP the levels of IL-6 and IL-8 always increase concurrently and that these positively correlate with the state of SAP [50].

Transforming growth factor (TGF)

Kimura et al. [51] studied the expression of TGF-β1 by means of immune electron microscopy and found that a marked effusion of the polymorphonuclear leukocyte and deposition of fibronectin and TGF-β1 among pancreatic lobules and inside lobules within 12–24 h after inducing pancreatitis. They therefore believed that this kind of change at the early stage of pancreatitis is related to the generation of fibronectin and type III collagen in the extracellular matrix during the reparative process of pancreatic tissues. Konturek et al. [52] proposed that TGF-β can induce non-inflammatory apoptosis to repair injured pancreatic tissues.

Phospholipase A_2 (PLA_2)

As a result of the increased quantities of inflammatory mediators released in SAP, PLA_2, as an important inflammatory mediator, will also be generated in large quantities [53]. Studies have shown that the level of PLA_2 is consistent with the state of SAP and also related to prognosis [54]. PLA_2, which is one of major body lipases, is widely distributed in the plasma and in the organelle membrane of various cells. The PLA_2 in the plasma is secreted mainly by the pancreas and only slightly by salivary gland, the prostate, and a number of other organs. Serum PLA_2 mainly originates from neutrophilic granulocytes, macrophages and platelets in the pancreatic acinus and various other tissues outside of the pancreas [55]. When SAP occurs, polymorphonuclear leukocytes and mononuclear macrophages that are stimulated by endotoxin can release numerous PLA_2 into the blood to attack and decompose the phospholipidic part of the membrane. PLA_2 not only destroys the stability of the cell membrane, resulting inthe massive leakage of lysosome enzyme out of the cell, but it also generates bioactive free fatty acids and soluble lecithin to destroy the function and structure of the systemic cell and organ system. One proposal is that PLA_2 is the important mediator for mediating viscera injury of pancreatic and other tissues after pancreatitis [56, 57]. In renal injury due to SAP, the level of PLA_2 rises, and it can hydrolyze the renal tubular epithelial cell membrane lecithin, leading to the generation of free fatty acid and hemolytic lecithin. This hemolytic lecithin can dissolve the renal tubular epithelial cell membrane.

Arachidonic acid metabolite thromboxane (TXA_2) and prostacyclin (PGI_2)

As the rate-limiting step of the arachidonic acid biosynthetic pathway, the secretion of PLA_2 can be increased to accelerate the generation of arachidonic acid under the pathological state. Under the effect of epoxidase, prostaglandin synthetase and thromboxane synthetase, arachidonic acid can produce a large quantity of TXA_2 and PGI_2. TXA_2 is a potent capillary vasoconstrictor substance and platelet aggregation promoter that is able to induce platelet deformation, release and secretion, cause local and/or systemic disturbance of hemorrhage blood coagulation and destroy the cell-protection mechanism [58, 59]. It also can promote neutrophilic granulocyte activation, release OFR and cause injury to the blood vessel endothelium [60]. Due to its extremely potent TXA_2 antagonist function, PGI_2 can greatly inhibit platelet aggregation and activation, inhibit leukocyte activation, protect lysosomes and prevent lysosomes from being released into the tissue [61, 62]. The concentration of TXA_2 in the plasma of SAP patients is markedly elevated, as is PGI_2. However, the increased level of PGI_2 is short term, and it soon drops back to normal, leading to an increase in the TXA_2/PGI_2 ratio. The absolute change in the level of either of these factors is not important, but the proportional balance is. Because both of these substances function in angiotasis regulation, the proportional imbalance of TXA_2/PGI_2 can cause vasomotion disturbance, the formation of microthrombus, vascular occlusion and other pathological changes [63], which must result in the abnormal contraction of vessels of the kidney, the decline in renal blood flow and nephridial tissue perfusion. These changes can cause serious injury to the kidney.

Platelet activating factor (PAF)

PAF is a phospholipidic inflammatory mediator with extensive bioactivities. It is considered to be the key inflammatory mediator in SAP external secretion and local/systemic inflammatory reactions [64]. The primary actions of PAF [65–68] include the activation of platelets, promotion of platelet adhesion and aggregation and formation of thrombus. Secondary actions include the elevation of adhesion factor β_2-integrin, changes in the endothelial cell skeleton, increases in capillary permeability, massive effusion of plasma, increase in blood viscosity and a slowdown of blood flow. It also participates in ischemia-reperfusion injury and stimulates other vasoactive substances, including the generation of cytokine and inflammatory mediators.

In SAP, PAF levels rise due to the cytokine cascade reaction activated by elevated levels of TNF-α [69]. On the

one hand, PAF promotes granulocyte aggregation and aggravates inflammatory reactions; on the other hand, it increases capillary permeability and aggravates renal tubule injury. The imbalance between PAF and vasoactive substances can initiate a vicious cycle that leads to a series of chain reactions and amplifying reactions—the cascade reaction. This reaction can increase tissue and organ injury, cause systemic inflammatory reaction syndrome (SIRS) and, eventually, multiple organ dysfunction syndrome (MODS) and/or multiple organ failure (MOF), or even death [70, 71]. Clinical studies have found that PAF antagonist Lexipafant has clear treatment effects on multiple organ failure of SAP patients and also lowers the serum levels of inflammatory mediators such as IL-8 and IL-6 [72].

The role of NF-κB and its regulation of ICAM-1 expression in SAP complicated with kidney injury

Nuclear factor κB (NF-κB) is a transcription factor that mainly participates in the regulation of inflammatory molecule expression [73, 74]. As a protein capable of bonding the κB sequence of a genetic initiator and enhancer region, it can start or enhance genetic transcription [75–78]. In silent cells, NF-κB exists in an inactive form in the cytoplasm; it can be activated by stimulation with nuclear translocation. It can then bond with the κB site of the target gene initiator or enhancer to start or enhance genetic transcription [79–82], and it can also participate in the injury process of the tissue [83–85]. The activation of renal NF-κB also plays an important role during the manifestation of AP renal injury. Satoh et al. [86] found that NF-κB activation increases markedly following the manifestation of SAP. The time-dependent NF-κB activation increases with time. The abnormal activation of NF-κB can promote the genetic transcription of pre-inflammatory factors (TNF-a, IL-1, IL-6). TNF-a and IL-1 are extracellular stimulation signals that are also able to activate NF-κB as well as enlargen the inflammatory reactions. NF-κB is capable of regulating body inflammatory reactions, and the genetic transcription of cytokines and inflammation transmitter-related immunization, stress, among others, has been recognized [73].

There is a NF-κB bonding site on the intercellular adhesion molecule (ICAM-1) initiator [87]. ICAM-1 is a member of the cell adhesion molecule immunoglobulin super family and mainly mediates the adhesion between the polymorphonuclear granulocyte (PMN) and vascular endothelial cells, playing an important role in the aggregation process of PMN with tissue. The aggregated PMN in the tissue can cause cell and organ injury. Due to the presence of the NF-κB binding site on the ICAM-1 initiator, renal NF-κB activation in SAP can promote the expression of ICAM-1 and make the neutrophilic granulocyte adhere to the endothelial cell, which results in the aggregation of neutrophilic granulocytes toward the inflammation focus. The aggregated inflammatory cells in glomeruli can induce direct toxic effects that cause cell morphological changes, proliferation, capillary injury and the formation of crescents. TNF-α can also activate the cytokine cascade reaction, cause the massive release of inflammatory mediators, and inflict further injury to the glomeruli.

Role of endotoxin

Endotoxin , which is mainly produced by Gram-negative bacteria, is a component of the lipopolysaccharide present in cell walls. Clinical studies show that endotoxemia occurs in AP and particularly in SAP, and that it is closely related to the onset, progression and complication of multiple organ failure in SAP. Windsor et al.'s [88] study demonstrated the link between endotoxin and the state of pancreatitis. Other researchers studying the relation between plasma endotoxin levels of AP patients and multiple organ injury have found that endotoxin has an important promoting effect during the progression of multiple organ injury. As the most potent stimulant of endothelin, endotoxin can elevate the endothelin level in vivo and in blood, potently contracting medium-sized arteries and arterioles, especially the renal artery and vein. This effect may be due to the high-affinity receptor on the renal artery and vein, which will greatly lower renal blood flow and cause renal ischemia, necrosis, dysfunction, or even failure. Increased endothelin levels will also aggravate ischemia in other tissues, enhance bacterial translocation, raise blood endotoxin and renin-angiotensin levels and form a vicious cycle chain of tissue ischemia and endothelin that aggravates tissue ischemia endlessly [89].

Role of oxygen-free radicals

The OFR is an oxygen-containing chemical group with high chemical reaction activities, mainly those involving the peroxide anion-free radical (O_2^-) and the hydroxy radical (OH·). By causing lipid oxidation, it can increase mucosa permeability, further enhance phagocyte activity, generate more OFRs and finally cause histiocyte injury. Scott et al. [90] demonstrated that in the pathological state, excessive OFRs can cause tissue and cell injury. OFRs can also participate in the formation of AP pancreatic edema and, possibly, in pancreatic necrosis and mediate leukocytes and platelets activated by TNF-α in all organs to

release lysosome, OFRs and lipid inflammatory mediators. OFR can react with protein and enzymes, leading to protein denaturation and enzyme inactivation.

The OFR peroxidation product lactoperoxidase (LPO) can cause the inactivation of membrane-bound enzymes and cell membrane injury, and increase vascular permeability. When the generation rate of OFRs greatly exceeds the anti-oxidation capacity of the body or the anti-oxidation capacity of the body has been exhausted and therefore incapable of clearing OFR in time, a serious oxidation storm will result in the lipid peroxidation of the cell and organelle plasma membrane and direct cell injury.

Luo Jun et al. [91] who synchronously measured the levels of superoxide dismutase (SOD), malonaldehyde (MDA) from lipid peroxidation in kidney as well as plasma MDA level during AP found that the pathological changes progress with disease course. Accompanied by a gradual decline in SOD level, MDA will elevate and inflict heavier renal injury. This proves that OFR and lipid peroxidation participate in the whole renal injury process in AP.

Nitrogen monoxidum (NO)

NO can regulate microcirculation, maintain capillary integrality, inhibit leukocyte adhesion, among others. The kidney is the earliest organ affected in SAP, and under pathological conditions, NO has completely different biological functions [92]. Molero et al. [93], who studied the relation between NO and pancreatic basal secretion in pancreatitis, recently found that NO synthetase inhibitor (L-NAME) can increase the formation of amylase and lipoidase and the activities of MPer to aggravate pancreas injury, which can be reversed by an NO donator (L-arginine). As such, NO can improve AP and its pathological changes by decreasing pankrin release and regulating microcirculation perfusion. The possible roles of NO in SAP renal injury are: (1) synergism of NO and cytokine. such as TNF-α induced by endotoxin to injury kidney [94]; (2) with the increase of systemic NO, it lowers the reaction of the blood vessel to stagnated substances and causes renal ischemia; (3) local excessive NO and OFR interact to have a toxic effect on renal cells directly [95].

Microcirculation disturbances

Microcirculation disturbances are those disturbances in both the form and function of the blood and blood vessels at the microcirculation level that arise mainly from abnormal rheology and blood components. Plusczyk et al. [96] believe that in SAP, injured endothelial cells can release ET-1 to promote disturbances in pancreatic microcirculation, which is an important causal factor in pancreatic cell necrosis. Cheng Guozuo et al. [97], who studied the dynamic changes in renal microcirculation and its relation with renal injury in SAP, have proven that renal injury occurs during the early stage of SAP and that it is possibly mainly due to disturbances in the renal microcirculation caused by renal ischemia and ischemia reperfusion injury. During SAP with SIRS, a large great quantity of inflammatory mediators and activated leukocytes can release numerous OFRs and lysosome enzymes, resulting in injury to the cell membrane. Concurrently, a large number of leukocytes adhere to the blood vessel endothelium to cause severe injury to the renal capillaries, platelet activating factor (PAF), release of the TXA2 agglutinate, the formation of microcirculation thrombus and ischemia-reperfusion injury (IRI).

At the early stage of SAP, inflammatory mediators cause potent contractions of the abdominal viscera capillaries, and changes in the neuroendocrine system cause visceral bloodflow redistribution and a rapid decline of renal blood flow. With the progression of the disease, the renal blood flow is further decreased, and renal function and renal pathologic injury become worse due to the decrease in the volume of the circulation and excessive activation of inflammatory mediators. Studies have shown that there is a close negative correlation among renal blood flow, renal function and renal pathologic injury, indicating that microcirculation disturbances may cause SAP renal injury directly. Foitzik et al. [16] found the improvement of renal and lung microcirculation can markedly alleviate the pathological injury and lower mortality in animals, which also indicates the significance of microcirculation disturbances in renal injury.

Renal hemodynamics dropout

In SAP, the blood sedimentation equation K value, red blood cell (RBC) aggregation index and whole blood viscosity rise markedly, indicating an increase in blood viscosity and a decline in blood liquidity. As a systemic change, the abnormal hemorheology affects not only pancreatic microcirculation, lowers pancreatic blood priming volume, aggravates ischemia and causes hypoxia, and pancreatic necrosis, but it also causes microcirculation disturbance in other important organs. It is the pathological and physiological basis of pancreatic and other organ injury, with a decline in renal microcirculation blood flow, an increase in renal vascular resistance and abnormal renal artery hemorheology. The whole blood viscosity and afferent vessel contraction here may directly cause an increase in glomeruli resistance to lower renal blood flow. The increase in whole blood viscosity and the decline in

RBC deformation, among others, can affect the microcirculation of the renal tubule capillary and cause renal cortex and medulla microcirculation disturbance, followed by renal failure [98].

The presence of active trypsin in the AP patient can markedly activate the renin-angiotensin system [99] to cause a temporary elevation in blood pressure under hypotension and hypovolemia, and cause an elevation of renal vascular resistance and a marked decline in glomeruli filterability and effective renal blood flow due to its potent action on the renal vascular system. In addition, SAP patients always manifest hyperlipemia, with lipids easily deposited around renal tubules and blood vessels; this factor can also not be neglected in terms of promoting renal blood vessel resistance. Nishiwaki et al. [100] also found a decline in renal microcirculation blood flow and an increase in renal blood vessel resistance at the early stage of AP in their experiments. It would therefore appear that renal hemodynamics dropout also causes injury.

Pancreatic nephrotoxin

Over the long term, it is the hypovolemia and hypotension due to AP that are considered to be the constant factors causing renal injury. Recent studies have shown these are potent renal toxic reactions that result from the kallikrein-kinin system activated by trypsin. In AP, increased pankrin is released into blood, including PLA_2, which can decompose the phospholipids and lecithin of the cell membrane. Abnormal lipid metabolites, such as free fatty acids, acylcarnitine, acyl-coenzyme and lysophosphatide, are all membrane-active factors that can destroy the cell membrane. The free fatty acid can also cause mitochondria oxidative phosphorylation and block the activity of the cell Na^+-K^+-ATP enzyme. The activated complement system can produce C5b and C5b and combine C6, C7, C8 and C9 to generate a ''membrane attack complex'' that destroys the cell membrane and results in irreversible cell injury [101].

The elevation in the blood trypsin levels can activate the kallikrein-kinin system, releasing the vasoactive polypeptide to cause an intense renal toxic reaction. At the same time, the pancreatic resolvase can release polypeptide during the degradation of the plasma protein to cause the increase in glomeruli permeability and the injury to renal tubule and interstitial tissue. High concentrations of trypsin can cause a systemic hypercoagulabale state; the renal function may the be destroyed by coagulation, and thrombus consisting of fibrin, platelet and cell debris may be formed in the blood vessels.

Electrolyte disturbances

In AP, the activated pankrin and numerous toxic substances not only digest pancreatic tissues, but they also injure viscera around the pancreas and abdominal viscera. Large quantities of inflammatory effusion and tissue fluid enter the third space to cause hypovolemia or even shock. At the same time, the body will release various tissue factors to aggravate the shock state and cause renal vasoconstriction, resulting in a declining renal blood flow, filterability and, ultimately, hypourocrinia. The decline of renal water discharge, increase of catabolism in vivo and endogenous water only causes water intoxication, but also results in dilutional hyponatremia. In AP, body catabolic and acid metabolites increase endlessly, but the kidney cannot discharge these in time, which causes metabolic acidosis. The acidosis can result in kalium ions being moved from inside the cell to outside the cell, decrease glomeruli filterability and kalium ion discharge and cause tissue injury, all of which result in an increase of kalium ion generation and, ultimately, lethal hyperpotassemia [102].

Hyperuricemia

When the level of blood uric acid increases, the increased discharge capacity of urine uric acid can injure the kidney. It is currently believed that the excretion of uric acid by the kidney can be regulated by three mechanisms—glomerular filtration, tubular reabsorption and tubular secretion. Almost all of the uric acid filtered by glomeruli is absorbed at the proximal-convoluted tubule; secreted uric acid isalso partially reabsorbed. Therefore, the uric acid excreted with urine is only that portion which remains after uric acid reabsorption. Many different organic acids, such as lactic acid, alcohol and ketones, can inhibit uric acid excretion by the renal tubule. However, the lactic acid content measured by some reports falls within the normal range. Therefore, it is believed that the release of toxic substances, the acceleration of histodialysis and the increase of the uric acid precursor after pancreatic injury are all related. This kind of hyperuricemia does not directly harm renal function recovery [103].

Others

Secondary lesion

Gallstone AP is often complicated with serious obstructive jaundice. Bilirubin can directly block the glomeruli capsular space and renal tubule to affect the excretion of urea

nitrogen. Jaundice can increase renal sensitivity to hypotension and hypoxia, and make kidney more injury-prone [104].

Apoptosis

Apoptosis is an initial step in the cellular death process that is regulated by genes in accordance with the cell's own procedures. There are two notable characteristics of apoptosis—the controlled degradation of chromatin and the synthesis of new protein [105]. Kaiser et al. [106] applied various methods to induce the AP model and observed a negative correlation between the state of pancreatitis and the incidence of pancreatic apoptosis.

Genes

Recent studies have proven that, during the progression of SAP, the expressions of the pancreatitis-associated protein (PAP) [107] gene, glutamic acid synthesis (GS) gene, intra-pancreas IL-1β gene [108] and TNF gene [109] are elevated and that all of these genes show trends towards continuing increased expression and tissue specificity. This increased expression is also related to pancreatic injury and the inflammation state.

Immune complex injury

Renal biopsies on AP patients complicated with glomerular nephritis reveal the presence of the sediment of complement systems C and IgM under the glomeruli intramembrane cells and in the immune complex, which may be the cause of renal injury.

Local factors

Because the anatomic site of the pancreas is close to kidney, the inflammatory pathological changes of and around the pancreas can constantly affect kidney.

In conclusion, SAP complicated with renal injury is caused by manifold factors. During the progression of SAP, these factors interact and mediate the occurrence and development of SAP, which ultimately result in renal injury.

Acknowledgements This work was supported by the technological foundation project of Traditional Chinese Medicine Science of Zhejiang province (No. 2003C130; NO.2004C142), foundation project for medical science and technology of Zhejiang province (No. 2003B134), grave foundation project for technological and development of Hangzhou (No. 2003123B19), intensive foundation project for technology of Hangzhou (NO.2004Z006), foundation project for medical science and technology of Hangzhou (No.2003A004) and foundation project for technology of Hangzhou (No. 2005224).

References

1. Bradley EL III (1993) A clinically based classification system for acute pancreatitis: summary of the international symposium on acute pancreatitis, Atlanta. Arch Surg 128:586–590 [PMID:8489394]
2. Yousaf M, McCallion K, Diamond T (2003) Management of severe acute pancreatitis. Br J Surg 90:407–420 [PMID: 12673741]
3. Hartwig W, Werner J, Muller CA, Uhl W, Buchler MW (2002) Surgical management of severe pancreatitis including sterile necrosis. J Hepatobil Pancreat Surg 9:429–435 [PMID: 12483264]
4. Hartwig W, Werner J, Uhl W, Buchler MW (2002) Management of infection in acute pancreatitis. J Hepatobil Pancreat Surg 9:423–428 [PMID:12483263]
5. Abu-Zidan FM, Windsor JA (2002) Lexipafant and acute pancreatitis: a critical appraisal of the clinical trials. Eur J Surg 168:215–219 [PMID:12440758]
6. Wu WK (2001) The etiological factor and pathology (in Chinese). World Chin J Digestol 9:410–411
7. He L, Chen SF, Cao XH, Zhang LD, Pan LL, Zhou Z (2003) Changes of serum level of IL-15, IL-18 and sTNF-1R in patients with acute pancreatitis (in Chinese). World Chin J Digestol 11:57–60
8. Wang CH, Qian DK, Zhu YL, Tang XQ (2001) Significance of changes of serum level of TNF and IL-6 in patients with acute pancreatitis (in Chinese). World Chin J Digestol 9:1434
9. Xia SH, Zhao XY, Guo P, Da SP (2001) Hemocirculatory disorder in dogs with severe acute pancreatitis and intervention of platelet activating factor antagonist (in Chinese). World Chin J Digestol 9:550–554
10. Li Y, Qian JQ, Qing RY, Shen M (2000) Changes of immune function in patients with acute pancreatitis (in Chinese). World Chin J Digestol 8:923–925
11. Yuan YZ (2001) New progress and new technology of pancreatology. Publishing Company of Shanghai Technology Literature, Shanghai
12. Makhija R, Kingsnorth AN (2002) Cytokine storm in acute pancreatitis. J Hepatobil Pancreat Surg 9:401–410 [PMID:12483260]
13. Keck T, Balcom JH IV, Fernandez-del Castillo C, Antoniu BA, Warshaw AL (2002) Matrix metalloproteinase-9 promotes neutrophil migration and alveolar capillary leakage in pancreatitis-associated lung injury in the rat. Gastroenterology 122:188–201 [PMID:11781293]
14. Shimada M, Andoh A, Hata K, Tasaki K, Araki Y, Fujiyama Y, Bamba T (2002) IL-6 secretion by human pancreatic periacinar mypfibroblasts in reponse to inflammatory mediators. J Immunol 168:861–868 [PMID:11777983]
15. Rau B, Baumgart K, Paszkowski AS, Mayer JM, Beger HG (2001) Clinical relevance of caspase-1 activated cytokines in acute pancreatitis: high correlation of serum interleukin-18 with pancreatic necrosis and systemic complications. Crit Care Med 29:1556–1562 [PMID:11505126]
16. Foitzik T, Eibl G, Hotz HG, Faulhaber J, Kirchengast M, Buhr HJ (2000) Endothelin receptor blockade in severe acute pancreatitis leads to systemic enhancement of microcirculation,stabilization of capillary permeability,and improved survival rates. Surgery 128:399–407 [PMID:10965310]
17. Lundberg AH, Granger DN, Russell J, Sabek O, Henry J, Gaber L, Kotb M, Gaber AO (2000) Quantitative measurement of P-and E-selectin adhesion molecules in acute pancreatitis: correlation with distant organ injury. Ann Surg 231:213–222 [PMID:10674613]

18. Kunsch C, Ruben SW, Rosen CA (1992) Selection of optimal kappa B/Rel DNA-binding motifs: interation of both submits of NF kappa B with DNA is required for transcriptional activation. Mol Cell Biol 12:4412–4421 [PMID:1406630]
19. Christman JW, Sadikot RT, Blackwell TS (2000) The role of nuclear factor- kappa B in pulmonary diseases. Chest 117:1482–1487 [PMID:10807839]
20. Orian A, Whiteside S, Israel A, Stancovski I, Schwartz AL, Ciechanover A (1995) Ubiquitin-mediated processing of NF kappa B transcriptional activator precursor p105: reconstitution of a cell-free system and identification of the ubiquitin-carrier protein, E2, and a novel ubiquitin-protein ligase, E3, involved in conjugation. J Biol Chem 270:21707–21714 [PMID:7665588]
21. Lipsett PA (2001) Serum cytokines, proteins, and receptors in acute pancreatitis: mediators, marker, or more of the same? Crit Care Med 29:1642–1644 [PMID:11505151]
22. Hirota M, Nozawa F, Okabe A, Shibata M, Beppu T, Shimada S, Egami H, Yamaguchi Y, Ikei S, Okajima T, Okamoto K, Ogawa M (2000) Relations ship between plasma cytokine concentration and multiple organ failure in patients with acute pancreatitis. Pancreas 21:141–146 [PMID:10975707]
23. Chen H, Li F, Cheng YF, Sun JB (2001) Pathogenic role of neutrophils in evolution of acute pancreatitis in rats (in Chinese) . World Chin J Digestol 9:776–779
24. De Dios I, Perez M, de la Mano A, Sevillano S, Orfao A, Ramudo L, Manso MA (2002) Contribution of circulating leukocytes to cytokine production in pancreatic duct obstruction-induced acute pancreatitis in rats. Cytokine 20:295–303 [PMID:12633572]
25. Descamps FJ, Van den Steen PE, Martens E, Ballaux F, Geboes K, Opdenakker G (2003) Gelatinase B is diabetogenic in acute and chronic pancreatitis by cleaving insulin. FASEB J 17:887–889 [PMID:12626433]
26. Ammori BJ (2003) Role of the gut in the course of severe acute pancreatitis. Pancreas 26:122–129 [PMID:12604908]
27. Shields CJ, Sookhai S, Winter DC, Dowdall JF, Kingston G, Parfrey N, Wang JH, Kirwan WO, Redmond HP (2001) Attenuation of pancreatitis-induced pulmonary injury by aerosolized hypertonic saline. Surg Infect 2:215–224 [PMID:12593711]
28. Demols A, Deviere J (2003) New frontiers in the pharmacological prevention of post-ERCP pancreatitis: the cytokines. JOP 4:49–57 [PMID:12555016]
29. Zhao H, Chen JW, Zhou YK, Zhou XF, Li PY (2003) Influence of platelet activating factor on expression of adhesion molecules in experimental pancreatitis. World J Gastroenterol 9:338–341 [PMID:12532462]
30. Zhou Z, Chen Y, Yu Y, Chen H (2002) Hemorheology and expression of neutrophil adhesion molecules CD18 and CD62L in pancreatic microcirculation of Caerulein induced experimental acute pancreatitis. Zhonghua Yufang Yixue Zazhi 36:528–530 [PMID:12411162]
31. Shields CJ, Winter DC, Redmond HP (2002) Lung injury in acute pancreatitis: mechanisms, prevention, and therapy. Curr Opin Crit Care 8:158–163 [PMID:12386518]
32. Song AM, Bhagat L, Singh VP, Van Acker GG, Steer ML, Saluja AK (2002) Inhibition of cyclooxygenase-2 ameliorates the severity of pancreatitis and associated lung injury. Am J Physiol Gastrointest Liver Physiol 283:G1166–G1174 [PMID:12381531]
33. Brady M, Bhatia M, Christmas S, Boyd MT, Neoptolemos JP, Slavin J (2002) Expression of the chemokines MCP-1/JE and cytokine-induced neutrophil chemoattractant in early acute pancreatitis. Pancreas 25:260–269 [PMID:12370537]
34. Clemons AP, Holstein DM, Galli A, Saunders C (2002) Cerulein-induced acute pancreatitis in the rats is significantly ameliorated by treatment with MEK1/2 inhibitors U0126 and PD98059. Pancreas 25:251–259 [PMID:12370536]
35. Hartwig W, Carter EA, Jimenez RE, Jones R, Fischman AJ, Fernandez-Del Castillo C, Warshaw AL (2002) Neutrophil metabolic activity but not neutrophil sequestration reflects the development of pancreatitis-associated lung injury. Crit Care Med 30:2075–2082 [PMID:12352044]
36. Mikami Y, Takeda K, Shibuya K, Qiu-Feng H, Egawa S, Sunamura M, Matsuno S (2002) Peritoneal inflammatory cells in acute pancreatitis: relationship of infiltration dynamics and cytokine production with severity of illness. Surgery 132:86–92 [PMID:12110800]
37. Cassatella MA (1995) The production of cytokines by polymorphonuclear neutrophils. Immunol Today 16:21–26 [PMID:7880385]
38. Ni QX, Zhang N, Zhang JH, Zhang YL, Xiang Y, Zhen SG, Luo JM (1998) Study on combined prevention and treatment of acute necrotizing pancreatitis lung injury by somatostatin and somatotropin (in Chinese). Chin J Exp Surg 15:404–406
39. Ogawa M (1998) Acute pancreatitis and cytokines: ''second attack'' by septic complication leads to organ failure. Pancreas 16:312–315 [PMID:9548672]
40. Hughes CB, Gaber LW, Mohey el Din AB, Grewal HP, Kotb M, Mann L, Gaber AO (1996) Inhibition of TNF alpha improves survival in an experimental model of acute pancreatitis. Am Surg 62:8–13 [PMID:8540653]
41. Klar E, Messmer K, Warshaw AL, Herfarth C (1990) Pancreatic ischemia in experimental acute pancreatic: mechanism, significance and therapy. Br J Surg 77:1205–1210 [PMID:2252994]
42. Persidskii IV, Kudriavets II, Barshtein IA (1991) The action of tumor necrosis factor on the microvascular endothelium and its role in the morphological changes in the internal organs. Biull Eksp Biol Med 3:294–297 [PMID:2054509]
43. Zhang QH, Cai R, Wu SJ, Jiang YF, Zhang YL (1997) Changes of inflammatory mediators in rats with acute necrotizing pancreatitis and effects of somatostatin. Chin Med J 5:355
44. Pohlman TH, Stanness KA, Beatty PG, Dchs HD, Harlan JM (1986) An endothelial cell surface factors induced in vitro by lipopolysaccharide interleukin-1 and tumor necrosis factor increases neutrophils adherence by a WD 18-dependent mechanism. J Immunol 136:4548–4553 [PMID:3486903]
45. Norman JG, Franz MG, Fink GS, Messina J, Fabri PJ, Gower (1995) Decreased mortality of severe acute pancreatitis after cytokine blockade. Ann Surg 221:625–631 [PMID:7794067]
46. Norman JG, Fink G, Franz M, Guffey J, Carter G, Davison B, Sexton C, Glaccum M (1996) Active interleukin-1 receptor required for maximal progression of acute pancreatitis. Ann Surg 223:163–169 [PMID:8597510]
47. Fink G, Yang J, Carter G, Norman J (1997) Acute pancreatitis-induced enzyme release and necrosis are attenuated by IL-1 antagonism through an indirect mechanism. J Surg Res 67:94–97 [PMID:9070189]
48. Kusske AM, Rongione AJ, Reber HA (1996) Cytokines and acute pancreatitis. Gastroenterology 110:639–642 [PMID:8566616]
49. Lentz SR, Tsiang M, Sadler JE (1991) Regulation of thrombomodulin by tumour necrosis factor-α: comparison of transcriptional and posttranscriptional mechanisms. Blood 77:542–550 [PMID:1846763]
50. Gross V, Andreessen R, Leser HG, Ceska M, Lehl E, Lausen M, Farthmann EH, Scholmerich J (1992) Interleukin-10 and neutrophil activation in acute pancreatitis. Eur J Clin Invest 22:200–203 [PMID:1582445]
51. Kimura Y, Torimura T, Ueno T, Inuzuka S, Tanikawa K (1995) Transforming growth factor beta 1 extracellular matrix and inflammatory cells in wound repair using a closed duodenal loop

pancreatitis model rat, immunohistochemical study. Scand J Gastroenterol 30:707–714 [PMID:7481536]
52. Konturek PC, Dembinski A, Warzecha Z, Ceranowicz P, Konturek SJ, Stachura J, Hahn EG (1997) Expression of transforming growth factor-beta 1 and epidermal growth factor in caerulein-induced pancreatitis in rat. J Physiol Pharmacol 48:59–72 [PMID: 9098826]
53. Pfeilschifter, Muhl H, Pignat W, Marki F, Vanden, Bosch H (1993) Cytokine regulation of group II phospholipase A2 expression in glomerular mesangial cells. Eur J Clin Pharmacol 44[Suppl 1]:S7–S9 [PMID:8387428]
54. Fink MP (1993) PLA2: potential mediators of the systemic inflammatory reponse syndrome and the multiple organ dys-function syndrome. Crit Care Med 21:957–959 [PMID: 8319474]
55. Makela A, Sternby B, Kuusi T (1990) Phospholipase A2 activity and concentration in several body fluids in patients with acute pancreatitis. Scand J Gastroenterol 25:944–950 [PMID: 2218399]
56. Mirkovic D (2000) The role of phospholipase A2 in the pathogenesis of respiratory damage in hemorrhagic necrotizing pancreatitis assessment of a new experimental model. Vojnosnnit Pregl 57:625–633 [PMID:11332353]
57. Nevalainen TJ, Haapamaki MM, Gronroos JM (2000) Roles of secretory phospholipases A2 in inflammatory diseases and trauma. Biochim Biophys Acta 1488:83–90 [PMID:11080679]
58. Mao EQ, Zhang SD, Han TQ, Wang JC, Zhang CL (1997) Pancreatic ishemia: a continuous injury factor in acute necrotic pancreatitis. Zhonghua Waike Zazhi 35:150–152 [PMID: 10374521]
59. Wang CH, Liao JX, Li DK, Liao XW, Qin M (1998) Plasma thromboxane A and prostacyclin changes in acute pancreatitis rats after perfusion of microcirculation improving drugs via various ways (in Chinese). Chin J Exp Surg 15:396–398
60. Zhou XZ, Mao QS, Chen YQ, Shen HX (2000) The relationship between pathological characters and changes of oxygen free radicals in rats with acute pancreatitis (in Chinese). World Chin J Digestol 8:108–109
61. Gong SW, Ai ZL, Zhou YK (1995) Protective effects of prostacyclin on acute necrotizing pancreatitis and its venal damage in rats. Zhonghua Waike Zazhi 33:197–200 [PMID:7587668]
62. Sun CL, Li JS, Zhu WM, Wang JJ (1998) Influence of prostaglandin E1 on pancreatic blood flow of pancreatitis (in Chinese). Rat Chin Crit Care Med 10:154–157
63. Gu JC, Qin ZY, Wang Y (1999) Changes of prostaglandin I2 and thromboxane A2 in severe acute pancreatitis rats complicated with lung injury (in Chinese). World Chin J Digestol 7:275
64. Bhatia M, Brady M, Shokuhi S, Christmas S, Neoptolemos JP, Slavin J (2000) Inflammatory mediators in acute pancreatitis. J Pathol 190:117–125 [PMID:10657008]
65. Kingsnorth AN (1996) Platelet-activating factor. Scand J Gastroenterol 31[Suppl 219]:28–31 [PMID:8865468]
66. Wang H, Tan X, Chang H, Gonzalez-Grussi F, Daniel G (1997) Regulation of platelet-activating factor receptor gene expression in vivo by endotoxin, platelet-activating factor and endogenous tumour necrosis factor. Biochem J 322:603–608 [PMID: 9065783]
67. Roudebush WE, Wild MD, Maguire EH (2000) Expression of the platelet-activating factor receptor in human spermatozoa: differences in messenger ribonucleic acid content and protein distribution between normal and abnormal spermatozoa. Fertil Steril 73:967–971 [PMID:10785222]
68. Reinhardt JC, Cui XY, Roudebush WE (1999) Immunofluorescent evidence of the platelet-activating factor receptor on human spermatozoa. Fertil Steril 71:941–942 [PMID:10231061]
69. Sandoval D, Gukovskaya A, Reavey P, Gukovsky S, Sisk A, Braquet P, Pandol SJ, Poucell-Hatton S (1996) The role of neutrophils and platelet activating factor in mediating experimental pancreatitis. Gastroenterology 114:1081–1091 [PMID: 8831604]
70. Ruo Q, Zhang SD (2000) Significance of systemic inflammatory reaction in pathogenesis of acute pancreatitis (in Chinese). Chin J Hepatobiliary Surg 6:76–77
71. Ji ZH, Wang BM, Li SH, Tang Y, Ding TK, Ma YG (1997) The role of platelet activating factor in pathogenesis of acute pancreatitis in dogs. Zhonghua Waike Zazhi 35:108–110 [PMID: 10374489]
72. Mckay CJ, Curran F, Sharples C, Baxter JN, Imrie CW (1997) Prospective placebo-controlled randomized trial of lexipafant in predicted severe acute pancreatitis. Br Surg 84:1239–1243 [PMID:9313702]
73. Li YY, Gao ZF (2001) Acute pancreatitis and nuclear factor kappa B (in Chinese). World Chin J Digestol 9:420–421
74. Suk K, Yeou Kim S, Kim H (2001) Regulation of IL-8 production by IFN gamma and PGE2 in mouse microglial cells: involvement of NF-κB pathway in the regulatory processes. Immunol Lett 77:79–85 [PMID:11377701]
75. Izumi T, Saito Y, Kishimoto I, Harada M, Kuwahara K, Hamanaka I, Takahashi N, Kawakami R, Li Y, Takemura G, Fujiwara H, Garbers DL, Mochizuki S, Nakao K (2001) Blockade of the natriuretic peptide receptor guanylyl cyclase-A inhibits NF-kappaB activation and alleviates myocardial ischemia/reperfusion injury. J Clin Invest 108:203–213 [PMID:11457873]
76. Antonelli A, Bianchi M, Crinelli R, Gentilini L, Magnani M (2001) Modulation of ICAM-1 expression in ECV304 cells by macrophage-released cytokines. Blood Cell Mol Dis 27:978–991 [PMID:11831864]
77. Ginis I, Jaiswal R, Klimanis D, Liu J, Greenspon J, Hallenbeck JM (2002) TNF-alpha-induced tolerance to ischemic injury involves differential control of NF-kappaB transactivation: the role of NF-kappaB association with p300 adaptor. J Cereb Blood Flow Metab 22:142–152 [PMID:11823712]
78. Wright G, Singh IS, Hasday JD, Farrance IK, Hall G, Gross AS, Roger TB (2002) Endotoxin stress-response in cardiomyocytes: NF-kappaB activation and tumor necrosis factor-alpha expression. Am J Physiol Heart Circ Physiol 282:872–879 [PMID: 11834481]
79. Lakshminarayanan V, Lewallen M, Frangogiannis NG, Evans AJ, Wedin KE, Michael LH, Entman ML (2001) Reactive oxygen intermediates induce monocyte chemotactic protein-1 in vascular endothelium after brief ischemia. Am J Pathol 159:1301–1311 [PMID:11583958]
80. Moine P, McIntyre R, Schwartz MD, Kaneko D, Shenkar R, LeTulzo Y, Moore EE, Abraham E (2000) NF-kappaB regulatory mechanisms in alveolar macrophages from patients with acute respiratory distress syndrome. Shock 13:85–91 [PMID: 10670837]
81. Valen G, Yan ZQ, Hansson GK (2001) Nuclear factor kappa-B and the heart. J Am Coll Cardiol 38:307–314 [PMID:11499717]
82. Omoya T, Shimizu I, Zhou Y, Okamura Y, Inoue H, Lu G, Itonaga M, Honda H, Nomura M, Ito S (2001) Effects of idoxifene and estradiol on NF-kappaB activation in cultured rat hepatocytes undergoing oxidative stress. Liver 21:183–191 [PMID:11422781]
83. Shames BD, Barton HH, Raznikov LL, Cairns CB, Banerjee A, Harken AH, Meng X (2002) Ischemia alone is sufficient to induce TNF-alpha mRNA and peptide in the myocardium. Shock 17:114–119 [PMID:11837786]
84. Wang Z, Castresana MR, Detmer K, Newman WH (2002) An IkappaB-alpha mutant inhibits cytokine gene expression and

proliferation in human vascular smooth muscle cells. J Surg Res 102:198–206 [PMID:11796019]
85. Theuer J, Dechend R, Muller DN, Park JK, Fiebeler A, Barta P, Ganten D, Haller H, Dietz R, Luft FC (2002) Angiotensin II induced inflammation in the kidney and in the heart of double transgenic rats. BMC Cardiovasc Disord 2:3 [PMID: 11835691]
86. Satoh A, Shimosegawa T, Fujita M (1999) Inhibition of nuclear factor-kB activation improves the survival of rats with taurocholate pancreatitis. Gut 44:253–258 [PMID:9895386]
87. Roebuck KA, Finnegan A (1999) Regulation of intercellular adhesion molecule-1(CD54) gene expression. J Leukoc Biol 66:876–888 [PMID:10614768]
88. Windsor JA, Fearon KCH, Ross JA, Barclay GR, Smyth E, Poxton I (1993) Role of serum endotoxin and antiendotoxin core antibody levels in predicting the development of multiple organ failure in acute pancreatitis. Br J Surg 80:1042–1046 [PMID:8402063]
89. Dun WH, Yan HM, Li CF, Wu YJ, Zhang X (1998) Discussion on renal dysfunction mechanism during acute necrotizing pancreatitis (in Chinese). Shanxi Med J 27:22–23
90. Scott P, Bruce C, Schofield D, Shiel N, Braganza JM, McCloy RF (1993) Vitamin C status in patient with acute pancreatitis. Br J Surg 80:750–754 [PMID:8330166]
91. Luo J, Ye DC (1995) Changes in hepatic and renal ultrastructures of acute pancreatitis rat and their relations with oxygen free radical. Chin J Exp Surg 3:133–134
92. Werner J, Revera J, Castille CF, Lewandrowski K, Adrie C, Rattner DW, Warshaw AL (1997) Differing roles of nitric oxide in the pathogenesis of acute edematous versus necrotizing pancreatitis. Surgery 121:23–30 [PMID:9001547]
93. Molero X, Guarner F, Salas A, Mourelle M, Puig V, Malagelada JR (1995) Nitric oxide modulates pancreatic basal secretion and response to cerulein in the rat: effects in acute pancreatic. Gastroenterology 108:1855–1862 [PMID:7539387]
94. Tome LA, de Castro I, Campos SB, Seguro AC (1999) Beneficial and harmful effects of L-arginine on renal ischaemia. Nephrol Dial Transplant 14:1139–1145 [PMID:10344352]
95. Lieberthal W (1998) Biology of ischemic and toxic renal tubular cell injury: role of nitric oxide and the inflammatory response. Curr Opin Nephrol Hypertens 7:289–295 [PMID:9617560]
96. Plusczyk T, Bersal B, Westerman S, Menger M, Feifel G (1999) ET-1 induces pancreatitis like microvascular deterioration and acinar cell injury. J Surg Res 85:301–310 [PMID:10423333]
97. Cheng GZ, Zhang JX, Li L, Qu JG, Wang XQ (2002) Dynamic changes of renal injury and renal microcirculation in acute necrotizing pancreatitis rat (in Chinese). J Hepatobiliary Surg 4:310–312
98. Yan YG, Ai ZL, Liu ZS, Xu G (2000) Protective effect of angelica injection on acute hemorrhagic necrotizing pancreatitis complicated with renal injury (in Chinese). Chin J Gen Surg 9:228–230
99. Geestein RJ, Krakoff LR, Felton K (1987) Activation of the renin system in acute pancreatitis. Am J Med 82:401–404 [PMID:3548344]
100. Nishiwaki H, Ko I, Hiura A, Hass, Satake K, Sowa M (1993) Renal micro circulation in experimental acute pancreatitis of dogs. Ren Fail 15:27–31 [PMID:8441833]
101. Hietaranta A, Kemppainen E, Puolakkainen P, Sainio V, Haapiainen R, Peuravuori H, Kivilaakso E, Neevalainen T (1999) Extracellular phospholipase A2 in relation to systemic inflammatory response syndrom(SIRS) and systemic complications in severe acute pancreatitis. Pancreas 18:385–391 [PMID: 10231844]
102. Yin BB, Cai R, Zhang YL (2002) Renal dysfunction of severe acute pancreatitis (in Chinese). Chin J Prac Surg 22:622
103. Marshall JB (1993) Acute pancreatitis. A review with an emphasis on new developments. Arch Intern Med 153:1185–1198 [PMID:8494472]
104. Liang YF, Fu HF (2004) Function of hemodialysis in treating severe acute pancreatitis (SAP) complicated with acute renal failure (ARF) (in Chinese). Guangdong Med J 25:686–687
105. Miller MJ, Correa P (1998) Carcinogenesis, apoptosis and cell proliferation. Br Med Bull 54:151–162 [PMID:9604439]
106. Kaiser AM, Saluja AK, Sengupta A, Saluja M, Steer ML (1995) Relationship between severity, necrosis, and apoptosis in five models of experimental acute pancreatitis. Am J Physiol 269:1295–1304 [PMID:7491921]
107. Fu K, Sarras MP, Delisle RC, Andrews GK (1996) Regulation of mouse pancreatitis-associated protein-I gene expression during caerulein-induced acute pancreatitis. Digestion 57:333–340 [PMID:8886577]
108. Fink GW, Norman JG (1996) Intrapancreatic interleukin-1 beta gene expression by specific leukocyte populations during acute pancreatitis. J Surg Res 63:369–373 [PMID:8661228]
109. Norman JG, Fink GW, Franz MG (1995) Acute pancreatitis induces intra-pancreatic tumor necrosis factor gene expression. Arch Surg 130:966–970 [PMID:7661681]