GENERAL REWIEV

UDC: 616.37-002.1-06-08
https://doi.org/10.2298/VSP151129328B

Pathophysiology of the abdominal compartment syndrome in acute pancreatitis: Dilemmas and critical points

Patofiziologija abdominalnog kompartment sindroma u akutnom pankreatitisu: dileme i kritične tačke

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Key words:
pancreatitis, acute, necrotizing; compartment syndromes; pathology; physiology; intra-abdominal hypertension; systemic inflammatory response syndrome; multiple organ failure; therapeutics.

Ključne reči:
pankreatitis, akutni, nekrotizirajući; kompartment sindromi; patologija; fiziologija; hipertenzija, intraabdominalna; sindrom sistemske zapaljenske reakcije; insuficijencije više organa; lečenje.

Introduction

Abdominal compartment syndrome (ACS) has been frequently described in patients with abdominal trauma, inflammatory conditions in abdominal cavity or as a consequence of a major and urgent abdominal surgery [1]. The influence of intraabdominal pressure (IAP) on lung functioning and abdominal content was the subject of scientific research in the 19th century. At that time the hypothesis of a reciprocal relationship between intrathoracic pressure and IAP was entrenched, and it was concluded that the lowering of the diaphragm was accompanied with elevation of IAP [2]. The effects of elevated IAP was noticed in the first half and the middle of the 20th century by several investigators. Bradley and Bradley [3] concluded that raised IAP reduces renal plasma flow and glomerular filtration rate while Emerson [4] found that excessive IAP reduces heart preload significantly with cardiac failure. Baggot [5] described the clinical effects after abdominal wall suture under tension and, for example, he demonstrated a death of a child after surgery for congenital abdominal wall deffect. In contrast to etiological factors and pathophysiology of muscular compartment syndrome that were described in the middle of the 19th century, the physiological mechanisms of the ACS were only proposed at the end of 19th and beginning of the 20th century [6].

Nowadays, the ACS is well described entity which importance in various clinical conditions was recognized in the last two decades. It is defined as a state of serious organ dysfunction resulting from sustained increase in IAP [7]. There is growing evidence in the literature data that the development of ACS in patients with severe form of acute pancreatitis (AP) has strong influence on the course of disease [8–11]. The incidence of intraabdominal hypertension (IAH) in patients suffering from severe form of AP is approximately 70%, while ACS can be found in up to 27% of patients with this form of AP [9, 10, 12, 13]. When we add to this a mortality rate of 49% of patients with severe form of AP and ACS [11], it is clear that IAH and ACS have become an issue of concern in patients with AP. In addition, it has been recently mentioned that the number of patients with AP and this complication increased, but still there have no standard recommendations for interventional treatment of patients who develop ACS during severe form of AP [14]. The step-up approach for conservative treatment of ACS was proposed several years ago [15]. However, the appropriate interventional procedure, including surgical technique, and optimal time for reacting in the treatment of the AP patients suffering from this serious condition is still discussed.

In a number of scientific papers the pathophysiology of the ACS in AP has been described roughly, without specifying potential crucial mechanisms that lead to the damage or to deterioration of already damaged organs in patients with severe form of AP. The understanding of the development of ACS in the course of AP may help in its prevention and timely administration of the best possible treatment [16].

The purpose of this review is to give the insight on the pathophysiology of ACS complicating AP, with some possible critical points in the ACS evolution which may represent either markers for monitoring or therapeutic targets. Also,

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the pathophysiology insight into ACS should fortify the interest of physicians to make additional research in order to support further strategies for the treatment of patients with this lethal complication of AP.

Definition of ACS

According to the World Society of Abdominal Compartment Syndrome (WSACS) [7], IAH is defined as persistent increase of IAP > 12 mmHg, whereas ACS is the combination of IAP > 20 mmHg and the new-onset organ dysfunction.

Definition of severe form of AP

According the revision of the Atlanta classification in 2012 [17], severe form of AP is characterized by the persistent organ failure (OF) (> 48 h). Persistent OF may be single or multiple OF. Three organ systems should be assessed to define OF: respiratory, cardiovascular and renal. OF is defined as a score of 2 or more for one of these 3 organ systems using the modified Marshall scoring system.

A brief look at the pathophysiology of AP

The AP is not only local disease. It is a systemic disease which is characterized by an inflammatory process that is initiated by intraacinar activation of pancreatic enzymes with subsequent systemic effects. Activated proteolytic enzymes lead to the autodigestive injury of the pancreas which is modulated by cytokines and other inflammatory mediators. Intrapancreatic and extrapancreatic inflammation is almost always accompanied by the systemic inflammatory response syndrome (SIRS) [18].

Although there are several risk factors responsible for the development of AP (gallstones, alcohol, hypertriglyce-ridemia, etc.), the subsequent sequence of events takes place according to a very similar scenario, regardless of the initiating factors. The mechanism of initiating AP is still unclear, but it is generally accepted that it develops only in cases when the intracellular protective mechanisms utilized to prevent trypsinogen activation or reduce trypsin activity are overwhelmed. These mechanisms include synthesis of trypsin as inactive proenzyme trypsinogen, autolysis of trypsin, enzyme compartmentalization, synthesis of specific trypsin inhibitors such as serine protease inhibitor Kazal type 1 (SPINK1) as well as relatively low intracellular ionized calcium concentrations [19].

After the activation of trypsinogen into active trypsin, inflammation is followed by the production of cytokines, nitric oxide, reactive oxygen species and arachidonic acid metabolites from pancreatic acinar cells, endothelial cells, neutrophils, macrophages and lymphocytes. Immune cells attracted by initially released cytokines release more cytokines, free radicals and nitric oxide [20]. The mediators involved in the inflammatory response during AP are proinflammatory and anti-inflammatory and their balance determines the course of the disease [21]. Perhaps this could be an issue where the answer can be found on why some patients develop edematous pancreatitis and others much more severe form of the disease with serious and lethal complications. Another interesting think in the early phase of AP is balance between apoptosis and necrosis. This balance may influence the severity of AP and decide the fate of acinar cells. Both caspase activation and cytosolic calcium signaling have influence on apoptotic and necrotic cell death pathways [22, 23].

Apart from the aforementioned, the alteration of the pancreatic microcirculation plays one of the central roles in the pathogenesis of AP. Derangement of pancreatic microcirculation in the early phase of disease could transform acute self-limited and edematous pancreatitis to severe, necrotizing pancreatitis [24–27]. In response to pancreatic acinar cell injury, multiple proinflammatory cytokines and vasoactive mediators are recruited to the pancreatic microcirculation and delivered to the acinar cells. One of the consequences of this is increasing of the vascular permeability of the capillaries. This causes significant extravasation of fluid leading to the acute edematous changes around the acinus. Also, decreased endothelial tone allows the extravasation of both inflammatory cells and inflammatory mediators [28–30]. Another vascular changes were described in AP which may aggravate the disease course. These changes include the formation of microthrombi, capillary vasoconstriction and vasospasm of intrapancreatic and extrapancreatic arteries [31–33].

Secreted inflammatory mediators and several activated inflammatory cascades have influence on different organs, not only on the pancreas (Figure 1). In the severe form of AP, the local injury rapidly leads to a generalized hyperinflammation, SIRS, what is associated with potential failure of distant organs (Figure 2).

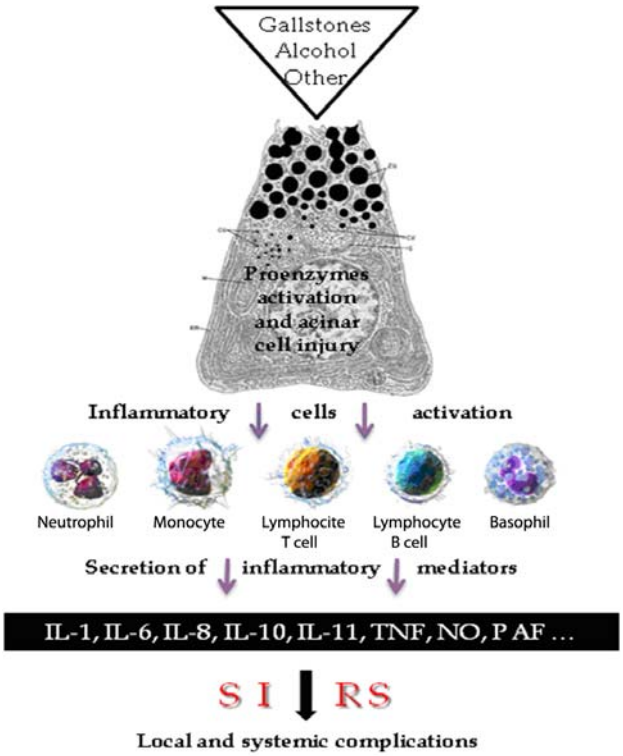

Fig. 1 – The schematic overview of the pathophysiology of acute pancreatitis.
IL – interleukin; TNF – tumor necrosis factor; NO – nitric oxide; PAF – platelet-activating factor;
SIRS – systemic inflammatory response syndrome.

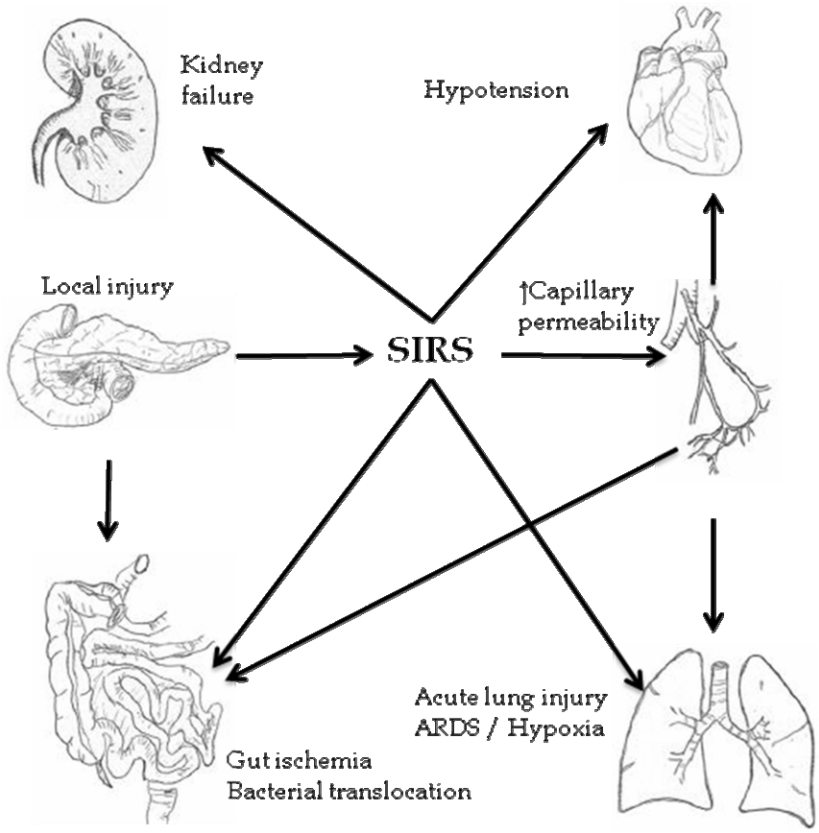

Fig. 2 – The generalized hyperinflammation in acute pancreatitis and its association with organs dysfunction. SIRS – systemic inflammatory response syndrome; ARDS – acute respiratory distress syndrome.

Pathophysiology of ACS during AP

Initial events leading to increasing of IAP

Hypovolemia is common in AP, especially in the severe form of the disease and is a result of a massive fluid loss to the retroperitoneal space and interstitial space overall. A complex series of pathophysiological events that lead to ACS development in patients with AP is shown in the Figure 3. However, an early substantial fluid loss in patients with severe form of the AP occurs in retroperitoneal space and interstitial space of gut. In addition to above mentioned factors resulting in increased capillary permeability, the other factors may contribute to the ischemic insult of the gut during AP. Mucosal ischemia of gut may be related to the endotelin-1 which is a strong vasoconstrictor produced from endothelium and macrophages [34, 35]. Also, intercellular adhesion molecule-1 (ICAM-1) mediates the adhesion of cytokine stimulated leukocytes to the capillary endothelium and their transendothelial migration. A significant increase in the systemic release of ICAM-1 was found in patients with necrotizing AP within 48 hrs of the onset of symptoms [36]. This event is associated with significant increase of leukocytes infiltration with histological changes and decreasing in intestinal and pancreatic perfusion [37, 38]. In the early stages of severe form of AP,

the profound fluid losses in a "third space" associated with inflammation of the pancreas may induce splanchnic vasoconstriction. Hypovolemia also leads to decrease in splanchnic perfusion with consequent cellular hypoxia especially in intestinal mucosa [39, 40]. A retroperitoneal and pancreatic inflammation, increased vascular permeability, interstitial edema, decreased intestinal perfusion and cellular and tissue hypoxia lead to development of a vicious circle with the reactivation of immune cells and secretion of *de novo* synthesized inflammatory mediators [39–41]. On the other hand, inflammatory process and increased vascular permeability allows protein-rich intravascular fluid to pass not only in the interstitial space but in the peritoneal cavity also. It was reported that patients with AP often have liters of intravascular leak to the peritoneum [42, 43].

The abdominal cavity is a single compartment and any change in volume within this cavity can elevate IAP further leading to IAH [44]. Although not fully compliant, the abdominal cavity is more amenable than most confined cavities, but can become increasingly rigid as it distends. It must be noted here that majority of the AP patients have severe abdominal pain which may result in abdominal rigidity causing a decrease in abdominal compliance [45]. All of these events including the paralytic ileus caused by severe inflammation are responsible for the initial bowel edema and subsequent initial elevation of IAP [44, 46, 47].

Reperfusion injury and IAP

Not the all patients with AP develop IAH. Also, the values of IAP are different in various patients on hospital ad-

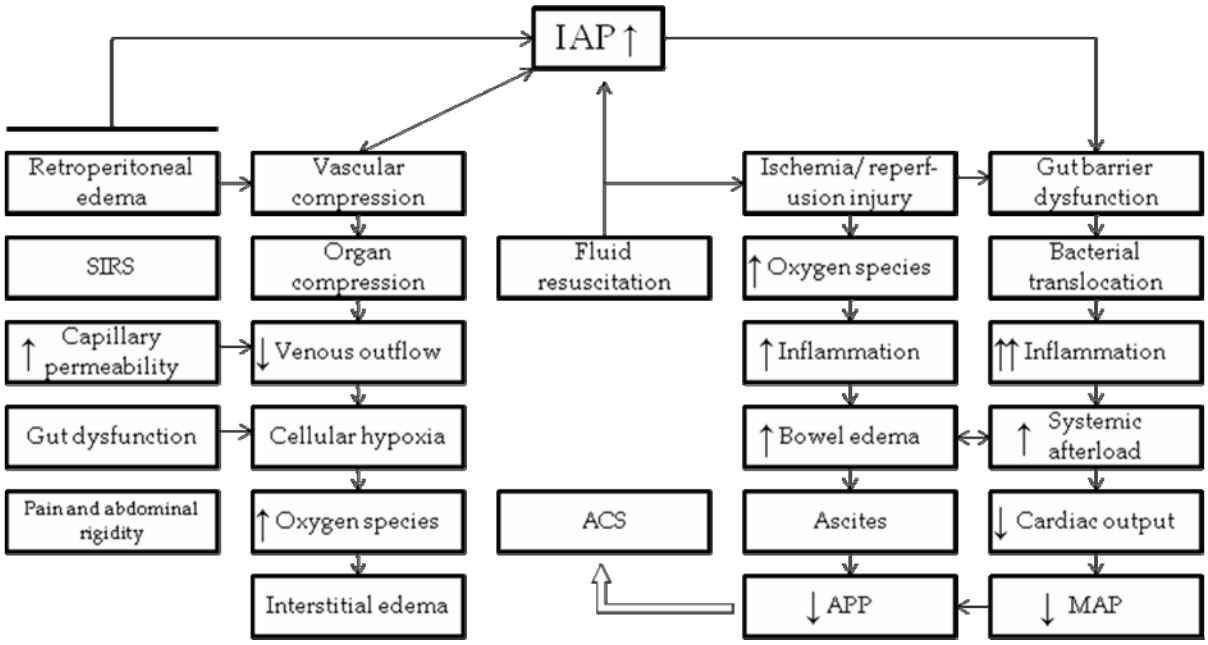

Fig. 3 – The pathophysiological mechanisms involved in the development of abdominal compartment syndrome (ACS) in patients with acute pancreatitis.
SIRS – systemic inflammatory response syndrome; IAP – intraabdominal pressure; APP – abdominal perfusion pressure; MAP – mean arterial pressure.

mission. There are only several papers in literature that reported the value of IAP in patients with AP on hospital admission. In these studies the value of IAP at 24 hrs of hospital admission in patients with AP varies from 12–28 mmHg [11]. This is an important issue because the value of IAP determines the severity and further course of AP [13]. In fact, elevated IAP causes intestinal hypoperfusion even at levels from 8 to 12 mmHg [40, 48], while IAH could contribute to pancreas hypoperfusion [13, 49, 50]. On hospital admission a number of the patients, especially those with severe form of AP, are in hypovolemia which requires aggressive rehydration [42, 51, 52].

Initial treatment of patients with AP is aggressive fluid replacement [51–53]. It seems that early aggressive fluid therapy may be a double-edged sword regarding further patophysiological events in AP. However, there is no evidence whether ACS development is a reflection of severe disease or the result of overzealous fluid resuscitation [52–54].

Without reference to the animal models of AP, the possibility of ischemia-reperfusion injury following volume resuscitation in patients with AP is certainly high. Intestinal reperfusion injury has been shown to have deleterious effects on the gut function and distant organs [55, 56]. Studies on both animals and humans showed that the intestinal ischemia and reperfusion result in a rapid accumulation of the circulating leukocytes and gut-associated macrophages with the subsequent cytokines releasing [57–61]. In addition, an oxygen free-radical injury is important pathophysiological event in AP. This is provided by the evidence showing improved outcomes in animal models using antioxidant therapy [62]. The pancreas is an organ highly susceptible to the ischemic damage and ischemia represents as an important factor in AP [63]. It is known that the ischemic/reperfusion injury may cause AP in the various clinical settings [64]. After the reduction of blood flow and free radicals generation in the early stage of AP, an additional damage of the pancreatic tissue probably occurs after initial fluid replacement. On the other hand, AP can induce mesenteric ischemia by mesenteric vasoconstriction, shock state and/or dehydration [65–68]. Therefore, not only a pancreas is a target for reperfusion injury, but also the all abdominal viscera including gut [69, 70]. This sequence of events leads to the reactivation of the immune response, and almost certainly to the edema of the all abdominal viscera with increasing in the volume of peritoneal free fluid and consequent further elevation of IAP.

Abdominal perfusion pressure and additional ischemia of the abdominal organs

Abdominal perfusion pressure (APP) is determined by the mean arterial pressure (MAP) and IAP that resists blood delivery to the abdominal organs. The APP is defined by the formula: APP = MAP–IAP. APP represents a very important parameter with a better and more accurate prediction of the visceral perfusion than IAP. Also, it was reported that it could be used as a potential endpoint for resuscitation [71]. It is recommended that the APP should be maintained above 60 mmHg and this was shown to correlate with improved outcomes. However, if the APP decreases under 50 mmHg the morbidity and mortality rate is increased [71–73]. In states of paralytic ileus, abdominal pain and abdominal wall rigidity, free fluid in the peritoneal cavity and retroperitoneal inflammation, the abdominal compliance would be decreased. As the abdominal compliance threshold is reached, the IAP rises

and the APP decreases [74, 75]. It has not yet been discovered what critical value of APP leads to a vicious circle of irreversible IAH, to the further elevation of IAP and subsequent organ dysfunction. In fact, it seems that the critical point of this sequence of events is reduced venous outflow in abdominal organs to the extent that affects arterial perfusion [76]. Venous stasis and the development of interstitial edema reduce arterial blood perfusion in the abdominal organs, especially gut, with ischemia and additional inflammation [77, 78]. This may be the beginning of the second insult for the induction of severe organ dysfunction in two-hit model of the multiple organ dysfunction syndrome (MODS) [9, 79]. If untreated, this leads to organ ischemia and ultimately to ACS [9, 13, 74, 75, 79].

IAH and organ dysfunction

When the APP is decreased under the critical level, a cellular hypoxia exacerbates due to low blood perfusion in the abdominal organs. The consequence of this hypoxic state is decline of the adenosine triphosphate (ATP) production. Due to the cellular energy deficit the potassium slowly leaks into extracellular space while sodium and calcium enter the cells along with water. The cells are swelling, the membranes lose their integrity, spilling its intracellular content into extracellular space and causing more inflammation throughout the body, not only in gut [39, 50, 69]. The SIRS triggered initially by AP is usually driven further with efforts to reperfusion aimed to restoring amounts of volume with intravenous fluid replacement. However, this action often promotes further tissue edema with reperfusion injury followed by another cycle of acute inflammatory response [9, 39, 53, 80], as discussed above. As the IAP continues to rise, the probability for the new onset organ dysfunction is higher. It is even higher in severe inflammation such as in patients with the severe form of AP [81].

It is still unknown whether the new onset organ dysfunction in patients with AP and IAH occurs as a result of critical level of IAP or as a consequence of the second-hit resulting from another cycle of inflammatory response [81]. However, it is certain that the gastrointestinal system and liver functions are the most vulnerable to the high IAP. Mainly two functions are altered: the mucosal barrier function (influencing both intermucosal nutrient flow and bacterial translocation) and the gastrointestinal motility. The reduction of splanchnic blood perfusion occurs at the level of IAP of 10 mmHg, with the exception of the adrenal glands [82, 83]. The metabolic changes in the gut, such as acidosis and decreased intestinal oxygenation, are evident at the IAP level of 15 mmHg [84]. It was shown that IAP from 20–25 mmHg in the duration of 60 minutes leads to the bacterial translocation from gut [85]. In our recent study we found a highly significant correlation between IAP and procalcitonin in patients with AP suggesting bacterial translocation [13]. The influence of IAH on the liver function and microcirculatory disturbances in liver parenchyma is apparent at the IAP of 20 mmHg and more [2]. The impact of elevated IAP on the gut is essential due to circumstantial evidences of relationship between bacterial translocation and MODS [50, 69, 86]. The raise of IAP leads to the diaphragm elevation with subsequent reduction of the static and dynamic respiratory compliance [87]. Total lung capacity, residual volume and functional residual capacity are reduced and leading to the ventilation-perfusion imbalance and hypoventilation. These changes are present at the IAP above 15 mmHg [72, 88].

Due to compression of inferior vena cava and portal vein under the elevated IAP, the cardiovascular system is affected throughout reduced venous return to the heart. Nonetheless, the reduction of cardiac output is exacerbated with frequent hypovolemia such as in the patients with AP. These effects occur at levels of IAP as low as 10 mmHg, while hypovolemic patients manifest it at even lower IAP [89].

IAH-induced renal dysfunction manifests as oliguria and anuria at the level of IAP from 15–30 mmHg in the presence of normovolemia and normal initial renal function [90, 91]. It seems that renal dysfunction in AP occurs in much lower IAP due to severe inflammation in such patients [92].

Elevated IAP reduces abdominal wall blood flow by a compression effect leading to the local ischemia and edema. This phenomenon is probably true for all muscles constituting the abdominal wall. Neurogenic mechanism of pain and abdominal rigidity in patients suffering from AP certainly have an impact on the abdominal wall functions. In particular, the blood flow throughout sheath of abdominal rectus muscles decreases to 58% of baseline at an IAP of only 10 mmHg, further worsening at 40 mmHg [93].

Several studies showed increased intracranial pressure as a consequence of elevated IAP. As a consequence of increased intracranial pressure, cerebral perfusion pressure is reduced. This could lead to serious neurological disorders [94].

Based on the all aforementioned, it is clear that AP is characterized by a variety of pathophysiological mechanisms which are interacting between each other, one event can cause another and all of them are involved in the development of IAH. Inflammatory mediators induce end-organ endothelial cell activation with subsequent increased capillary permeability; leaking microvessels cause a loss of intravascular fluid which lead to hypotension along with vasodilatation leading to the development of the shock states; accumulation of inflammatory cells in the tissues, interstitial edema, reperfusion injury along with microvascular coagulation disorders further impair oxygen supply of tissues. The final result of all these events is MODS which develops early during the course of AP [95]. It is still a pathophysiological dilemma which of the above mentioned events is the most responsible for the development of MODS [16, 47]. However, it seems that the increased capillary permeability and the microcirculatory disturbances in the gut are the initial and crucial events leading to a vicious circle of the IAP elevation and further tissues injury in the patients with AP.

Although it is unclear what is a critical value of IAP that leads to the organ dysfunction in the AP patients, it is obvious that if the IAP is higher, the number of organ systems in dysfunction will be higher also [11, 47, 92]. When the IAP reaches a level of 20 mmHg, the sustained derangement of normal physiological function ensues. Whether the ACS

in the AP patients occurs as a result of multiorgan failure or is it occurring with other organ dysfunction, it needs to be proven in the future [13, 14, 81]. Although the unpredictable nature of its course makes it difficult to establish the causal link between AP and ACS, the understanding of the complexity of pathophysiological mechanisms involved in ACS development may help in designing of the experimental and randomized clinical studies and may help in its prevention and timely administration of the best possible treatment.

Conclusion

The complex cascades of pathophysiological events in the patients suffering from AP lead to the initial elevation of IAP. The ACS is a result of a vicious circle of the severe inflammation and impaired perfusion of abdominal organs, especially gut. The understanding of the development of ACS in the course of AP may help in its prevention and timely administration of the best possible treatment.

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Received on November 29, 2015.
Revised on August 16, 2016.
Accepted on August 18, 2016.
Online First November, 2016.