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Experimental Models on Abdominal Compartment Syndrome

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Abstract

Aims: Intra-Abdominal Hypertension (IAH) and Abdominal Compartment Syndrome (ACS) are life threatening conditions in critically ill patients. During the last decades a lot of experimental animal models had been evolved to explain the pathomechanism, the triggering conditions, the diagnostic methods and the ideal treatment strategy of IAH/ACS. The aim of this review is to compare animal models which have relevance in clinical investigations and to give an interpretation for the optimal model of IAH/ACS investigations.

Methods: Review of literature

Results: Small animal models (mouse, rat, rabbit) are cost-effective, easily applicable, with less infrastructural needs. They can be successfully applied for pathophysiological, biochemical, histological and immunohistochemical investigations. Large animal models (dog, sheep, pig) are expensive and require quite a lot of infrastructure, however they can represent renal, cardiovascular and gastrointestinal functions. They are ideal to investigate anatomical changes, surgical and intensive care techniques.

Conclusions: Pig has very close anatomy and physiology to human. This similarity gives an excellent opportunity for modelling different surgical and emergency conditions and also allows to measure cardiovascular, respiratory and urinary parameters.

Introduction

The definitions of the Intra-Abdominal Hypertension (IAH) and Abdominal Compartment Syndrome (ACS) were declared by the World Society of Abdominal Compartment Syndrome (current name: World Society of Abdominal Compartment). IAH refers to elevated Intra-Abdominal Pressure (IAP) over 12 mmHg. ACS occurs when the IAP rises to 20 mmHg with Abdominal Perfusion Pressure (APP) below 60 mmHg with one or more new organ dysfunction. Despite of high level intensive care the ACS remains a life-threatening condition, when any delay in diagnosis and/or treatment leads to multi-organ failure and death [1-5].

Although during the last decades a lot of publications/investigations were done on IAH/ACS, the real pathomechanism, the exact triggering conditions, the ideal diagnostic and treatment options require further investigations in the future [6-67].

There are many reports on different animal models of experimental ACS. The most important fields of investigation are the pathophysiological effects of IAH, the diagnostic tools and the treatment options [6-67]. The most suitable model for a certain experimental field has not been clarified yet.

The aim of this paper is to compare animal models which have relevance in clinical investigations and to give an interpretation of the optimal model for IAH/ACS investigations.

Method

PubMed® database was used for search of publications related to small and large animal models of IAH/ACS. In agree with Schachtrupp's method [1], articles published before 2007 were excluded, except those three papers which were important to underly a finding or statement. Current literature of IAH/ACS

definitions, treatment and open abdomen therapy also has been reviewed.

Discussion

Criteria of ACS in animal models

There are several reports about animals used for IAH/ACS model to answer questions related to pathomechanism, pathophysiology, diagnostic and treatment options [6-69]. The available articles (except of reviews) are showed in Table 1. The definition of ACS in animal model is an artificially elevated IAP resulting in circulatory, respiratory and renal failure, which requires cardiac output reduction and mechanical ventilation. The ideal model is cost-effective, simple and easily reproducible [1].

Authors (ref.nr.)	Species	Applied IAP (mmHg)	Duration of IAP	Induction method of IAH	Aims of the study
Chang, et al. [8]	mouse	5,10,20 cmH_2O	24 h	saline solution intraperitoneally	mechanism of IAH in hepatorenal syndrome
Zhang, et al. [11]	mouse	5,10,20 cmH_2O	24 h	albumin intraperitoneally	mechanism of IAH in hepatopulmonary syndrome
Jahromi, et al. [24]	mouse	20	4 h	mineral oil intraperitoneally	effect of IAH alone and combined with head trauma on the permeability of the blood-brain barrier
Youssef, et al. [23]	mouse	20	4 h	mineral oil intraperitoneally	effect of IAH on the permeability of blood-brain barrier
Q.He, et al. [41]	mouse	15,20,30,40 cmH_2O	8 h	peritoneal dialysis solution	survival time, liver function in IAH and changes after oxygen therapy
Runck, et al. [15]	rat	7,9,11,13	30 min	helium pneumoperitoneum	effect of IAH on respiratory system compliance at different PEEP levels
Chang, et al. [53]	rat	nd	nd	haemorrhage and fluid (RL) resuscitation	model for secondary IAH
Tihan, et al. [12]	rat	20	2 h	CO_2 pneumoperitoneum	if glutamine improves reperfusion-induced oxidative injury of IAH
Bishara, et al. [37]	rat	7,10,14	45 min	CO_2 pneumoperitoneum	if phosphodiesterase-5 inhibition protects against renal effects of IAH+ congestive heart failure
Sukhotnik, et al. [31]	rat	6	2 h	air pneumoperitoneum	effect of IAH and hyperoxia on superior mesenteric artery blood flow, enterocyte proliferation and apoptosis
Meier, et al. [28]	rat	40	nd	gelatine solution intraperitoneally	whether compartment pressure of the rectus sheath reflects IAP
Gong, et al. [54]	rat	20	4 h	nitrogen pneumoperitoneum	whether IAP of 20 mmHg is comparable with ACS in humans

Meier, et al. [29]	rat	20	3 h	gelatine polysuccinate intraperitoneally	if monitoring the rectus abdominis muscle by microdyalisis means early detection of organ dysfunction in ACS
Düzgün, et al. [7]	rat	15,20,25	1 h	polyethylene glycol intraperitoneally	relationship between intestinal ischemia and serum D-lactate levels in IAH
Leng, et al. [57]	rat	4,8,12,16,20	90 min	nitrogen pneumoperitoneum	effect of slightly elevated IAP on intestinal mucosa
Lima, et al. [3]	rat	12	3 h	cotton surgical dressing	model for ACS
Meier, et al. [10]	rat	20	3 h	gelatine polysuccinate intraperitoneally	IAH and decompression induced reperfusion injury
Akkapulu, et al. [55]	rat	15	1,4 h	air pneumoperitoneum	morphological/functional alteration of the adrenal glands in IAH
Chen, et al. [42]	rat	20.25	24 h	air pneumoperitoneum	effects of open and conservative closure techniques on liver function in IAH+sepsis
Liu, et al. [43]	rat	20	4 h	air pneumoperitoneum	if melanocortin-4 receptor agonist reduces intestinal injury in IAH
Chadi, et al. [45]	rat	20	2 h	CO_2 pneumoperitoneum	mechanisms of tissue and microvascular injury in ACS
Cagido, et al. [51]	rat	10	2x15 min	air pneumoperitoneum	effect of alternating ventilation in IAH
Mahjoub, et al. [58]	rabbit	20	1 h	glycine solution intraperitoneally	effect of IAH on left ventricular relaxation
Ünlüer, et al. [9]	rabbit	25	1 h	CO_2 pneumoperitoneum	role of cobalt- albumin binding assay for the early diagnosis of ACS
Yagci, et al. [17]	rabbit	15,20,25	12 h	intraabdominal balloon	bacterial translocation at various levels of IAH
Yoshino, et al. [1]	rabbit	0,8-45,1	nd	instillation of RL intraperitoneally	relationship between rabbit and human IAP
Balci, et al. [36]	dog	45 cmH2O	4 h	saline solution intraabdominally	effect of IAH on gastric emptying time

Avraamidou, et al. [32]	pig	25-30	3 h	helium pneumoperitoneum	effect of ischaemic preconditioning on hemodynamic, biochemical and inflammatory alterations caused by IAH
Henzler, et al. [30]	pig	30	2x9 h	CO_2 pneumoperitoneum	effect of preserved spontaneous breathing during mechanical ventilation on hemodynamics, gas exchange, respiratory function and lung injury in IAH
Kotzampassi, et al. [27]	pig	12	30+60 min	helium pneumoperitoneum	if combination of PEEP ventilation and IAH alter splanchnic hemodynamics greater than alone
Cortes-Puentes, et al. [26]	pig	5-25	nd	air pneumoperitoneum	influence of IAH and PEEP on airway plateau pressure and bladder pressure
da Silva Almeida, et al. [22]	pig	20	4x30 min	air pneumoperitoneum	cardiopulmonary effects of PEEP equalization to IAH and acute lung injury
Mohan, et al. [33]	pig	20	4 h	CO_2 pneumoperitoneum	effects of IAP on physiologic changes of abdominal wall reconstruction and component separation
Jaques, et al. [35]	pig	30	2x30 min	abdominal banding	evaluate dynamic indices of fluid responsiveness
Gruenewald, et al. [34]	pig	20	nd	CO_2 pneumoperitoneum	compare three continuous cardiac output monitoring methods and a bolus thermodilution CO technique in IAH
Regli, et al. [39]	pig	18.26	nd	air-filled intraabdominal balloon	impact of IAP and PEEP on femoral venous pressure and femoral venous oxygen saturation
Regli, et al. [59]	pig	18.26	nd	air-filled intraabdominal balloon	effect of PEEP on functional residual capacity and oxygen delivery in IAH
Moller, et al. [18]	pig	20.25	12 h	CO_2 pneumoperitoneum and saline-filled intraabdominal bag	whether two methods used to create IAH has different impacts on organ dysfunction
Kubiak, et al. [13]	pig	30	nd	CO_2 pneumoperitoneum	if IAH and atelectasis would be reflected by transpulmonary pressure but independent of airway plateau pressure
Vivier, et al. [4]	pig	30	nd	abdominal banding	effects of gradual increase in IAP on central circulation
Shah, et al. [52]	pig	20	nd	portal vein occlusion and haemorrhage	develop a large animal model of ACS incorporating hemorrhagic shock/resuscitation
Argyra, et al. [14]	pig	20.35	45-60+45-60 min	helium pneumoperitoneum	if natriuretic peptides are produced in IAH

Formenti, et al. [21]	pig	15	nd	insufflation	the ability of PEEP to affect the reduction of resting lung volume in IAH, unilateral pleural effusion and their combination
Regli, et al. [20]	pig	18.22	30 min	intraabdominal balloon	respiratory and cardiac effects of PEEP in IAH+ sick lungs
Benninger, et al. [6]	pig	30	nd	CO_2 pneumoperitoneum	if compartment pressure of the rectus sheath reflects IAP
Nielsen, et al. [49]	pig	25	4 h	CO_2 pneumoperitoneum	if D-lactate could be a useful biochemical marker of intestinal ischaemia
Du, et al. [46]	pig	>12	2 h	haemorrhage and fluid (RL) resuscitation	if speckle tracking imaging is useful in assessment of myocardial contractibility in IAH
Correa-Martin, et al. [40]	pig	30.20	5 h	CO_2 pneumoperitoneum	if gastric air tonometry is an early predictor of inadequate splanchnic perfusion and its relation to abdominal perfusion pressure
Chopra, et al. [60]	pig	30	nd	CO_2 pneumoperitoneum	evaluate IAP measurement techniques
Diaz, et al. [61]	pig	22	nd	fluid instillation (Voluven 6% ®)	effect of tidal volume on pulse pressure and stroke volume variation and prediction of fluid responsiveness in IAH
Leventi, et al. [50]	pig	30.25	3h, 15 min	helium pneumoperitoneum	if ischemic preconditioning can modify oxidative stress induced by IAH
Otto, et al. [44]	pig	30	12 h	CO_2 pneumoperitoneum	effect of IAH on pancreatic histology and ultrastructure
Olofsson, et al. [48]	pig	50	nd	CO_2 pneumoperitoneum	gastric, intestinal and renal cortex microcirculation and central hemodynamics and respiration in stepwise increase of IAP
Lu Ke, et al. [25]	pig	25	6,9,12 h	nitrogen pneumoperitoneum	perfect time of decompression
Skoog, et al. [16]	pig	30	4,6 h	CO_2 pneumoperitoneum	metabolic response and circulatory changes after decompression in IAH
Lu Ke, et al. [56]	pig	30.20	12 h	nitrogen pneumoperitoneum	effect of SAP+ IAH on hemodynamics, systemic oxygenation, organ damage
Elvevoll, et al. [62]	pig	30.15	2+2 h	helium pneumoperitoneum	effect of IAH on microvascular fluid exchange and microcirculation

Brenninger, et al. [5]	pig	30	nd	fluid-filled intraabdominal bag	comparison of volume reserve capacity and development of IAH after forced primary abdominal closure and different TAC techniques
Hlebowicz, et al. [38]	pig	nd	nd	nd	microvascular blood flow in the intestinal wall and the omentum before and during NPWT
Kaussen, et al. [19]	pig	30.15	24 h	CO_2 pneumoperitoneum	bacterial translocation to mesenteric lymph nodes in IAH
Correa-Martin, et al. [47]	pig	20.30	3 h	CO_2 pneumoperitoneum	indirect measurement techniques of IAP
Nemeth, et al. [69]	pig	30	3 h	fluid-filled intraabdominal bag	microcirculatory and micro-rheological alterations in ACS, using various temporary abdominal closure methods, including NPWT
Csiszkó, et al. [69]	pig	30	3h	fluid-filled intraabdominal bag	microcirculation of organs, haemorrheological changes, pressure distribution in the abdominal cavity during NPWT
Ferrara, et al. [63]	sheep	20	2 h	saline solution intraabdominally	effect of IAH on intestinal and renal blood flow, urine output

The most adequate animal models for the different fields of investigations still remained unclear, as well to determine the adequate IAP level, the period of IAH and the method of IAH creation to represent the human conditions better.

The most often used animals are rats and pigs. The application of animal research to human scenarios is challenging due to the differences in abdominal wall elasticity. Rabbits have the lowest, followed by dogs, and humans has the highest elasticity [68]. Pig chest and abdominal wall contours are different from human [24].

Methods for developing IAH/ACS

The significant elevation of IAP (>12 mmHg) usually is secondary to intra-abdominal bleeding, sudden development of fluid accumulation (ascites, peritonitis), oedema of the organs and/or retroperitoneal space caused by extra-abdominal condition (burn, cardiac arrest, sepsis). This is often observed in severe acute pancreatitis, bowel distension and/or obstruction. Iatrogenic IAH could be secondary to excessive fluid resuscitation [2,4,5].

IAH can be induced by inflating the abdomen with gas (air, Nitrogen, Carbon-Dioxide (CO_2), helium or argon) or injecting fluid (saline, polyethylene glycol solution, glycine solution, mineral oil, dextran, hydroxyethyl starch, gelatine polysuccinate, peritoneal dialysis solution) into the peritoneal cavity [1,10,11,15, 21,27,30,32,34,44,57,61].

Both gases and fluids can be applied directly or using an intra-abdominal plastic bag [67]. Although in case of direct intraperitoneal application the distribution of pressure is more equal than in case of balloon placement, the absorption of the material has to be taken in consideration, especially when air carbon-dioxide or crystalloids were used [1]. CO_2 may cause hypercapnia and acidosis [21]. It has been proved that CO_2 is cost effective, easily available and controllable, sustainable for a long period. Its absorption does not result organ insufficiency and the absorbed amount is minimal in case of IAP higher than 15 mmHg [22]. Helium and argon are inert but expensive, and argon can affect hemodynamic parameters [1]. Nitrogen is a colourless, odourless, tasteless, inert material [28].

Fluid instillation represents best the so-called 'Pathologic' model described by Schachtrupp, et al. where bowel oedema is the etiologic factor of IAH, induced by haemorrhage or systemic inflammation followed by fluid resuscitation [1]. Kaussen, et al. succeeded to reproduce IAH- induced pathologic changes, bacterial translocation in a 'Non-pathologic' model, where ACS was not triggered by intra-abdominal pathologic condition [22]. Glycine solution is non-absorbable in contrast to crystalloids [1]. Dextran, hydroxyethyl starch may contribute with immune response. Gelatine polysuccinate seems not to cause fluid redistribution [31]. Mineral oil for this indication has been described as a non-toxic, inert, incompressible, non-absorbable material [26].

IAH induction by gas or fluids may be completed or stabilized by an abdominal restraint device, a mechanical cast around the abdomen [7,38,56]. Lima, et al. induced IAH with Zobec® (cotton surgical dressing) insertion and found IAP constant during experiment [6].

IAH can be supplemented by other interventions: animals can be haemorrhaged and resuscitated or kept hypovolemic. Bowel ligation can be performed to represent obstruction, or punctured to induce sepsis [1]. Acute pancreatitis, acute lung injury can also be induced [23,25,59]. Bishara, et al. created a congestive heart failure rat model with creation of fistula between the abdominal aorta and inferior caval vein, or with occlusion of the left anterior descending artery [40]. Chang, et al. worked up portal hypertension in rat model by partial ligation of the portal vein [56]. Based on the connection between IAH and blood-brain barrier, disruption can be examined with head trauma imitation in mice [27]. Keeping the IAP at 20 mmHg during four hours can result blood-brain barrier disruption in mice, which is reversible performing decompression [26]. Mohan, et al. emphasized that primary closure of the abdomen in case of large abdominal wall defects can lead to IAH in pigs, and component separation was advised as a new hernia repair technique [36].

Which pressure is able to generate ACS?

IAH caused organ dysfunction can be examined on both small and large animal models [6,10,11,14,20-23,25-27,30,32-34,39,43,47,48,51,52,56,58-60,62,64-66]. The pressure applied is usually between 12 and 30 mmHg. The duration of the high pressure period is between 30 minutes and 24 hours regardless of animal type [6,10-15,17-23,25-28,30-33,35-39,43-50,52-54,58-61,65-67]. Very similar cardiorespiratory, urinary and histological changes were found to human data in Gong's rat model applying 20 mmHg IAP for 4 hours. The IAH was induced by nitrogen neumoperitoneum followed by four hours' reperfusion period [57]. In large animal models the most commonly used pressure was 30 mmHg [7-9,16,17,19,22,33,35,38,47,50,53,63,65]. This pressure level is required in pigs to indicate changes in gastric or intestinal mucosal blood flow [50]. 15 mmHg IAP during four hours was able to induce functional but no morphological changes of the adrenal glands in rat model [58]. Reperfusion caused injury of the liver, lung, intestines and myocardium can be observed in rats after third hour of IAP=20 mmHg [13].

Mild elevation of IAP (8 mmHg) can result bowel mucosal ischaemia in rat model, highlighting that IAH requires very urgent treatment [60]. Renal and respiratory dysfunctions with early inflammatory changes and deficient perfusion of the liver was demonstrated in Chadi's rat model using fluorescence microscopy. The neutrophil activity was represented by myeloperoxidase. [48]. Laparoscopy and post-desufflation reperfusion caused bowel isquemia was observed during superior mesenteric artery blood flow measurements in rat model applying 6 mmHg IAP for two hours [34].

Gradual increase of IAP helps to observe the effects of ischemic preconditioning in pig model [35,53], especially when it leads to redistribution of blood volume to the thorax [51]. It is also possible to examine isquemia reperfusion caused changes in different periods of decompression [15,19,53,55].

Diagnostic procedures in animal models

To avoid delay in diagnosis making and to prevent multi organ failure, continuous monitoring of IAP is highly recommended. The optimal pressure measurement method is still a debating question, however there are many publications underlying the advantages of the widely used urinary catheter technique [2,4,9,28,31,43,50,63]. The bladder pressure measurement in human is a relatively small strain for the patient. This technique is safe, cost-effective, easily applicable and widely available, however there are few contraindications like injury or obstruction of the urinary bladder [1,20,43,63].

An indirect method of pressure measurement was investigated by Meier in rectal sheet. It seems to be a good alternative, applied for diagnosis and monitoring, although it has to be considered that the extensibility of the rat abdominal wall is different from that of humans [28]. Pig rectal sheet compartment pressure was studied by Benninger's team during IAH and found that it reflects IAP well [9].

In a proper position of the animal the level of the fluid in the catheter reliably shows IAP when IAH is induced by free fluid instillation into the peritoneal cavity [44]. In rat models usually two percutaneous catheters (one for inflation and another for measurement) used to be placed [34]. IAP monitoring through nasogastric catheter showed too low values in pigs, however another working group has found gastric air tonometry (gastric pH) sensitive enough in IAH and closely related to splanchnic hypoperfusion in pigs [43,63]. Comparing transvesical, transgastric and transperitoneal measurement techniques in pig model, it can be concluded that the transvesical method provides the most similar results to the direct measurement techniques [50]. Femoral venous pressure monitoring cannot be recommended to asses IAP in pigs [42]. Direct measurement of IAP at different parts of the abdomen is possible with placement of special sensors and a multichannel monitoring device [67]. Measurement of the microcirculation by Laser Doppler Flowmetry can be a useful tool for estimation of organ damage [41,65-67].

Abdominal rectal muscle microdialysis in rats is a promising tool for monitoring IAP and early detection of organ damage [32]. This technique is able to show early (after one hour) and more pronounced increase of interstitial concentration of lactate, glycerol level and lactate/pyruvate ratio. Brain natriuretic peptide

was found elevated in pigs during IAH, therefore it could be an alternative marker of ACS [17]. Other parameters like serum D-lactate level -product of intestinal bacterial metabolism- may be an early indicator for increased IAP before intestinal isquemia occurs in rats. Lactate level is elevated in the portal vein secondary to increased mucosal and capillary permeability [10,52].

Conservative therapy of ACS in animal models

Conservative treatment options in human medicine are sedation, diuretics, hemodialysis, muscle relaxation, decompression of the gastrointestinal tract, evacuation of the abdominal fluid through a percutaneous catheter, etc. [2,4,5]. The two most important parts of intensive therapy are still under debate: which is the optimal ventilation strategy, and which is the quality and quantity of fluid should be given for resuscitation and to maintain mean arterial pressure without enlargement of organ oedema or intra-abdominal fluid collection.

Lima et al. has found that IAH with hypovolaemia causes more severe damage to the intestines after three hours, reason why hypovolaemia should be urgently corrected [6]. Rat model seemed to be ideal to demonstrate the effects of different resuscitation fluids on IAP [56].

IAH rat model is suitable for respiratory parameter measurement and mechanical ventilation technique evaluation [54]. It has been proved that 100% oxygen inhalation improves survival of the liver and intestines in IAH mice and rats [34,44]. Positive End Expiratory Pressure (PEEP) ventilation effects on IAH/ACS have been investigated by several authors. No negative effect on oxygenation and hemodynamics related to PEEP was found in rats [18]. PEEP effect was assessed in IAH pig model with healthy and sick lungs by Regli. It was found that PEEP is recommended in lung injury to prevent ARDS and atelectasis. In porcine model, PEEP not lower than IAP is advisable because of the favourable effect on functional residual capacity and oxygen delivery. Higher PEEP levels do not result further elevation of IAP [25,62]. Henzler has proved that spontaneous breathing besides Bilevel Positive Airway Pressure does not improve respiration, nor hemodynamics and causes lung damage in pigs [33]. In contrast, Kotzampassi highlighted that PEEP and IAH act cumulatively and both causes hypoperfusion of the liver and intestines [30]. IAH and PEEP have influence on airway plateau pressure and bladder pressure [29]. Plateau pressure and transpulmonary pressure in IAH pig model was examined by Kubiak. Transpulmonary pressure was found useful to set mechanical ventilation in critically ill [16].

Therapeutic effects of different drugs were investigated by several working groups, for example tadalafil (phosphodiesterase-5-inhibitor) on IAH induced renal dysfunction [40], melanocortin-4-receptor agonist on intestinal inflammatory changes and ischaemia in ACS rats [46]. Norepinephrine effects were examined by Ferrara in sheep model and no change was found in intestinal blood flow, neither in intestinal villi microcirculation, nor on renal perfusion [66]. Some protective effects were found from glutamine to avoid reperfusion induced damage in rats [15].

Surgical treatment of ACS in animal models

When conservative therapy fails urgent de-compressive laparotomy followed by open abdomen management is necessary [2,4,5,19,28,41,45]. Identify the critical level of IAP or IAH period when the surgery is indicated remained controversial questions. The well-known, but nowadays only historical Bogota Bag insertion still could have important role in war situations, in mass casualty incidence or in the Third World countries. The Negative Pressure Wound Therapy (NPWT) become "Gold standard" for open abdomen management [4,5,64,67] (Table 2.). The mode of application, the effects and side effects also require further evaluation.

IAH/ACS treatment
A. Conservative
1. Improvement of abdominal wall compliance:
sedation
analgesia
neuromuscular blockade
avoid Trendelengerg position
consider reverse Trendelenberg position
2. Decompression of the gastrointestinal tract:
nasogastric and/or rectal tube
prokinetic agents
minimize enteral nutrition
colonoscopic decompression
3. Correct fluid balance:
avoid excessive fluid resuscitation
diuretics
colloids/hypertonic fluids
4. Organ support:
optimize ventilation
hemodyalisis
vasoactive mediators
B. Semi-conservative
Evacuation of intraabdominal fluid collections:
paracentesis
percutaneous drainage
C. Surgery- open abdomen therapy
1. skin approximation with clips or sutures
2. Bogota-bag
3. synthetic meshes
4. zipper system
5. Wittmann-patch
6. NPWT
7. combinations

Table 2: IAH/ACS Treatment.

The timing of decompression is also a crucial question. In pig model it seemed to be reasonable after six hours of 25 mmHg, when improved intestinal blood flow, normalized intra-peritoneal lactate/pyruvate ratio -referring better oxygenation of the organs- were detected [19,28].

Pig and rat models were used for evaluation of abdominal wall reconstruction after decompressive laparotomy [8,13,41,45,69]. No significant differences were found with regard to the hemodynamic and pulmonary parameters, but bag silo and zipper had higher volume reserve capacity (adding volume into the bag) than NPWT. NPWT application is highly advised, because it provides better conditions for delayed fascial closure [8]. The pig model is ideal for microvascular blood flow monitoring with Laser Doppler Flowmetry. It has been proved that with increasing levels of negative pressure applied, intestinal blood flow lowers, promoting fistula formation [41]. Nemeth et al. investigated microcirculatory and micro-rheological data in ACS pig model during Bogota-bag and NPWT application. NPWT at pressure levels -100 mmHg and -50 mmHg resulted better outcome. Important finding from this study that the worst microcirculatory parameters were measured in the omental fat tissue both in NPWT and Bogota Bag groups, probably due to its exposed position during the experiment [67]. In human conditions this finding probably even more significant, considering that the omentum in pig is a rudimentary organ compared to human and hardly covers the intestines.

In another pig model [69] -also from our team- it has been proved that the protective layer provides equal and effective negative pressure distribution for the lateral parts of the abdominal cavity as well. This finding underlines the effectiveness of NPWT. According to our findings, -100 mmHg negative pressure seems to be the most preferable to apply in clinical conditions [69].

Are there any further investigating fields of ACS animal models?

Cardiac events were assessed in some experimental IAH/ACS models [7,23,49,51,59,61,64]. Left ventricular relaxation can be measured in rabbits [61]. Continuous cardiac output monitoring techniques may be investigated in pigs allowing early detection of hemodynamic instability [37]. It has been proved in IAH pig model that ischaemic preconditioning can modify organ damage level, hemodynamic, biochemical and inflammatory parameters [35,53]. Du, et al. has investigated the speckle tracking imaging, a useful method for myocardial contractibility assessment in mini pig IAH model [49].

Pancreatitis is one of the most frequent etiology of IAH. The ongoing pancreatitis with rising tissue necrosis results higher and higher IAP [47]. Intraductal sodium taurocholate was used to create experimental Severe Acute Pancreatitis (SAP) in pigs by Lu Ke's team. It was found that due to the good abdominal wall compliance the pig has broad space in the abdomen, therefore SAP creation has to be combined with nitrogen neumoperitoneum to induce IAH [59].

Bacterial translocation from the gastrointestinal tract occurs at higher levels of IAP (15-20 mmHg) in rabbits, and at 15-30 mmHg in pigs after 24 hours [20,22]. Cobalt-albumin binding assay can help in early diagnosis making of ACS detecting intestinal ischaemia in rabbits [12].

Pulse pressure variation and stroke volume can be examined in IAH pig model in means of fluid resuscitation needs [38,64,65].

Ascites and cirrhosis can be induced in mice by intraperitoneal administration of albumin and subcutaneous carbon tetrachloride injection to examine hepatopulmonary syndrome and IAH [14]. Mouse model can be used to describe the correlation between hepatorenal syndrome and IAH [11]. Gastric empty time was measured with scintigraphy in dogs by Balci's team. Close correlation was found between IAP and gastric empty time. Close monitoring of this factor is advised in ACS patients to prevent gastric reflux and aspiration [39].

Acute lung injury can be induced by lavage with a surfactant deactivating material or oleic acid to study acute lung injury and IAH effects in pigs [23,25]. It was found in pleural effusion pig models that early abdominal decompression improves the lung restriction [24].

Conclusions

Small animal models (mouse, rat, rabbit) are cost-effective, easy to apply, with less infrastructural needs. They are suitable for experiments require large sample numbers. They can be successfully applied for pathophysiological, biochemical, histological and immunohistochemical investigations. Anatomy and physiology of these small animals may differ from that of humans, but they are closer to infants'. Small animal models can be applied for several investigation fields of IAH/ACS, and give well correlating results to large animal data.

There is consensus about large animal models (dogs, sheep, pigs), which are closest to human conditions. Although they are expensive and require quite a lot infrastructure, they can represent renal, cardiovascular and gastrointestinal functions. Large animal models are ideal to investigate anatomical changes, surgical and intensive care techniques.

Both small and large animal models have certain limitations, which have to be taken into consideration during data evaluation and before to apply in clinical use.

According to literature and to our experience, porcine models are ideal for IAH/ACS experiments. Pig has very close anatomy and physiology to human which provides excellent opportunity for

tissue (histology) and bacteriological sampling, for measurements on microcirculation and for pressure monitoring at different points of the abdomen. The pig model also allows respiratory, cardiovascular parameter and urinary output monitoring, and evaluation of new surgical techniques.

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