

Lung tissue apoptosis in abdominal hypertension

Apoptosis and necrosis of lung tissue in abdominal hypertension

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Abstract

Objectives The aim of this study was to evaluate lung tissue histopathologic changes and the number of apoptosis with the increase of abdominal pressure.

Methods The study rats were randomly assigned into the following five groups: a sham operated group and groups 1, 2, 3 and 4, in which the intra-abdominal pressure was increased to 11, 15, 18 and 22 mmHg for 60 min, respectively. Lungs were harvested for histopathologic changes and the tissue apoptotic analysis were carried out in a blinded manner.

Results All of the data showed that the number of apoptotic cells and necrosis were increased in accordance with the pressure level. However, this increase was

statistically significant, especially in groups 3 and 4 (18 and 22 mmHg, respectively; $p < 0.05$) when compared to the sham operated rats. There were no differences observed between groups 1 and 2 (11 and 15 mmHg, respectively) and the sham operated rats. There was also no difference between groups 1 and 2. There were findings of coagulation necrosis and the number of apoptotic cells linearly increased when the abdominal pressure was increased. The cut-off value was 15 mmHg.

Conclusion The available findings suggest that intra-abdominal pressure greater than 15 mmHg could irreversibly damage pulmonary cells and both coagulation necrosis parameters and the number of apoptosis increase in accordance with the pressure level.

Keywords Open abdomen · Abdominal · Experimental trauma surgery · General trauma · Thoracic · Thoracic and abdominal

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Introduction

Intra-abdominal pressure (IAP) is the pressure generated inside the abdominal cavity [1]. An IAP exceeding 12 mmHg is considered to be pathologically elevated and has been termed intra-abdominal hypertension (IAH). An IAP exceeding 20 mmHg with evidence of organ dysfunction/failure is defined as abdominal compartment syndrome (ACS) [2–5]. The most common causes of IAH are intra- and retro-peritoneal haemorrhage, visceral oedema related to post-resuscitation states, pancreatitis, laparoscopy with pneumoperitoneum, bowel distension and intra-abdominal infection [5].

IAP can markedly affect pulmonary cells and the function of the respiratory system. In particular, IAH

increases chest wall elasticity and plays a relevant role in the caudal–cranial displacement of abdominal content and the diaphragm, with consequent changes in lung mechanics and function [1]. One, but not the only, cause of ACS is ischaemia/reperfusion injury [4, 5]. Reversible changes are expected in this type of injury, but at high IAP, tissues may be irreversibly damaged. The aim of this study was to evaluate the histopathological changes and apoptosis in lung tissue during an increase of IAP.

Methods

All procedures were approved by the Kocatepe University Animal Ethics Committee. The study protocol was designed in accordance with the 1996 revision of the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health. Unnecessary animal suffering was avoided throughout the study.

Twenty-five adult female, specific pathogen-free Wistar–Hannover rats (200–220 g; Suleyman Demirel University Experimental Research Laboratories, Isparta, Turkey) that had been isolated from male rats were included in this study. The animals were housed in standard laboratory cages and were allowed free access to food and water until 12 h before the surgical procedure.

Experimental design

This study was designed as an experimental, randomised, controlled trial with blind assessment of the outcome. Rats were randomly assigned to five groups of five rats each. In the rats in groups 1–4, the IAP was surgically increased to 11, 15, 18 and 22 mmHg, respectively, for 60 min. The rats in the fifth (sham operated) group underwent the same surgical procedure, but the abdominal pressure was not increased.

Surgical procedure

The rats were anaesthetised with 100 mg/kg ketamine (KetalarTM amp; EIP, Istanbul, Turkey) and 60 mg/kg xylazine (Bayer, Istanbul, Turkey). A rectal probe was placed to monitor the body temperature. A heating pad was used to maintain the body temperature at 37°C until the rats recovered from the anaesthesia.

A 1-cm midline abdominal incision was made under aseptic conditions. A sterile cannula connected to a tube was inserted completely into the abdomen. The other end of the tube was connected to physiological saline solution (Eczacıbaşı, Turkey) kept at room temperature and to a linear manometer to directly check the IAP. The abdomen was filled with physiological saline until the IAP reached the desired level.

The IAP was stabilised at 11, 15, 18 or 22 mmHg and was maintained for 60 min. IAH was graded as follows: grade I, IAP 12–15 mmHg; grade II, IAP 16–20 mmHg; grade III, IAP 21–25 mmHg; and grade IV, IAP > 25 mmHg [3].

After the surgical procedure, the incision was closed and the physiological saline solution was removed from the abdomen. The lungs were harvested and stored in 10% neutral buffered formalin for later histopathological and tissue apoptotic analyses. The samples were blocked in paraffin.

A code number (from 1 to 25) randomly produced by a computer was assigned to each lung tissue sample. The code list was collected by a person who had no connection with the research, so that both the histopathological and apoptotic analyses were performed blindly.

Histopathological analysis

The 4-µm sections were cut and stained with haematoxylin–eosin. Mounted slides were examined under a light microscope (Eclipse E600W; Nikon, Tokyo, Japan) and photographed using a digital camera (Microscope Digitale DP70 camera, Tokyo, Japan). The presence and degree of peribronchial inflammation, perivascular inflammation, intra-parenchymal infiltration and fibrosis, intra-parenchymal vascular congestion, thrombosis and haemorrhage, respiratory epithelial proliferation, nodular aggregates, macrophages in the alveolar and bronchiolar lumens, type 2 pneumocytes, alveoli destruction, emphysematous changes and bronchoalveolar haemorrhage were assessed.

The level of changes in each section was determined as follows. First, the intensity and diffusion were semi-quantitatively scored on separate scales [5]. For intensity, the scale was as follows: 0 none; 1 mild; 2 moderate; and 3 intense. Diffusion was scored as follows: 0, none; 1, focal; 2, 3–4 foci; and 3, all lung tissue affected. Both intensity and diffusion were scored for each observation and the scores were summed for each section. The level of changes was assigned according to the final score as follows: 0 no changes; 1+ minimal; 2+ low; 3+ moderate; 4+ strong; 5+ heavy; and 6+ most heavy [6–8]. All scoring was performed by an investigator who was blinded to the group assignments.

Apoptosis detection

The 4-µm-thick sections from the lung sample blocks were mounted on poly-L-lysine-coated slides (Lab Vision, Fremont, CA, USA) for apoptotic cell detection with a TUNEL-based apoptosis kit (FragEL DNA Fragmentation Detection Kit; Calbiochem, Darmstadt, Germany). The sections were deparaffinised, rehydrated and permeabilised with proteinase K. Endogenous peroxidases were

Table 1 The histopathologic changes of lung tissue: study groups compared with sham operated rats

	Group 1	Group 2	Group 3	Group 4	Sham
Inflammatory infiltration of peribronchial tissue					
Mean $\pm$ SD	0.80 $\pm$ 1.09	1.40 $\pm$ 1.34	2.40 $\pm$ 0.55*	4.20 $\pm$ 0.44*	0.00 $\pm$ 0.00
Median (min–max)	0 (0.00–2.00)	2 (0.00–3.00)	3 (2.00–3.00)	4 (4.00–5.00)	0 (0.00–0.00)
Haemorrhage of alveolar and bronchial tissue					
Mean $\pm$ SD	0.00 $\pm$ 0.00	1.80 $\pm$ 1.09*	2.40 $\pm$ 0.54*	4.20 $\pm$ 0.44*	0.00 $\pm$ 0.00
Median (min–max)	0 (0.00–0.00)	2 (0.00–3.00)	2 (2.00–3.00)	4 (4.00–5.00)	0 (0.00–0.00)
Intra-parenchymal and vascular congestion and thrombosis					
Mean $\pm$ SD	0.00 $\pm$ 0.00	1.80 $\pm$ 1.09*	2.40 $\pm$ 0.54*	4.00 $\pm$ 0.70*	0.00 $\pm$ 0.00
Median (min–max)	0 (0.00–0.00)	2 (0.00–3.00)	2 (2.00–3.00)	4 (3.00–5.00)	0 (0.00–0.00)
Alveolar destruction					
Mean $\pm$ SD	0.00 $\pm$ 0.00	1.80 $\pm$ 1.09*	2.40 $\pm$ 0.54*	4.20 $\pm$ 0.44*	0.00 $\pm$ 0.00
Median (min–max)	0 (0.00–0.00)	2 (0.00–3.00)	2 (2.00–3.00)	4 (4.00–5.00)	0 (0.00–0.00)
Macrophages in alveolar and bronchial lumen					
Mean $\pm$ SD	0.08 $\pm$ 1.09	1.80 $\pm$ 1.09*	2.40 $\pm$ 0.54*	4.00 $\pm$ 0.70*	0.00 $\pm$ 0.00
Median (min–max)	0 (0.00–2.00)	2 (0.00–3.00)	2 (2.00–3.00)	4 (3.00–5.00)	0 (0.00–0.00)
Intra-parenchymal inflammatory infiltration					
Mean $\pm$ SD	0.00 $\pm$ 0.00	1.80 $\pm$ 1.09*	2.40 $\pm$ 0.54*	4.00 $\pm$ 0.70*	0.00 $\pm$ 0.00
Median (min–max)	0 (0.00–0.00)	2 (0.00–3.00)	2 (2.00–3.00)	4 (3.00–5.00)	0 (0.00–0.00)

* $p < 0.05$

inactivated by 10% H_2O_2 . For DNA labelling, a Tdt labelling reaction mix and Tdt enzyme mix were used. A solution of DAB in H_2O_2 /urea was used to detect the reaction, and 3% methyl green was used for counter-staining. Then, the slides were dehydrated and mounted with xylene. The TUNEL-positive, brown cells were accepted as apoptotic cells, in concordance with the positive control supplied by the manufacturer.

Image analysis for apoptosis

All of the stained FragEL slides were evaluated under a light microscope (Nikon Eclipse E600W). During the evaluation, TUNEL-positive cells in 25 different areas were counted under 20 $\times$ magnification. The UTHSCSA ImageTool for Windows 3.0 image analysis software was used for the counting tasks.

Statistics

The results were decoded and statistically analysed. Data are expressed as mean $\pm$ standard error of the mean (SEM). Median and range values are also presented because of the small sample size of the groups. Statistical analyses for histopathological changes were performed using the Kruskal–Wallis and Mann–Whitney U -tests. Apoptosis data were also analysed by one-way analysis of variance (ANOVA) with Tukey's HSD post-hoc test. SPSS

Table 2 The mean and median values of apoptotic cells of the study groups

Group	Pressure (mmHg)	Median (min–max)	Mean $\pm$ standard error
Sham	–	0 (0–3)	0.36 $\pm$ 0.17
1	11	0 (0–4)	0.48 $\pm$ 0.20
2	15	0 (0–11)	2.60 $\pm$ 0.70
3	18	3 (0–10)	3.12 $\pm$ 0.61*
4	22	9 (0–16)	7.72 $\pm$ 1.05*

* $p < 0.05$ compared with sham operated rats

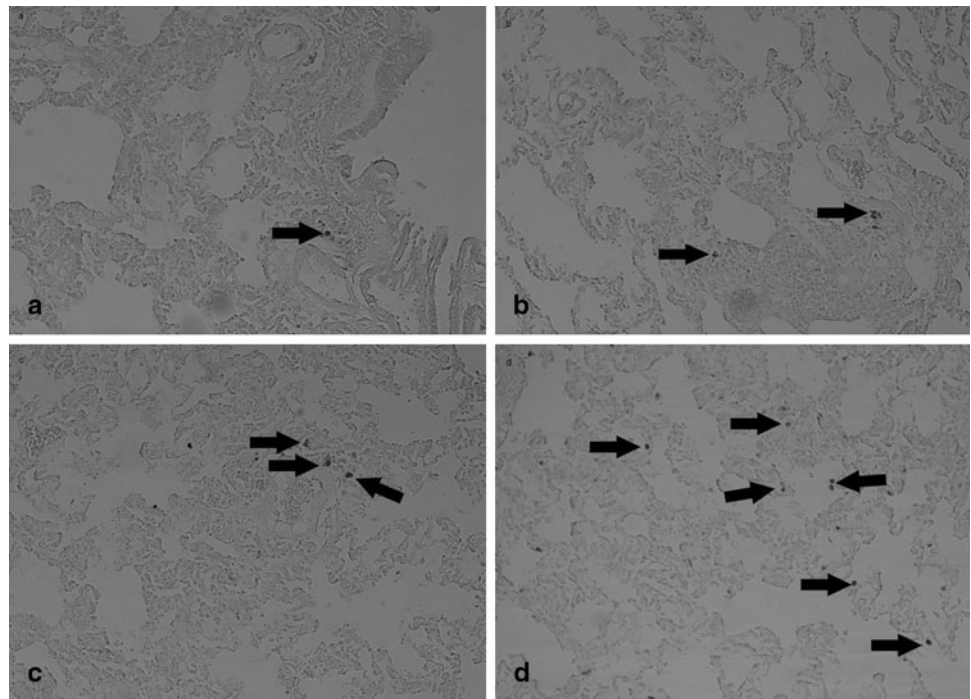
for Windows 15.0 (SPSS, Inc., Chicago, IL, USA) was used. A p -value < 0.05 was considered to be significant.

Results

The results are summarised in Tables 1 and 2. The necrosis and apoptosis data are shown in Figs. 1 and 2.

The number of apoptotic cells and necrosis increased with increasing IAP. These increases were statistically significant, especially in groups 3 and 4 (IAP 18 and 22 mmHg, respectively; grades II and III; $p < 0.05$) as compared with the sham group. Groups 1 and 2 (IAP 11 and 15 mmHg, respectively; grade I) did not differ from each other or from the sham group. Findings of coagulation necrosis and the number of apoptotic cells increased linearly with increases in the IAP. The cut-off value was 15 mmHg (grade I).

Fig. 1 Apoptosis in the study groups (**a–d** for groups 1, 2, 3 and 4, respectively). The *arrows* indicate apoptotic cells



Discussion

The mechanism of ACS and its derangements are not completely understood. ACS has a high mortality rate if undiagnosed and untreated in the early phases [4, 5].

Effects of IAH on pulmonary function

Pulmonary complications are one of the main causes of IAH-related mortality. Clinical manifestations of pulmonary complications include high intra-thoracic pressure, elevated airway pressure, decreased pulmonary compliance, hypoxia, hypercapnia and increased pulmonary shunt fraction. Elevated intra-thoracic pressure reduces left ventricular compliance, which impairs ventricular filling, increases after-load and elevates systemic vascular resistance mediated by capillary bed compression. The profound effects of IAH limit effective ventilation. Passive elevation of the diaphragm allows transmission of the IAH to the pleural cavity, reducing static and dynamic lung compliance. Basal atelectasis occurs while the hemidiaphragms are partially elevated [4, 9–14].

Effects of IAH on inflammation and pulmonary oedema

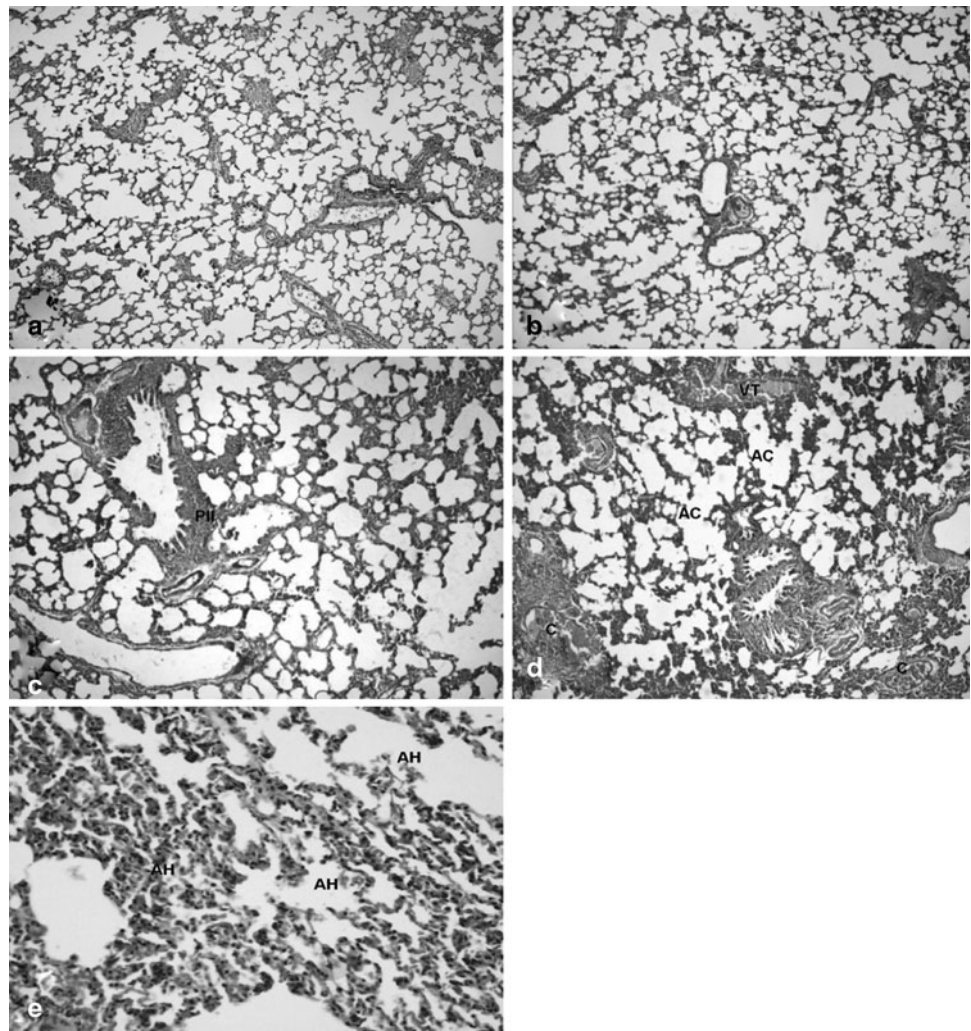
IAH provokes the release of pro-inflammatory cytokines such as tumour necrosis factor- α , interleukin (IL)-6 and IL-1-b, which may serve as a second insult for inducing multiple organ failure [15]. The same researchers demonstrated haemorrhagic shock after trauma as the priming

insult and ACS as the activating event. In one report, maximal circulating neutrophils provoked acute lung and liver injury and resulted in 33% mortality [16]. Several procedures in critically ill patients may increase IAP and its effects, such as heavy sedation, bowel hypomotility and partial loss of diaphragmatic tone. In cases of acute lung injury/acute respiratory distress syndrome, any increase in IAP creates a potentially dangerous condition, not only by reducing the gas content of an already diseased lung, but also by potentially inducing an increase in pulmonary oedema. High pulmonary capillary pressure can cause oedema in the lungs, with altered permeability. An increase of IAP may favour oedema and may impair its clearance from the lung. In fact, the clearance of lung oedema can take three routes: a lymphatic pathway, reabsorption through the pulmonary capillaries when the interstitial pressure exceeds the capillary pressure and reabsorption through the pleural capillaries, leading to pleural effusion. Nevertheless, all of these pathways have the thoracic veins, which are subjected to intra-thoracic pressure, as a final common route to clear oedema. In animal models, raising the intra-thoracic pressure reduces lymphatic flow and impairs the clearance of lung oedema. An IAP of 18 mmHg resulted in increased oedema formation and decreased clearance [17, 18].

Management strategies for IAH

Intensive therapy with invasive measurement of haemodynamic parameters and IAP, and urgent decompressive

Fig. 2 Histopathologic view of lung tissue in the study groups and sham operated rats. **a–e** The sham group and groups 1, 2, 3 and 4, respectively. *PII* peribronchial inflammation, *VT* venous thrombosis, *AC* alveolar congestion, *AH* alveolar haemorrhage



laparotomy (laparostomy) are the primary management strategies for IAH. Additional treatment may include the improvement of abdominal wall compliance with sedation and pain relief, evacuation of intra-luminal contents and peri-intestinal and abdominal fluids, correction of capillary leak (i.e. source control with antibiotics), restoration of fluid balance, and specific therapeutic interventions such as continuous negative external abdominal pressure. The timing of laparostomy is still controversial, because after decompression, the patient is at risk for ischaemia/reperfusion injury, venous stasis and a fatal pulmonary embolism. Maintaining adequate preload and abdominal perfusion pressure (APP) is the key to success [19]. APP, calculated as the mean arterial pressure – IAP, has been proposed as a more accurate predictor of visceral perfusion and a potential end-point for resuscitation. A target APP of at least 60 mmHg correlates with improved survival from IAH and ACS. Schachtrupp et al. [20] showed that extensive fluid resuscitation preserves cardiac output, diuresis and serum parameters in a porcine model of ACS.

Despite normalised parameters, histological organ damage can occur as a result of venous congestion and disturbed microcirculation. From a clinical perspective, these results support decompressive laparotomy in the case of pathologically high IAP exceeding 20 mmHg or associated with organ failure constituting ACS [2].

Study limitations

The results obtained in animal models, which are often tested under extreme conditions, cannot be generalised to patients. Our study lacked the effect of fluid resuscitation and decompression. The level of IAH that warrants decompression and fluid resuscitation awaits further studies.

Several approaches have been chosen to induce IAH in animal models. IAH in ACS is caused mainly by massive intestinal oedema, ascites or haemorrhage, either intra- or retro-peritoneally. Thus, the induction of IAH with intra-peritoneal fluid instillation seems to be the most

appropriate technique to simulate the clinical condition [21, 22]. However, intra-peritoneal instillation of crystalloid solutions is associated with massive absorption of fluid, which negatively interferes with the pathophysiological response to IAH [23]. This is one of the weak points of our study.

Evidence of significant organ dysfunction has been demonstrated at an IAP of 11 mmHg (grade I), and the maintenance of normovolaemia is recommended for patients with grade I IAH. Ivatury and Sugerman [24] suggested that the critical IAP value is near 18 mmHg. Hypervolaemic resuscitation may overcome the adverse haemodynamic effects of moderately increased IAP in patients with grade II disease. Most patients with grade III disease undergo decompression, whereas those with grade IV disease should undergo both decompression and re-exploration, because these patients are at risk for bowel ischaemia [25]. The highest level of IAP in our study was 22 mmHg, which was below some values observed in clinical settings with high mortality rates, but, nevertheless, affected lung tissue necrosis parameters and apoptosis.

We did not measure the volume of the instillation fluid in the study groups, so we could not calculate abdominal compliance, which could affect IAH. The effects of laparotomy and reperfusion injury on lung tissue necrosis and apoptosis are still a subject of research.

IAH decreases total respiratory system compliance by decreasing chest wall compliance, while lung compliance remains unchanged [23]. The best positive end expiratory pressure (PEEP) should be set to counteract IAP, while at the same time avoiding the over-inflation of already well-aerated lung regions. The pulmonary artery occlusion pressure is above 18 mmHg for patients with IAH and secondary acute respiratory distress syndrome. IAH increases lung oedema [17] and the combination of capillary leak and positive fluid balance along with increased IAP poses exponential danger for lung oedema in the patient. Mechanical ventilation settings, lung tissue PEEP, follow-up of the haemodynamic situation and the drift of the saline solution through the peritoneum need to be resolved with further studies.

Effect of IAH on lung tissue

It is important to vigilantly monitor amelioration or negative progression to the limits of adaptation capacity in pulmonary cells [5, 9], because cell injury can develop when adaptation capacity is exceeded. Injury is reversible within certain limits, and cells return to a stable baseline; however, with severe or persistent stress, irreversible injury results, and the affected cells die. Two principal patterns of cell death are recognised; these have distinct mechanisms, but there is also considerable overlap between the two

processes. The first is necrosis, which occurs after the loss of blood supply and is characterised by cellular swelling, protein denaturation and organelle breakdown. This cell death pathway may result in considerable tissue dysfunction. The second process, apoptosis, occurs as a result of an internally controlled suicide program, after which the dead cells are removed with minimal disruption to the surrounding tissue. Apoptosis occurs in response to irreparable mutational damage of pathologic states [25]. Pathologic effects can include the release of cytokines, formation of oxygen free radicals and decrease of cellular production of adenosine triphosphate. These effects can lead to the translocation of bacteria from the gut and intestinal oedema, predisposing the animal to multi-organ dysfunction syndrome, which affects vital body systems [4, 9, 10]. If IAH exceeds the limits of adaptation, serious clinical lung complications can develop [2–5, 26]. The available findings suggest that abdominal pressures above 18 mmHg could irreversibly damage pulmonary cells, and both coagulation necrosis parameters and the number of cells undergoing apoptosis would increase with increased pressure.

Conflict of interest None.

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