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Liver Necrosis and Apoptosis During Increased Intra-Abdominal Pressure Alleviated by Ischaemic Preconditioning

Experimental Study

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Abstract

Aim: Intra-abdominal hypertension (IAH) is known to have a negative impact on liver function. The aim of this study was to observe the degree of liver necrosis and apoptosis during IAH and to test the hypothesis as to whether liver ischaemic preconditioning can alleviate these changes.

Methods: The study involved three groups of 8 pigs. In the first group (Pn), pneumoperitoneum with Helium was established and intra-abdominal pressure (IAP) was increased to 30 mmHg for 3 hours, after which the abdomen was decompressed. Liver biopsies were obtained through a mini-laparotomy before establishing pneumoperitoneum, immediately after decompression, and one hour after decompression. In the second group (IscPr), IAP initially increased to 25 mmHg for 15 minutes, followed by an equal period of decompression, after which the protocol for the first group was adopted. The third group comprised controls in which IAP was unchanged; liver biopsies were obtained during the same time periods as the Pn and IscPr groups.

Results: Liver necrosis after abdominal desufflation was significantly higher in the Pn group compared to the control group ($p=0,004$) and the degree of necrosis was significantly lower in the IscPr group compared to the Pn group ($p=0,009$). Liver apoptosis during IAH was significantly higher in the Pn group compared to that in the control Group ($p=0,002$), while liver apoptosis was significantly lower in the IscPr group compared to the Pn group ($p=0,008$). After abdominal desufflation, apoptosis was significantly higher in the Pn group compared to the control group ($p<0,001$) and significantly lower in the IscPr group compared to the Pn group ($p<0,001$).

Conclusions: IAH resulted in significantly increased liver necrosis and apoptosis. Moreover, ischaemic preconditioning resulted in a significantly smaller degree of liver necrosis and significantly reduced apoptosis.

Key words:
Intra-abdominal hypertension, Ischaemic preconditioning, Liver necrosis, Liver apoptosis

Introduction - Aim

The increase in intra-abdominal pressure (IAP) can have significant effects on abdominal and extra-abdominal organs [1-3]. The location of the liver, its histological structure, and its central metabolic role have prompted researchers to study the effects of intra-abdominal hypertension (IAH) on the structure and function of the liver [4-6]. Clinical and experimental studies show that an increase in liver enzymes and associated histological alterations occur after prolonged pneumoperitoneum [4, 7].

Clinical and experimental studies have also shown that the application of pneumoperitoneum during laparoscopic surgery, or more severely during IAH and abdominal compartment syndrome (ACS), results in ischaemia of intra-abdominal organs, while subsequent decompression is followed by an ischaemia/reperfusion injury [8-12]. The damage that occurs after ischaemia and the subsequent restoration of blood flow is due, not only to hypoxia, but also to the inflammatory response that follows [13, 14].

Although cell death from ischaemia/reperfusion injury is generally considered to result from necrosis, it has been increasingly recognized that cell death may also arise from apoptosis [15, 16]. However, during apoptosis controlled and programmed cell death and tissue damage occurs, a physiological process which prevents excessive cell death induced by harmful stimuli, important in maintaining homeostasis. Apoptosis differs from necrosis, not only in terms of histological alterations, but also in relation to mediator-induced mechanisms of injury [15-19].

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In the liver, apoptosis of hepatocytes has been noted in both normal and abnormal conditions. Hepatocyte apoptosis is a normal event during liver development, as well as in the process of repair and renewal. On the other hand, a number of harmful conditions, including ischaemia, drug toxicity, other toxicities, viral inflammation, malignancy, endotoxaemia, and immunologically mediated conditions, have been shown to trigger hepatocyte apoptosis [19]. Currently, clinical and experimental research has revealed that resistance of vital organs (heart, liver, kidneys, etc) to ischaemia may be increased through the use of ischaemic preconditioning (IP). IP is an endogenous protective mechanism through which repetitive short periods of ischaemia followed by reperfusion confers protection against subsequent sustained ischaemia /reperfusion injury [20, 21].

Taking into account current knowledge of the impact of IAH on liver function and histology, we conducted an experimental study in order to investigate the effect of IAH on hepatocyte necrosis and apoptosis and further demonstrate the effect of ischaemic preconditioning on both processes.

Methods

The research protocol was approved by the Ethics Committee of Aretaieion Hospital of Athens University and the local Department of Veterinary Service. The animals used for this protocol were 24 female swine weighing between 20-33 kg which were deprived of food for 24 hours before each experiment, but were given free access to water.

Anaesthetic protocol

Ketamine (3 mg/kg) and midazolam (0.5 mg/kg) were administered intramuscularly. General anaesthesia was achieved with Thiopental (5 mg/kgr) and Fentanyl (100γ) and was maintained with sevoflurane (1-2% MAC), fentanyl (~5g/kg/h), and vecuronium (~1.5 mg/h). During the experiment, all animals received 100-150 ml/kg of a Ringer's lactate solution. A nasogastric tube was introduced and electrocardiogram (ECG), oxygen saturation, end-expiratory carbon dioxide (CO2) and transrectal temperature were monitored throughout the experiment. Through a lateral vertical neck incision, a 3-lumen catheter 7.0 Fr, 20 cm, (Central Venous Catheter Kit, Hospira, Inc. Illinois, U.S.A) was inserted into the ipsilateral internal jugular vein for central venous pressure (CVP) measurements and a PiCCO catheter (PULSION Medical Systems AG –Munich Germany), was inserted into the common carotid artery for haemodynamic monitoring.

Groups of animals

As previously stated, the purpose of the study was to investigate the impact of IAH on liver histology through the determination of the extent of hepatocyte necrosis and apoptosis. The potential for the development of resistance in the liver following ischaemic preconditioning was also determined. Pigs were used as experimental subjects due to the anatomical and histological similarity between human and porcine livers. The pigs were randomly divided into 3 groups of 8 animals. In the first group (Pn), pneumoperitoneum with Helium was established via an infraumbilically inserted Verress needle and IAP was increased from baseline (0-5 mmHg) to 30 mmHg for 3 hours, after which the abdomen was decompressed. Liver biopsies were obtained through a mini laparotomy before establishing pneumoperitoneum, immediately after decompression, and one hour after decompression. In the second group (IscPr), IAP was initially increased to 25 mmHg for 15 minutes, followed by a 15 minute period of decompression (IAP = 0 mmHg), after which the protocol for the first group was adopted. The third group comprised controls, in which IAP was unchanged; liver biopsies were obtained during the same time periods as in the Pn and IscPr groups. Helium gas was used rather than carbon dioxide in order to avoid the adverse effect of hypercapnia and subsequent acidosis [22]. Liver biopsies were obtained during laparotomy, taking special care to avoid blood loss. Diathermy was not used to protect the specimens from heat. Tissue specimens, each measuring approximately 15x20 mm, were obtained from the edge of the right hepatic lobe. Biopsies were then delivered to the Pathology Laboratory.

Histopathological examination

A histopathological study of the liver biopsies was performed by standard methodology. Specifically, all histological specimens were stained with hematoxylin-eosin (H-E). Each section was then studied with a light microscope by a single pathologist blinded to the identities of the specimens. The presence of necrotic cells was marked as grade I to III, according to the features of necrosis. Specifically, fatty degeneration of the hepatic cells was considered as grade III. All other forms of degeneration (hydropic or vesicular) were considered as grade I to II. Apoptotic hepatocytes were identified in H-E-stained sections as necrotic cells without an inflammatory reaction. Apoptotic cells were also identified with TUNEL staining 15-17 using a commercial kit (Boehringer Manheim Co., Indianapolis, IN).

TUNEL-positive nuclei were counted under 40x magnification and quantified by the % of positive nuclei / 1000 cells.

Statistical analysis

The normal distribution of quantitative variables was determined using the Kolmogorov-Smirnov test. Quantitative variables that were not normally distributed were expressed as the median and interquartile range. Comparison between 2 groups was performed using the Mann-Whitney test, while comparison between more than two groups was made using the Kruskal-Wallis test. To compare proportions, the Pearson's chi-square test was used and, where necessary, the Fisher's exact test. To control for Type I errors due to multiple comparisons, the Bonferroni correction was applied using a significance level of 0.05 / k (k = number of comparisons). Tests were 2-tailed. A statistical level of less than 5% was considered significant. Statistical analysis was performed using the software statistical package for the social sciences 13.0 (SPSS 13.0–IMB company USA).

Results

- Pneumoperitoneum (Pn) group:
  a. Liver necrosis was significantly increased during intra-abdominal hypertension (p=0,001), an effect that was sustained even after abdominal desufflation (p<0,001) (Fig. 1a);
  b. Similarly, liver apoptosis was significantly increased during IAH (p=0,002) and significantly maintained after abdominal desufflation (p<0,001) (Fig. 1b).
- Ischaemic preconditioning (IscPr) group:
  a. Hepatic necrosis did not change significantly throughout all the experimental phases (Figure 2a);
  b. However, apoptosis increased significantly during IAH (p=0,004), as well as after abdominal desufflation (p=0,002) (Fig. 2b).
- Control group: no significant changes in necrosis and apoptosis were observed. (Fig. 3)
- Comparisons between groups:
  a. The degree of necrosis after abdominal desufflation was significantly higher in the Pn group compared to the control group (p=0,004), while it was significantly lower in the IscPr group compared to the Pn group (p=0,009) (Fig. 4). This demonstrates that ischaemic preconditioning significantly alleviates the extent of liver necrosis induced by pneumoperitoneum alone.
  b. Liver apoptosis during IAH was significantly higher in the Pn group compared to the control group (p=0,002), while it was significantly lower in the IscPr group compared to the Pn group (p=0,008) (Fig. 5a). This effect was sustained even after abdominal desufflation. After abdominal desufflation, apoptosis was significantly higher in the Pn group compared to the control group (p<0,001) and significantly lower in the IscPr group compared to the Pn group (p<0,001) (Figure 5b). It is apparent that ischaemic preconditioning has a protective role against liver apoptosis.
  c. The comparison of the IscPr group with the control group regarding both apoptosis and necrosis was not statistically significant.

Discussion

The adverse effects of IAH on liver histology and function are currently recognized and thoroughly studied [4-7]. Moreover, it has been shown that the hepatic blood flow can be directly affected by pneumoperitoneum. Indeed, even at the lowest levels of 10mmHg, IAP can depress the dual blood supply of the liver, while a severe reduction of hepatic arterial and portal venous flow is demonstrated beyond the critical level of 20mmHg [4-6]. Diebel et al [5] showed that in pigs, IAP at 30mmHg severely depressed the oxidative and reductive capacity of the liver which further decreased energy production, despite adequate arterial oxygenation. In our study, we similarly used pneumoperitoneum of 30 mmHg in order to induce warm ischaemia in the liver and study hepatocyte damage during IAH and, more importantly, after abdominal decompression during which reperfusion injury occurs. This suggests that the experimental model of pneumoperitoneum followed by decompression is analogous to the ischaemia / reperfusion injury occurring in vivo [8-12, 23]. In our study, liver necrosis and apoptosis were significantly increased during IAH, an effect that was significantly sustained, even after abdominal decompression, reflecting the negative impact of IAH on liver ischaemia and reperfusion.

Extensive clinical and experimental research has demonstrated the protective role of ischaemic preconditioning on tissue ischaemia and reperfusion injury. It has been confirmed that ischaemic tissue damage is reduced if a prior exposure of tissues to repeated short periods of ischaemia and reperfusion is applied [20, 21]. Currently, IP of the liver can be achieved by the application of short periods of inflow occlusion through clamping the portal triad (Pringle's manoeuvre) followed by restoration of blood flow. In pigs, it has been shown that the ideal duration of occlusion and reperfusion is 10 minutes for each phase [24, 25]. In our study, we used the

aforementioned warm ischaemia instead of Pringle's manoeuvre, increasing IAP over the critical level of 20mmHg, and created IP conditions using IAP of 25 mmHg for 15 min followed by a 15 min reperfusion period. Our results showed that the degree of liver necrosis and apoptosis were significantly lower when IP was applied in comparison to the group of animals in which pneumoperitoneum without IP was used, signifying a protective role of IP in ischaemia/reperfusion liver injury.

Interestingly, the histopathological findings of our study demonstrate significantly greater necrotic hepatocyte death compared to apoptotic hepatocyte death. This picture is compatible with similar studies [16, 24, 26]. The morphological and biochemical features of apoptosis are different from those of necrosis [15-19]. Necrosis is characterized by non-fragmented degradation of DNA, cell membrane damage, as well as destruction of mitochondria and other organelles. In apoptosis, apoptotic cells exhibit nuclear and cytoplasmic condensation followed by the degradation of the nuclear membrane and formation of apoptotic features. In addition, mitochondria remain intact during apoptosis. Necrosis normally occurs in large cell groups and causes a local inflammatory reaction, while apoptosis does not cause an inflammatory reaction. Apoptotic cells are rapidly removed by macrophages via phagocytosis. Necrosis is always a consequence of pathological lesions. In contrast to apoptosis, however, necrosis is a passive phenomenon of uncontrolled energy. Apoptosis is primarily a physiological mechanism that contributes to cell regulation and proliferation and plays a key role in maintaining tissue homeostasis. However, like necrosis, apoptosis is also likely to be caused by various predisposing factors and can have an important role in the pathogenesis of various diseases. Drugs, toxins, viruses, cancers, and the immune response are among the factors that can trigger apoptosis of hepatocytes [15, 16, 19]. This experimental model demonstrates that IAH might be yet another mechanism that triggers apoptosis of hepatocytes, by which ischaemic preconditioning of the liver can be protective, alleviating the impact of IAH in the liver.

In conclusion, this study showed that IAH created conditions of liver ischaemia which induced increased necrosis and apoptosis of hepatocytes.

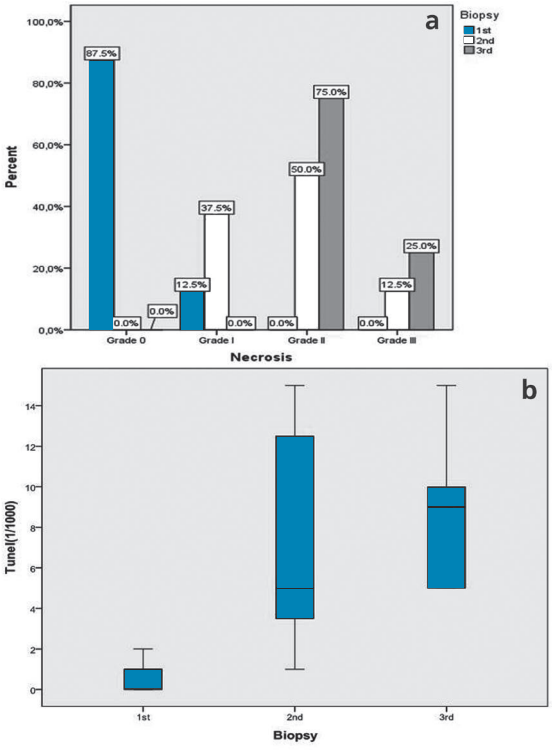

Fig.1 **a**. The extent of hepatocyte necrosis per biopsy in group Pn. Necrosis of hepatocytes in the second and third biopsy specimens were significantly increased, p = 0,001 and p <0,001 respectively, compared to the first biopsy specimens. **b.** Apoptosis in the Pn group. TUNEL values in the second and third biopsy specimens were significantly increased compared to the first biopsy specimens (p = 0,002 and p <0,001 respectively).

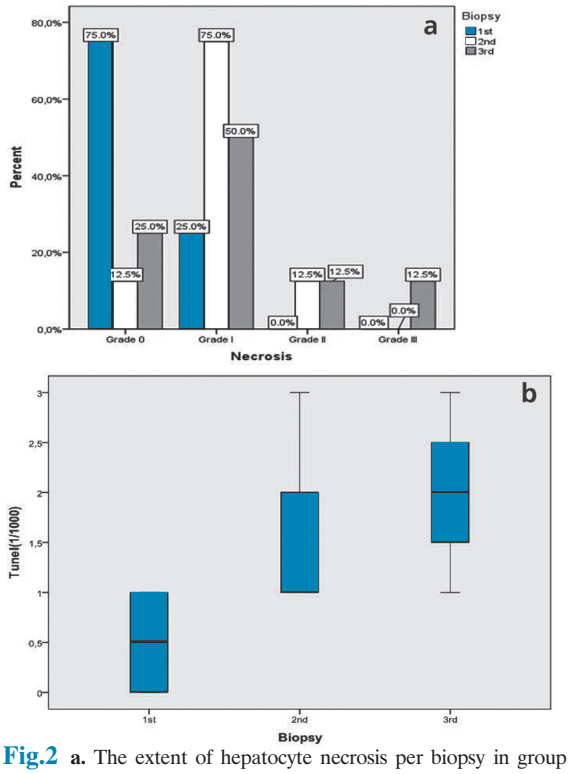

Fig.2 **a.** The extent of hepatocyte necrosis per biopsy in group IscPr. There was no significant change in the degree of necrosis between the biopsies. **b.** Apoptosis in the IscPr group. TUNEL values were significantly increased in the samples of the second and third biopsy specimens compared to the first biopsy specimens (p = 0,004 and p = 0,002 respectively).

Additionally, ischaemic preconditioning significantly alleviated the degree of hepatocyte necrosis and apoptosis, acting protectively against the ischaemia/reperfusion injury. These results may suggest that implementation of ischaemic preconditioning via pneumoperitoneum could be an interesting modality that warrants further studies in a clinical setting, such as in advanced laparoscopic liver procedures (hepatectomy) where alleviation of the degree of necrosis and apoptosis of the liver remnant is considered critical to the patient's outcome.

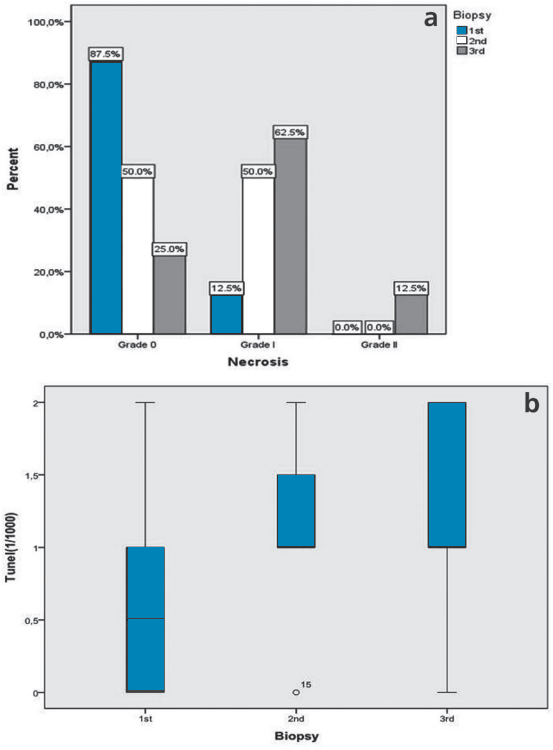

Fig.3 **a.** The extent of hepatocyte necrosis per biopsy in the control group. There was no significant change in the extent of hepatocyte necrosis between biopsies. **b.** Apoptosis in the control group. TUNEL values did not differ significantly between the specimens.

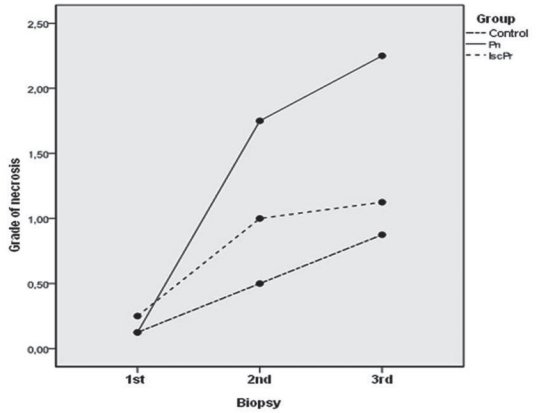

Fig.4 Differences in the extent of necrosis between groups. The degree of necrosis in the third biopsy specimens was significantly higher in the Pn group compared to the control group (p = 0,004) and the IscPr group (p = 0,009).

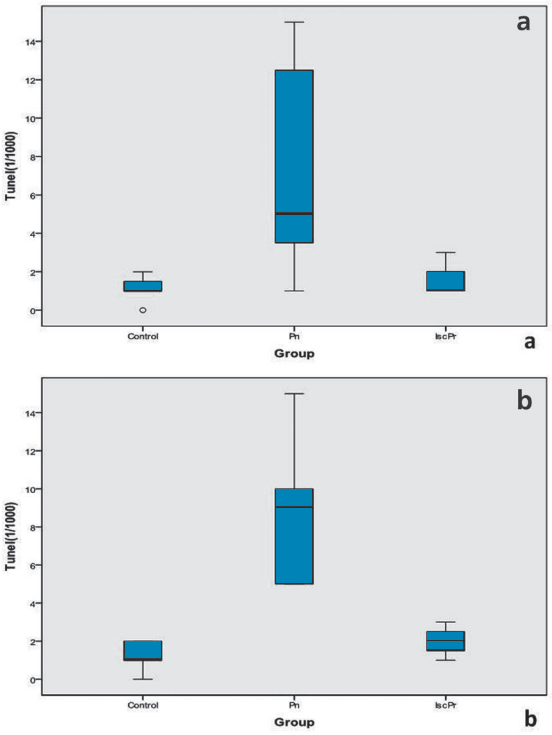

Fig.5 **a.** The TUNEL values (apoptosis) in the second biopsy specimens were significantly higher in the Pn group compared to those in the control group (p = 0,002) and the IscPr group (p = 0,008). **b.** The TUNEL values (apoptosis) in the third biopsy specimens were significantly higher in the Pn group compared to the control group (p <0,001), and the IscPr group (p <0,001).

Conflict of interest

The authors declare that they have no conflict of interest.

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Comments

Intra-abdominal hypertension (IAH), a rise in intra-abdominal pressure (IAP), above 12 mm Hg, acute or chronic, if not recognized and dealt appropriately can have deleterious consequences for the patient leading to abdominal compartment syndrome (ACS). The modern history of IAH/ACS begins in1980 but the advent of laparoscopic surgery in the 90's has surged clinical and experimental research.

Although the effects of IAH on liver haemodynamic has been studied in depth [1], the functional and structural alterations have lagged behind both at clinical and experimental level mainly due to methodological discordance. In this context the paper is a significant contribution to the subject of cellular response to acute IAH. Mogilner et al [2] have looked into hepatocyte damage from a different angle. This interesting effect needs further elucidation since apart from IAH it has ramifications to other fields of general and transplantation surgery.

Another important research aim of the study was the protective effect of liver preconditioning to sustain cell injury. In the translational research era we are living in this observation demands further research and clinical applications beyond liver transplantation as currently used. For example in surgical oncology, regional chemotherapy by the stop-flow technique takes advantage of ischemia to enhance the cytotoxic effect of the drug and maximize apoptosis.

Research into IAH may benefit critically ill patients and improve the dismal prognosis of the syndrome but it may as well be advantageous to other fields of surgery and therefore papers as this are welcomed.

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Η Εφαρμογή της Ισχαιμικής Προγύμνασης για Άμβλυνση της Ηπατικής Νέκρωσης και Απόπτωσης που Παρατηρείται στην Αυξημένη Ενδοκοιλιακή Πίεση

Πειραματική Μελέτη

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Περίληψη

Εισαγωγή: Είναι γνωστό ότι η Ενδοκοιλιακή Υπέρταση (ΕΚΥ) μπορεί να επηρεάσει δυσμενώς την ηπατική λειτουργία. Σκοπός της πειραματικής μας μελέτης ήταν να καταγράψουμε την νέκρωση και απόπτωση των ηπατοκυττάρων κάτω από συνθήκες ΕΚΥ και να δοκιμάσουμε την υπόθεση του κατά πόσο η εφαρμογή Ισχαιμικής Προγύμνασης (ΙΠ) μπορούσε να καταστήσει το ήπαρ ανθεκτικότερο ως προς τις συνέπειες αυτές.

Μέθοδοι: Μελετήθηκαν 3 ομάδες με 8 χοίρους η καθεμιά. Στην πρώτη ομάδα (Pn) εφαρμόσαμε πνευμοπεριτόναιο με αέριο ήλιο κι αυξήσαμε την Ενδοκοιλιακή Πίεση (ΕΠ) στα 30 mmHg για 3 ώρες, μετά την οποία η κοιλιά αποσυμπιέσθηκε. Ελήφθησαν βιοψίες ήπατος μέσω μικρής λαπαροτομής τόσο πριν την εγκατάσταση του πνευμοπεριτοναίου, όσο αμέσως μετά την αποσυμπίεση καθώς και μια ώρα μετά από αυτή. Στη δεύτερη ομάδα της ΙΠ (IscPr) η ΕΠ αυξήθηκε στα 25mmHg για 15 λεπτά μετά την οποία ακολουθήθηκε ισόχρονη περίοδος αποσυμπίεσης, ενώ στη συνέχεια εφαρμόσθηκε το πρωτόκολλο όπως στην πρώτη ομάδα. Χρησιμοποιήθηκε επίσης και μια ομάδα αναφοράς (control) στην οποία η ΕΠ παρέμεινε αμετάβλητη, ενώ ελήφθησαν βιοψίες στις ίδιες χρονικές περιόδους όπως στις ομάδες Pn και IscPr.

Αποτελέσματα: Η ηπατική νέκρωση κατά την φάση της αποσυμπίεσης ήταν σημαντικά υψηλότερη στην ομάδα Pn συγκρινόμενη με την ομάδα control ($p=0,004$), αλλά σημαντικά μικρότερη στην ομάδα IscPr σε σχέση με την ομάδα Pn ($p=0,009$). Η ηπατική απόπτωση κατά τη φάση της ΕΚΥ ήταν σημαντικά υψηλότερη στην ομάδα Pn συγκρινόμενη με την ομάδα control ($p=0,002$), αλλά σημαντικά μικρότερη στην ομάδα IscPr συγκρινόμενη με την ομάδα Pn ($p=0,008$). Μετά την αποσυμπίεση η απόπτωση ήταν σημαντικά υψηλότερη στην ομάδα Pn συγκρινόμενη με την ομάδα control ($p<0,001$) και σημαντικά μικρότερη στην ομάδα IscPr συγκρινόμενη με την ομάδα Pn ($p<0,001$).

Συμπεράσματα: Η ΕΚΥ είχε ως συνέπεια την αύξηση της ηπατικής νέκρωσης κι απόπτωσης. Επιπρόσθετα, η εφαρμογή Ισχαιμικής Προγύμνασης είχε ως αποτέλεσμα μικρότερο βαθμό ηπατικής νέκρωσης και σημαντικά μικρότερη απόπτωση.

Λέξεις κλειδιά

Ενδοκοιλιακή υπέρταση, Ισχαιμική προγύμναση, Ηπατική νέκρωση, Ηπατική απόπτωση.

- Β' Χειρουργική Κλινική και Α' Αναισθησιολογική Κλινική του Εθνικού Καποδιστριακού Πανεπιστημίου Αθηνών, Αρεταίειο Νοσοκομείο Αθηνών