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ORIGINAL ARTICLE

The impact of ischemic preconditioning on hemodynamic, biochemical and inflammatory alterations induced by intra-abdominal hypertension: an experimental study in a porcine model

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Abstract
Purpose Intra-abdominal hypertension (IAH) has several pathophysiologic implications on human organs and systems. The aim of this experimental study was to investigate whether ischemic preconditioning (IP), namely the application of IAH for a small period of time prior to establish pneumoperitoneum, can attenuate the hemodynamic, biochemical and inflammatory alterations observed during IAH.
Methods Twenty-four pigs were divided into three groups: group A (control group), group B (pneumoperitoneum of 30 mmHg) and group C (ischemic preconditioning, consisting of pneumoperitoneum of 25 mmHg for 15 min and subsequent pneumoperitoneum of 30 mmHg). Hemodynamic (central venous pressure, cardiac index, mean arterial pressure, heart rate, stroke volume index, systemic vascular resistance index, global end-diastolic index, intrathoracic blood index and extravascular lung water index), biochemical (serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvate transaminase (SGPT), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GT), urea and creatinine) and inflammatory (tumour necrosis factor-α, interleukin (IL)-6, IL-10 and C-reactive protein) parameters were measured.
Results (a) *Hemodynamics:* The increase of central venous pressure monitoring and heart rate and the decrease of cardiac index, mean arterial pressure, stroke volume index, global end-diastolic volume index and intrathoracic blood volume index with the establishment of pneumoperitoneum were attenuated by IP. Systemic vascular resistance index and extravascular lung water were not affected. (b) Urea significantly increased with the pneumoperitoneum. IP, however, attenuated this effect. Other biochemical parameters (SGOT, SGPT, ALP, γ-GT and creatinine) had a similar upward trend during IAH, which was reversed with IP. (c) *Inflammatory parameters:* CRP was increased with pneumoperitoneum, an effect that was attenuated with the application of IP. No significant differences were observed for interleukins.
Conclusions Ischemic preconditioning seems to attenuate the pathophysiologic alterations of several hemodynamic, biochemical and inflammatory parameters observed during IAH.

Keywords Abdominal compartment syndrome · Ischemic preconditioning · Laparoscopy · Reperfusion · Cytokines · Hemodynamic parameters

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Introduction

The implications of increased intra-abdominal pressure (IAP) have been reported 150 years ago and are currently thoroughly studied. Definitions, recommendations, pathophysiological sequelae, research guidelines as well as therapeutic algorithms have been published recently, clarifying this syndrome [1–6]. Intra-abdominal hypertension (IAH) is defined as any IAP beyond 12 mmHg [1–3], while abdominal compartment syndrome (ACS) is defined as IAP >20 mmHg, with or without abdominal perfusion pressure (APP) <60 mmHg that is associated with new organ dysfunction/failure [2, 3].

IAH induces several important pathophysiologic alterations in many systems, which are expressed by hemodynamic, pulmonary, biochemical and inflammatory changes. During intra-abdominal hypertension, preload is decreased and reflected by the decrease of global end-diastolic volume (GEDV) [7] and intrathoracic blood volume (ITBV) [7–9], while extravascular lung water (EVLW) is increased [10]. IAH also limits the contractility of the left ventricle which is expressed by reduced global ejection fraction (GEF) [9]. IAH is also accompanied by a reduction in lung compliance which subsequently leads to disturbances in the ventilation/perfusion ratio, pulmonary hypertension and cor pulmonale [11, 12].

Biochemical alterations reflect the pathophysiologic sequelae of IAH on several organs. Decline in renal blood flow and glomerular filtration rate [11, 13, 14], increase of intracranial pressure and reduction in cerebral and spinal perfusion pressure [3, 12, 15], gut hypoperfusion and bowel ischemia [16, 17] as well as congestion and ischemia of the liver which leads to hepatocellular dysfunction [18, 19] following IAH have been fairly well-studied. Moreover, during IAH, the organism responds defensively by cytokine production (interleukin (IL)-6, IL-10 and tumour necrosis factor (TNF-α)), whose overproduction is considered to promote the emergence of the multi-organ dysfunction syndrome (MODS) [20].

Another important concept is ischemic preconditioning (IP). IP is defined as the application of a brief or repeated periods of ischemia through which a tissue becomes resistant to the deleterious effects of prolonged ischemia and reperfusion [21]. Pathophysiologically, ischemic reperfusion injury (IRI) develops during reperfusion of an ischemic tissue during which an imbalance is created between NO and the oxygen-free radicals, i.e. decrease of NO action and increase of peroxide action. Furthermore, inflammatory mediators are released (platelet activated factor, TNF), which in turn enhance the accumulation of leukocytes [22]. This cascade of reactions following IRI also activates inflammatory cells in distant tissues [23–25] with subsequent micro-vascular damage and the development of MODS [25–27]. IP is responsible for the removal of free radicals which are followed by inflammatory mediators as mentioned above, so IP seems to have a protective role against IRI [21].

Taking into consideration that IAH produces conditions of tissue ischemia, we tested the hypothesis whether IP can attenuate the hemodynamic (preload, afterload and cardiac contractility parameters), biochemical (serum glutamic pyruvate transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GT), urea and creatinine) and inflammatory (TNF-α, IL-6, IL-10 and CRP) changes observed during increased IAP. This may have further clinical implications in advanced laparoscopic surgical procedures.

Material and methods

The study was performed in the Experimental Laboratory 'Kostas Tountas' of the Second Department of Surgery at the Aretaieion University Hospital (Athens School of Medicine, National Kapodistrian University of Athens). Twenty-four young female piglets with a mean weight of 25 kg (range 20–33 kg) and mean height of 95 cm (range 80–104 cm) were studied. In addition, two animals were initially used as pilots where IAP of 20 mmHg and IP of 15 mmHg were applied. Unfortunately, no changes of the parameters under study were observed. Thus, we decided to apply higher pressures (IAP 30 mmHg and IP 25 mmHg) in order to augment possible changes to the parameters studied.

The animals were divided in the following groups: eight where the control group (group C), in another eight, pneumoperitoneum (P) 30 mmHg was applied (group P) and to the remaining eight, P (30 mmHg) and IP (25 mmHg) were applied (group IP). All animals where fasted for 12 h before the experiment, with free access to water.

Anaesthesia and instrumentation

Pre-medication included i.m. administration of ketamine 2 mg/kg and midazolam 2 mg/kg, 20–30 min before anaesthesia induction. The pre-medication allowed the easy transfer of the animal to the operating table where anaesthesia was induced. Posterior auricular vein was catheterized (Venflon 22 G catheter) and basic monitoring (electrocardiogram, oxygen saturation, non-invasive pulse and arterial pressure monitoring and rectal temperature) was applied.

Following pre-oxygenation, anaesthesia was induced with midazolam 0.2 mg/kg, fentanyl 5–10 γ/kg and

thiopental 10 mg/kg. The animals were intubated using a straight laryngoscope blade with a 5–6-Fr endotracheal tube, depending on the anatomy of the animal. A nasogastric tube was inserted to drain the stomach. After intubation, a bolus injection of vecuronium 0.3 mg/kg was given and maintenance of anaesthesia consisted of sevoflurane 1–1.5 MAC, vecuronium 0.4 mg/kg/h and fentanyl 12 γ/kg/h. The animal was mechanically ventilated (Drager Sulla 808V, type Ventilog-2, Drager, Berlin, Germany) using the following parameters: VT, 14 ml/kg; freq., 20/min; with an O_2/air ratio, 2:3. Normal saline and colloids in an infusion rate 20 ml/kg/h were given.

The right internal jugular vein and common carotid artery were exposed surgically. The right internal jugular vein was catheterized with a double lumen catheter (Arrow 14G and 18G) which was used for central venous pressure monitoring (CVP) and for blood sampling. A PiCCO pulsiocath catheter (PV2014L22, diameter, 4 Fr; length, 22 cm, Pulsion Medical Systems AG, Stahlgruberring 28, 81829 Munich, Germany) was introduced into the right common carotid artery for continuous monitoring of the arterial pressure. Cardiac index (CI), mean arterial pressure (MAP), heart rate (HR), stroke volume index (SVI), systemic vascular resistance index (SVRI), global end-diastolic volume index, intrathoracic blood volume index, extravascular lung water index, were measured by the PULSION PiCCO plus device (Pulsion Medical Systems AG, Stahlgruberring 28, 81829 Munich, Germany.)

Serum concentrations of biochemical parameters were determined using the following enzymatic commercial kits (‘biosis’—Biotechnological Applications, Athens, Greece): ALP (DGKC method), SGOT (International Federation of Clinical Chemistry (IFCC) method), SGPT (IFCC method), γ-GT (SZASZ method), urea (urease/GLDH method) and creatinine (Jaffe's kinetic method). The inflammatory parameters that were studied included IL-6, IL-10, TNF-α and CRP. IL-6 and TNF-α were chosen due to their intense proinflammatory action and their ability to induce acute reactive proteins such as CRP. IL-10 was chosen because it has a great anti-inflammatory action and its receptor uses similar signalling mechanisms for transcription with IL-6 receptors. [28]. Thus, IL-6, IL-10 and TNF-α measurements offer a reliable description concerning the inflammatory status of our porcine model [29]. The parameters quantitatively determined by ELISA include: IL-6 Porcine kit (R&D Systems Cat. No. P6000), IL-10 Porcine kit (R&D Systems Cat. No. P1000), TNF-α Porcine kit (R&D Systems Cat. No. PTA00) and CRP Porcine kit (ALPCO Diagnostics Cat. No. 41-CRPPO-E01). All samples were analysed at the Laboratory of Experimental Surgery and Research of the Medical School of Athens (Athens, Greece).

Experimental phases

After instrumentation, the hemodynamic parameters were measured (via PiCCO), and blood sampling and blood samples were taken (phase T1). In group P, pneumoperitoneum was established using helium via an infraumbilically inserted Veress needle. Intra-abdominal pressure was gradually increased to 30 mmHg and maintained stable for 3 h. These experimental settings where chosen to simulate IAH grade IV. Based on the current knowledge [2], we hypothesised that under these conditions, a wide range of the biochemical and inflammatory changes of the syndrome will be revealed. Hemodynamic measurements and blood samples were repeated at 2 h (phase T2) and 3 h (phase T3). One hour after abdominal desufflation, the same measurements were conducted (phase T4). In group IP, establishment of pneumoperitoneum of 25 mmHg for 15 min was followed by abdominal desufflation for another 15 min, after which pneumoperitoneum of 30 mmHg for 3 h was induced. Measurements were obtained in the same time periods as in group P. In the control group, neither pneumoperitoneum nor IP were applied. Blood samples were obtained in similar time periods as in the other groups.

Based on results of previous research showing that increased IAP provokes similar conditions to ischemia in many organs [1, 2], we hypothesised that a brief period of application of pneumoperitoneum will act as IP in a same way that brief artery occlusion is used to produce IP in cardiac surgery [21]. We arbitrarily used a pneumoperitoneum of 25 mmHg for 15 min followed by desufflation for another 15 min as a method of IP. Studies used pneumoperitoneum of 10 or 15 mmHg of different duration (5, 10 or 15 min) as IP have been reported in rats [30–33]. We are not aware of similar studies using pigs as experimental animals.

Study end points

The study end point was to observe the role of ischemic preconditioning on the effects of IAH and IP on hemodynamics (CVP, CI, MAP, HR, SVI, SVRI, GEDI, ITBI and EVLWI), biochemical parameters (SGOT, SGPT, ALP, γ-GT, creatinine and urea) and inflammatory factors (IL-6, IL-10, TNF-α and CRP).

Statistical analysis

Statistical analysis of all parameters was conducted using the statistical software SPSS 11.0 (SPSS Inc., Chicago, IL, USA). Initially, we analysed the rate of percentage change of each indicator during T2, T3 and T4 experimental phases

in comparison to T1 (indicated as T1–2, T1–3 and T1–4, respectively). To perform the comparison of the average changes among the different groups and different times, an analysis of variance was conducted. Differences among different groups and different times were performed, with Tukey's multiple comparisons test. The statistical significant level of $p=0.05$ was utilised.

Results

Hemodynamic factors

Preload parameters IAH increased CVP, an effect which is attenuated by IP (Fig. 1a–c). GEDI had a decreasing trend in the P group, which was attenuated in the IP group. ITBI was

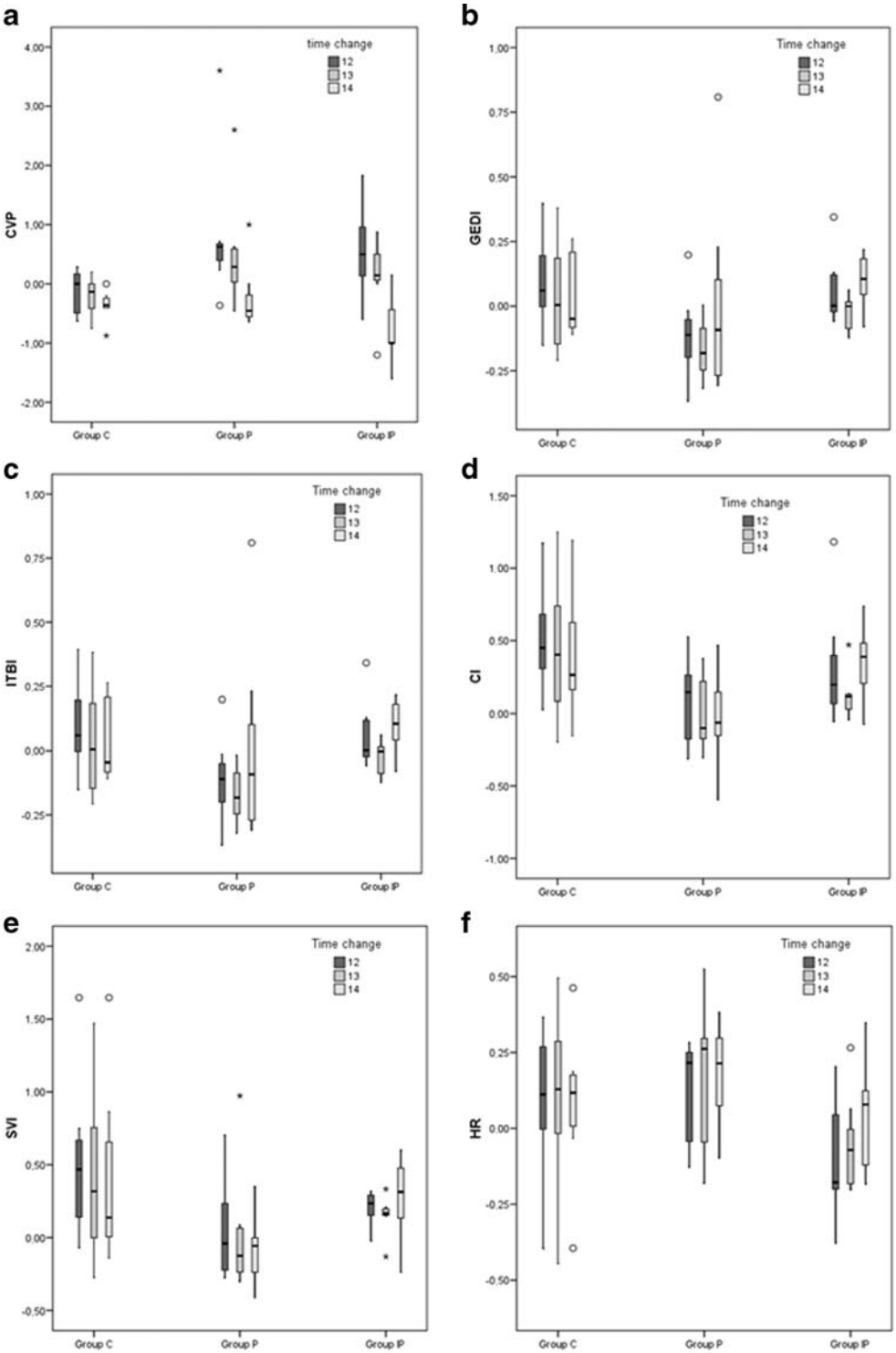

Fig. 1 Schematic presentation of the rates of percentage changes of hemodynamic parameters as box plots with median, normal distribution and min/max values: central venous pressure (*CVP*), global end-diastolic volume index (*GEDI*), intrathoracic blood volume index (*ITBI*), cardiac index (*CI*), stroke volume index (*SVI*) and heart rate (*HR*). *First box* (*black*) indicates rate of percentage changes from baseline phase (T1) to phase T2; *second box* (*grey*) indicates rate of percentage changes between experimental phases T1 to T3; and *third box* (*white*) indicates rate of percentage changes between phases T1 and T4. *C* is the control group, *P* is the pneumoperitoneum group and *IP* is the ischemic preconditioning group

statistically significantly decreased (T1–3, $p=0.043$) which was attenuated in the IP group.

Cardiac contractility and frequency CI and SVI had a decreasing trend in the P group which was attenuated in the IP group (Fig. 1d–f). HR had an increasing trend which was similarly attenuated in the IP group.

Afterload SVRI and EVLW: There were no significant differences between experimental phases and groups.

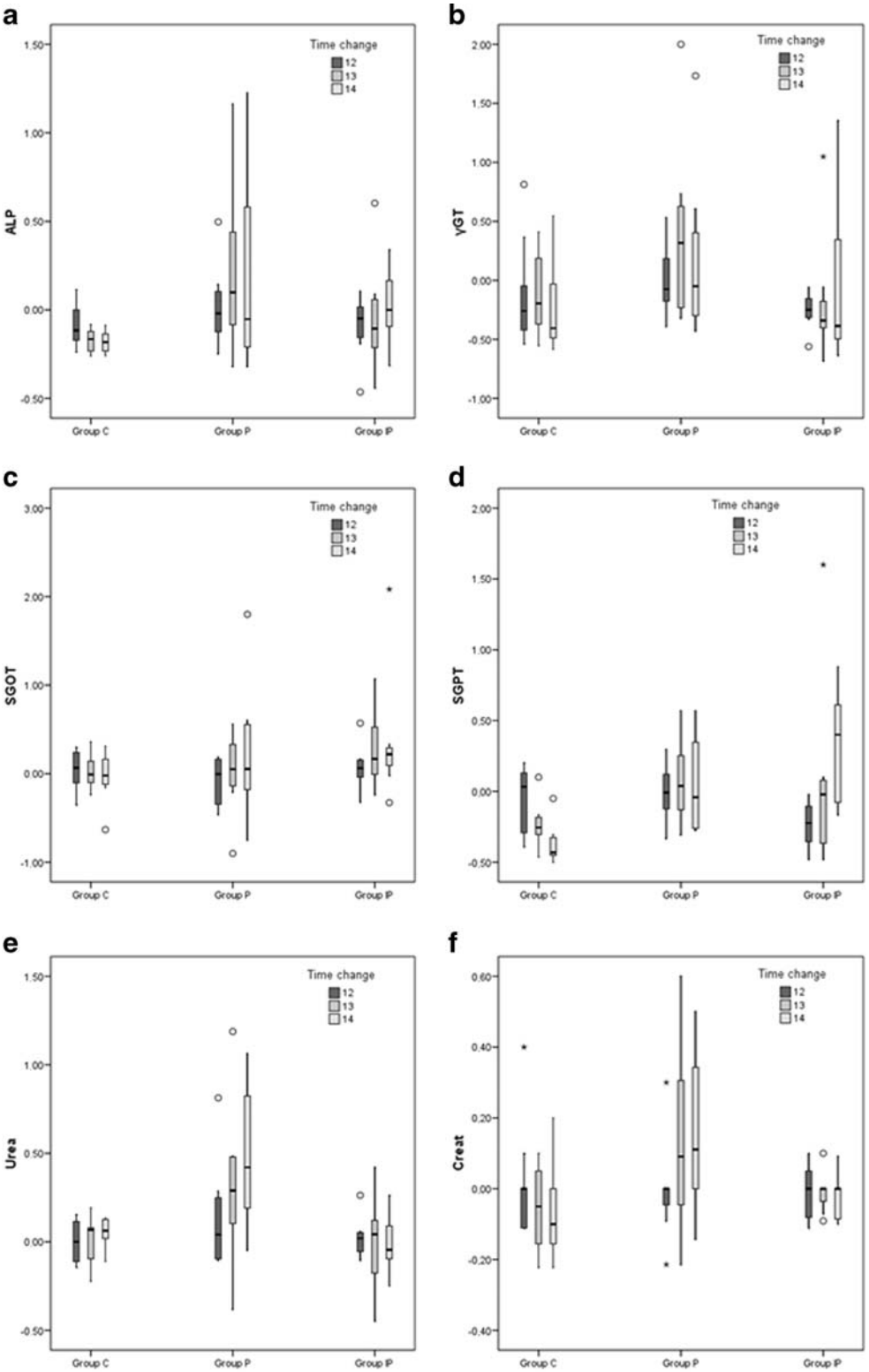

Fig. 2 Schematic presentation of the rates of percentage changes of biochemical parameters as box plots with median, normal distribution and min/max values: alkaline phosphatase (*ALP*), γ-glutamyl transpeptidase (*γ-GT*), serum glutamic oxaloacetic transaminase (*SGOT*), serum glutamic pyruvate transaminase (*SGPT*), urea and creatinine (*Creat*). *First box* (*black*) indicates rate of percentage changes from baseline phase (T1) to phase T2; *second box* (*grey*) indicates rate of percentage changes between experimental phases T1 to T3; and *third box* (*white*) indicates rate of percentage changes between phases T1 and T4. *C* is the control group, *P* is the pneumoperitoneum group and *IP* is the ischemic preconditioning group

Biochemical parameters

ALP, γ-GT and SGOT An increasing tendency in group P in comparison to group C was observed in all experimental phases, which was attenuated by IP (Fig. 2a–c).

SGPT After abdominal desufflation (phase T4), SGPT was significantly increased in the P group (T1–4, p=0.002), an effect that was attenuated in the IP group (Fig. 2d).

Urea Similarly, urea was significantly increased in the P group (T1–4, p=0.011), an effect significantly reduced by IP (T1–4, p=0.005) (Fig. 2e).

Creatinine Creatinine was significantly increased in the P group (T1–4, p=0,029), an effect attenuated by IP (Fig. 2f).

Inflammatory factors

CRP Pneumoperitoneum increased CRP during all experimental phases, an effect that was attenuated by IP (Fig. 3a).

TNF-α, IL-6 and IL-10 There are no significant differences between experimental phases and groups (Fig. 3b–d).

Discussion

In the present report, we studied the impact of IAH on hemodynamic, biochemical and inflammatory parameters and looked at the possible protective effects of ischemic preconditioning against the hemodynamic instability, the renal and hepatic dysfunction and the inflammatory reaction induced by IAH. The main results of our experimental study were as follows: IAH resulted in hemodynamic compromise, by reducing the preload and cardiac contractility and increasing heart rate; liver and renal function was compromised as well, reflected by the relative increase in biochemical tests, an effect that was sustained even after abdominal desufflation; and C-reactive protein was increased throughout all experimental phases. No differences concerning the other inflammatory mediators (TNF-α, IL-6 and IL-10)

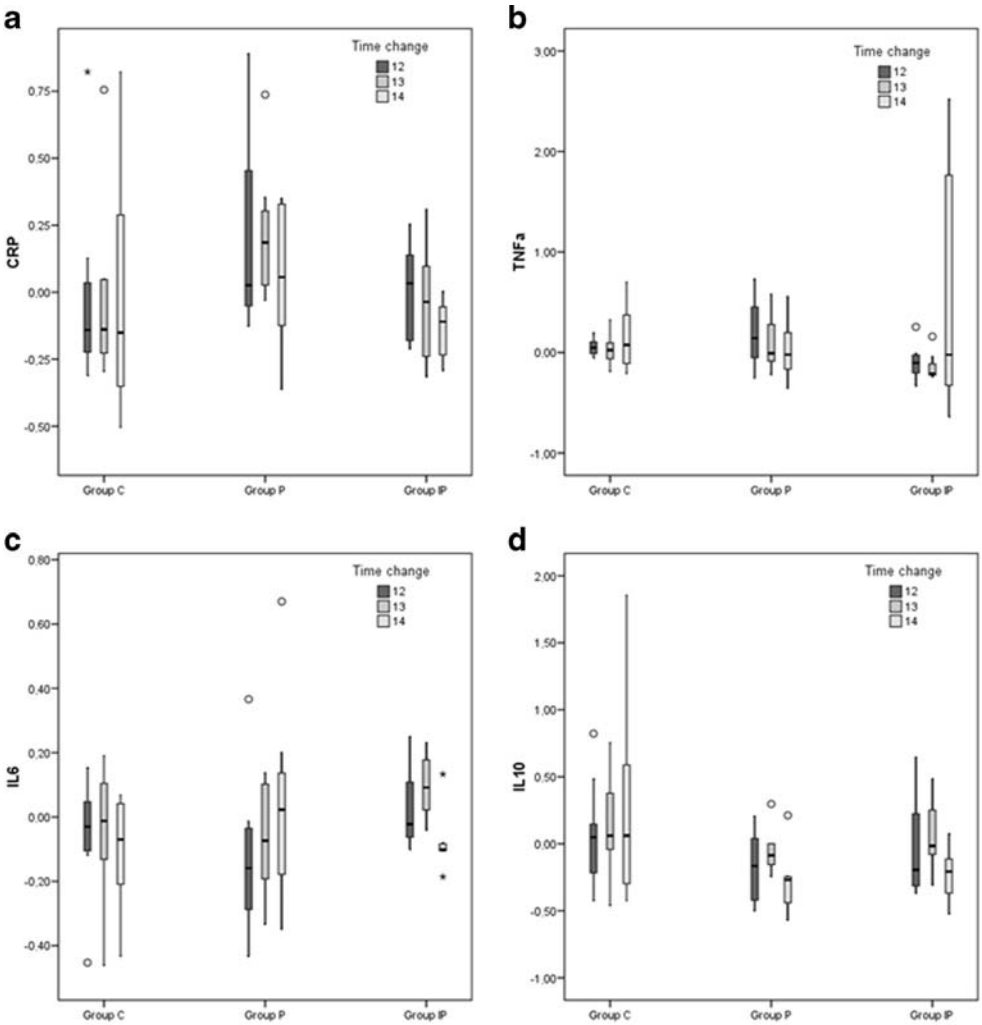

Fig. 3 Schematic presentation of the rates of percentage changes of inflammatory markers as box plots with median, normal distribution and min/max values: C-reactive protein (*CRP*), tumour necrosis factor alpha (*TNF-α*), interleukin-6 (*IL-6*) and interleukin-10 (*IL-10*). *First box* (*black*) indicates rate of percentage changes from baseline phase (T1) to phase T2; *second box* (*grey*) indicates rate of percentage changes between experimental phases T1 to T3; and *third box* (*white*) indicates rate of percentage changes between phases T1 and T4. *C* is the control group, *P* is the pneumoperitoneum group and *IP* is the ischemic preconditioning group

were observed; IP attenuated all these effects, possibly by exerting a protective action against IAH-induced changes.

The pathophysiological hemodynamic alterations during IAH include the reduction of the preload, which is expressed by the GEDV [7] and the ITBV [7–9], reduction of cardiac contractility expressed by the GEF [9] and increased systemic vascular resistances expressed by SVRI [10]. The hemodynamic factors studied in this experimental study exhibit a similar change, which appear to be tempered by the IP. The increased heart rate observed is possibly a result of the reduced stroke volume (SV). However, this effect could not compensate the reduction of SV, so a decreased CI was observed. IP attenuated all these hemodynamic alterations.

The liver and kidneys are the organs most frequently affected by increased IAP in experimental and clinical studies, as well as in laparoscopic procedures [34–38]. Pathophysiologically, IAH reduces both the hepatic artery and portal perfusion [36]. Also, the kidneys can suffer the devastating consequences of the constricted renal blood flow and IRI after prolonged pneumoperitoneum [35, 37, 38]. According to its definition, IP renders tissue resistance under conditions of ischemia as well as to IRI [39]. The IP has been particularly studied in the heart cell in which brief episodes of cardiac ischemia render the myocardium more resistant to subsequent prolonged periods of ischemia. The liver [40] and kidney [41, 42] may benefit from this process when preceded by a brief interruption in their perfusion. In our experimental study, the IP appears to prevent the increase in liver enzymes caused by the IAH. Moreover, the effect of the IP in renal function appears remarkable. Specifically, urea and creatinine are increased significantly especially after abdominal desufflation, despite the adequate animal hydration (prior free access to water and supplementary i.v. infusion during the experiment). However, IP appears to attenuate this effect. Similar results have been reported elsewhere. In one study, preconditioning consisting of 10 min of pneumoperitoneum of 15 mmHg decreased the oxidative stress induced by sustained pneumoperitoneum in the plasma, liver and kidney of rats. Plasma ALT as well as plasma, liver and kidney malondialdehyde (MDA) levels were measured. Preconditioning significantly limited liver and kidney injury after prolonged pneumoperitoneum in rats [32].

Besides the above-mentioned effects of increased IAH, studies also indicate the involvement of cytokines in the pathophysiology of this syndrome [43, 44]. In this experimental study, IAH increased CRP, an effect attenuated by the application of IP. Cytokines TNF-α, IL-6 and IL-10, however, did not show significant differences during IAH and IP. Despite our results, in a recent experimental study using intra-abdominal pressure of 20 mmHg for 90 min in rats, elevated levels of IL-1β and IL-6 were observed [20]. In the same study, increased levels of TNF-α were observed after desufflation, an effect justified by the ischemia–reperfusion injury occurring in a tissue subjected to prolonged ischemia. In another experimental study, blood and peritoneum MDA (a factor of oxidative stress), TNF-α and IL-6 in rats decreased in the ischemic preconditioning group in comparison with the pneumoperitoneum group. Ischemic preconditioning was defined as 10 min of pneumoperitoneum with 15 mmHg of intra-abdominal pressure followed by 10 min of deflation. IP could be effective in reducing ischemic insult associated with laparoscopy [33].

The fact that some of the results of the present study are not statistically significant compared to the studies mentioned above cannot be easily interpreted. Several inherent limitations could possibly explain these discrepancies. A porcine model of IP using IAH has not yet been reported in the current literature. Thus, arbitrarily parameters were used taking in account similar studies performed in other animal models (i.e. rats) [30–33]. Possibly, the levels of IAP (25 mmHg), as well as the duration (15 min), are critical factors influencing our results. Another limitation is the small sample used and perhaps the duration of the pneumoperitoneum. However, further studies are necessary in order to standardise a porcine model for IP using pneumoperitoneum. An IP approach may exert a beneficial effect prior to advanced laparoscopic procedures where pneumoperitoneum sometimes is high and may last for extended periods.

Conclusions

Ischemic preconditioning tends to attenuate the pathophysiologic alterations of several hemodynamic, biochemical and inflammatory parameters observed during IAH. However, these conclusions should be further evaluated and studied in order to draw statistically significant results. The effect of IP during IAH may probably have further clinical implications especially in elderly or patients with impaired cardiac, renal or hepatic function undergoing laparoscopic procedures.

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Conflicts of interest None.

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Ethical standards

This study conforms to our institutional standards and is under the appropriate license of the veterinary authorities and in adherence to National and European regulations for animal studies.