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Experimental Article

Respiratory mechanics in a porcine model of abdominal hypertension with or without sepsis

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ABSTRACT

Respiratory mechanics in a porcine model of abdominal hypertension with or without sepsis.

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Increased Intraabdominal Pressure (IAP) is common in critical care patients and has detrimental effects on organs and systems. Several mechanisms and causes are involved in its pathogenesis. The aim of the present study was to investigate and record IAP effects alone and in combination with sepsis on respiratory mechanics. Sixteen male pigs were included in the study, which were randomized in two groups of 8 pigs (Group A & B). After baseline measurements, IAP increased in

both groups by Helium insufflation to 25mmHg and remained elevated throughout the study period. In Group B, sepsis was induced after 60min by intravenous lipopolysaccharide (LPS) administration. Recorded parameters included PIP_{AW}, PIP_{ES}, $EIP_{AW,}$ EIP_{ES}, $Pmean_{AW}$, $Pmean_{ES}$, $PEEP_{AW}$, $PEEP_{ES,}$ $C_{RS,}$ C_{CW}, C_L, R_{inspRS}, R_{expRS} R_{inspCW}, R_{expCW}, Vexp and were measured at baseline and every 20min for 3hrs. Airway pressures in Group A (PIP_{AW}, EIP_{AW}, $Pmean_{AW}$) increased after IAP elevation but returned to their baseline values after IAP normalization. In Group B airway pressures increased even further after LPS administration and decreased after IAP normalization but they never reached their baseline values. On the contrary esophageal pressures (PIP_{ES}, EIP_{ES}, $Pmean_{ES}$) showed similar alterations in both groups. PEEP did not change in any of the study groups. Respiratory system compliance decreased in both groups and returned to baseline values only in Group A. Chest wall compliance showed similar alterations in both groups. Lung compliance decreased after IAP increase in both groups and showed a further decrease after LPS administration in Group B, which remained after IAP normalization. Respiratory system inspiratory resistances increased only in Group B, whereas respiratory system expiratory resistances increased in both groups. Chest wall inspiratory resistances did not show any alterations. Our study results showed that the effects of IAP increase are reversible, whereas the effects of coexisting sepsis remain even after IAP normalization.

Keywords: Mechanics of Respiratory system, abdominal hypertension, abdominal compartment syndrome

Abbreviations: *PIP_{AW}: Peak Inspiratory Airway Pressure (cmH_2O), PIP_{ES}: Peak Inspiratory Esophageal Pressure (cmH_2O), EIP_{AW}: End Inspiratory Airway Pressure or (plateau pressure - Pplat) (cmH_2O), EIP_{ES}: End Inspiratory Esophageal Pressure (cmH_2O), PEEP: Positive End Expiratory Pressure (cmH_2O), $Pmean_{AW}$: Mean Airway Pressure (cmH_2O), $Pmean_{ES}$: Mean Esophageal Pressure (cmH_2O), C_{RS}: Compliance of the Respiratory System (ml/cmH_2O), C_{CW}: Compliance of the Chest Wall (ml/cmH_2O), C_L: Compliance of the Lung (ml/cmH_2O), $Rinsp_{RS}$: Inspiratory Resistances of the Respiratory System ($cmH_2O/L/min$), $Rinsp_{CW}$: Inspiratory Resistances of the Chest Wall ($cmH_2O/L/min$), $Rexp_{RS}$: Expiratory Resistances of the Respiratory System ($cmH_2O/L/min$), $Rexp_{CW}$: Expiratory Resistances of the Chest Wall ($cmH_2O/L/min$), Vexp: Expiratory Flow (L/min).*

INTRODUCTION

Intraabdominal pressure (IAP) increase and the related Abdominal Compartment Syndrome (ACS) are common in critical care patients, are of high clinical importance and several mechanisms and causes are involved in their pathogenesis. Intraabdominal Hypertension (IAH)

has detrimental effects on organs and systems both in and outside the abdominal cavity. IAH and ACS have been previously described and have been recognized as important morbidity and mortality factors in medical and surgical critically ill patients. IAH and ACS can coexist even without primary intraabdominal underlying pathology and both contribute to increased morbidity and mortality whether or not they are the cause or the result of a clinical situation.

The aim of the present study was to investigate and record IAP effects alone and in combination with sepsis on respiratory mechanics.

Intraabdominal Hypertension

The abdominal cavity could be defined as a closed compartment, partially rigid (due to the spinal column and the pelvis) and partially flexible due to the abdominal wall and the diaphragm. In a normal daily setting, IAP is affected by diaphragm and ribs movement, abdominal muscle contraction and bowel content. Therefore, IAP increases during inspiration (diaphragm contraction and downward movement) and decreases during expiration[1].

IAP is normally zero (0mmHg) or slightly negative in patients with spontaneous breathing, although it can increase in obese, cirrhotic patients, in patients with ascites and in pregnant women. In patients under positive pressure ventilation IAP is slightly positive due to the transmission of the positive pleural pressure to both sides of the diaphragm[2,3]. After abdominal surgery, IAP ranges between 3 to 15mmHg and this increase is attributed to the postsurgical visceral edema and the abdominal wall compliance decrease because of pain[4].

According to the guidelines of the World Society of the Abdominal Compartment Syndrome [WSACS] IAH is defined by a sustained or repeated pathological elevation in IAP equal to or more than 12 mmHg[5-7].

Moreover, IAH is graded from I to IV based on the IAP level:

Grade I: IAP 12-15 mmHg

Grade II: IAP 16-20 mmHg

Grade III: IAP 21-25 mmHg

Grade IV: IAP>25 mmHg.

Effects of intraabdominal pressure on respiratory function

Thorax and abdomen are in a constant interaction since they are separated by the diaphragm. It has been proven in both experimental and clinical studies that a significant percentage of IAP (in average a 50%) is transmitted to the chest[8]. This interaction is of great clinical importance in critically ill patients in the Intensive Care Unit (ICU) and its management is a real challenge.

IAP increase pushes the diaphragm upward and causes an increase in the intrapleural and intrathoracic pressures[9,10]. This results in a decrease of respiratory system compliance mainly due to reduction of the chest wall compliance[11].

IAP increase causes a complete deterioration of respiratory mechanics[11,12] lung volume reduction and compression of the lungs. All of the

respiratory pathophysiological alterations which are caused by IAP increase are directly associated with the IAP level, are reversed by IAP normalization and resemble restrictive pulmonary disease[13-16].

Sepsis

Sepsis is a life threatening organ dysfunction, which is caused by a dysregulated host response to infection[17,18]. Sepsis can be caused both by hospital and community acquired infections. The most frequent cause of sepsis is pneumonia followed by intraabdominal and urinary tract infections[19].

Sepsis has detrimental effects on several organs and systems and is a significant risk factor for ARDS.

Respiratory mechanics

Respiratory mechanics refer to the physical properties of all anatomical structures and components of the respiratory system, the related mathematical formulas and the way they change during breathing and more specifically during alterations of lung volumes and thoracic dimensions. Mechanical ventilation works by delivering flow and positive airway pressure aiming at providing a given tidal volume. Under general anesthesia and controlled mechanical ventilation (CMV), the positive airway pressure is usually applied via the endotracheal tube and is intermittent positive (IPPV)[20].

Monitoring and recording of respiratory parameters (flow, pressure and volume) is considered as a necessary prerequisite for the safe and efficient achievement of all before mentioned goals but also for the study of respiratory mechanics[21].

Pressures are measured by specific devices (manometers or pressure sensors) and regardless of the specific location of the measurement they are called airway pressures (P_{AW}). In essence, pressure measurements at a specific location reflect changes per unit of time distal to the location[22].

In addition to that, monitoring and recording of other pressures such as esophageal and gastric, their calculated difference and transdiaphragmatic pressures are considered useful in specialized clinical and experimental settings[23-26].

Flow is measured by specific devices (flow meters) placed either in the inspiratory limb of the breathing circuit or more often in the expiratory limb. Lung volume measurement during mechanical ventilation is usually performed by using a specific formula to convert the electrical signal which flow creates[27,28].

The specific location in the ventilator-lung circuit, at which measurements of respiratory mechanics are made, has an impact on measured values especially on pressure values[21]. Namely, measurements obtained at the airway end of the circuit (proximal airway-airway opening) reflect respiratory system mechanics (RS), measurements obtained via an esophageal catheter with a balloon (EB) reflect chest wall mechanics under MV and muscle relaxants and finally

lung mechanics are calculated indirectly during ventilation[21].

Diagrams of respiratory parameters (pressure-volume graphs, flow-volume graphs and pressure-flow graphs) comprise the same information, which can be also derived from the simple curves of each of the parameters per unit of time. However, diagrams allow better analysis and interpretation of clinical data due to the fact that is easy to notice and to understand the information that is displayed compared to a couple of simple waveforms. Those diagrams are the graphical display of specific mathematical equations and formulas of respiratory parameters and reflect respiratory mechanics[29-31].

The pressure-volume diagram is a graphic display of the equation C=V/P (Compliance=Volume in ml / Pressure in cmH_2O) and the pressure-flow diagram is a graphic display of the equation R=P/V (Resistance= Pressure in cmH_2O / flow in $L \cdot sec^{-1}$)[32,33].

Those two derived parameters namely compliance and resistance, which are depicted on diagrams, are calculated by the slope of the corresponding lines on the curves and are easily visualized by the shape of the waveforms[21,34].

MATERIAL AND METHODS

This experimental study was conducted in the animal laboratory at AHEPA University Hospital Thessaloniki after obtaining the appropriate approval by the ethics committee for the use of experimental animals of the National Board on Animal Care and Use. Sixteen Landrace pigs were included in the study (age: 3 months and BW: 25kg). Animals were randomized in two groups of eight, Group A and B. After obtaining baseline measurements, IAH was induced by Helium insufflation in both groups (IAP was maintained at 25mmHg throughout the study). After 60min, sepsis was induced in Group B by intravenous lipopolysaccharide (LPS) admini stration.

Premedication, induction and maintenance of general anesthesia were identical in both groups and elective surgical tracheostomy was performed in all animals for definitive airway management. The endotracheal tube, which was used, had a diameter of 6,5mm with cuff (Portex-Blue Line HV tracheostomy tube) and the breathing circuit was elastic with rings (Taema-Air Liquide). A straight M/F 22/14 connector with a Luer Lock output was placed at the end of the Y piece of the breathing circuit and was used for the connection of the proximal airway pressure measurement (Paw) line, which was a rigid extension F/F tube.

Throughout the whole study period controlled mechanical ventilation under general anesthesia with muscle relaxants was applied. For that purpose Ceasar Ventilator, Taema-Air Liquide was used. Ventilation settings included constant inspiratory flow of 20L/min (Vinsp), inspiratory tidal volume of 10-12ml/kg BW (V_{TI}), respiratory rate of 12-15/min (RR), Positive Endexpiratory Pressure of $5cmH_2O$, inspired oxygen

concentration of 50% (FiO_2), inspiration to expiration ratio 1:2 (T_I/T_E) and duration of zero flow during inspiration equal to 10% of the total inspiratory time.

IAP increase was achieved by Helium insufflation via a device used in laparoscopic surgery for pneumoperitoneum induction (Wisap, Semm System, Sauerlach Germany).

Sepsis was induced by intravenous administration 100μg/Kg LPS within 20 min, via an electronic infusion pump (ANNE, Abbott Laboratories LTD, North Chicago, IL, USA).

After initiation of general anesthesia with muscle relaxants and application of mechanical ventilation, data of respiratory parameters were obtained and recorded in real time under BTPS conditions (Body Temperature Pressure Saturated). Data was collected in the form of numerical values, simple waveforms of pressure, volume and flow per unit of time and complex diagrams of pressure-volume, pressure-flow and flow-volume.

Airway pressures, PIP_{AW}, EIP_{AW} and $Pmean_{AW,}$ were measured at the corresponding port of the Y connector and reflected respiratory system alterations.

Esophageal pressures, PIP_{ES}, EIP_{ES} and $Pmean_{ES}$, were measured via an esophageal balloon catheter at the Ext port of the ventilator and reflected chest wall alterations. $Pmean_{AW,}$ $PEEP_{AW,}$ $Pmean_{ES}$ and $PEEP_{ES}$ measurements were based on the corresponding indicators diplayed by the ventilator.

End - inspiratory pressures were measured by end inspiratory prolongation of zero flow and end - expiratory pressures were measured by end expiratory prolongation and occlusion maneuver for auto PEEP detection.

Inspiratory and expiratory flows were measured via a ventilator flow sensor by using the hot wire method.

Inspiratory (Vinsp) and expiratory volumes (Vexp) were recorded by using the exact same set up and methodology.

Minute ventilation, RR and FiO_2 were recorded automatically by the ventilator.

Both the waveform and the corresponding numerical data of end expiratory carbon dioxide ($ETCO_2$) were recorded continuously by a capnograph (Capnograph Datex).

A specific software based on the equation $C = \Delta V/\Delta P \Rightarrow C = V_{Ti}$ /EIP – PEEP was used by the ventilator to record the pressure-volume diagram (Fig. 1). The slope of the line, which passes through the end- inspiratory and end - expiratory points (EIP and PEEP) on the curve was used to measure compliance (C). Respiratory system compliance was calculated based on EIP_{AW} and $PEEP_{AW}$ and chest wall compliance based on EIP_{ES} και $PEEP_{ES}$ respectively. Lung compliance was calculated by the following equation$1/C_{RS} = 1/C_{CW} + 1/C_L$. Compliance measurements were obtained at zero flow conditions and refer to the static compliance C_{Static}.

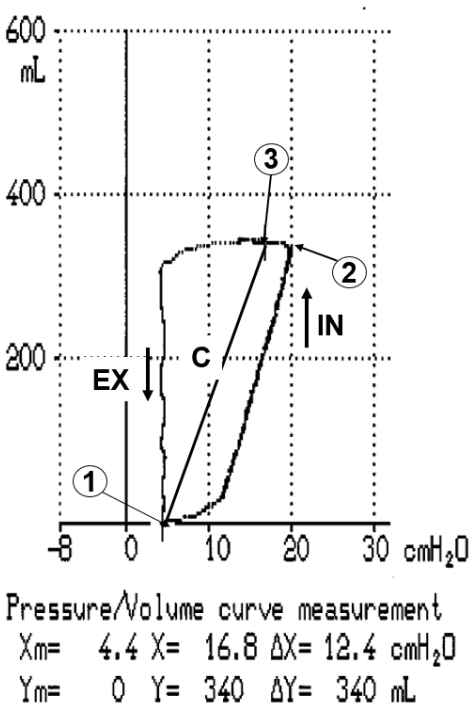

Figure 1. Pressure-Volume diagram under controlled mechanical ventilation.

Paw is depicted on the horizontal axis and volume V on the vertical one. Inspiration starts at point (1), which corresponds to PEEP= =5cmH_2O, continues counterclockwise and passes through point (2) which corresponds to PIP and terminates at point (3) which is EIP. The slope of the line that passes through PEEP and EIP represents compliance of the system.

Pressure-flow diagram [R = ΔP / ΔV] was used for resistance measurement. For inspiration, resistance was calculated by the slope of the line that passes through PIP and EIP points on the inspiratory limb of the diagram [R = (PIP – EIP) / V] and for expiration by the slope of the corresponding line on the expiratory limb of the diagram. PIP_{AW} EIP_{AW} and PIP_{ES} EIP_{ES} were used for respiratory system resistance R_{RS} and chest wall resistance R_{CW} calculations respectively.

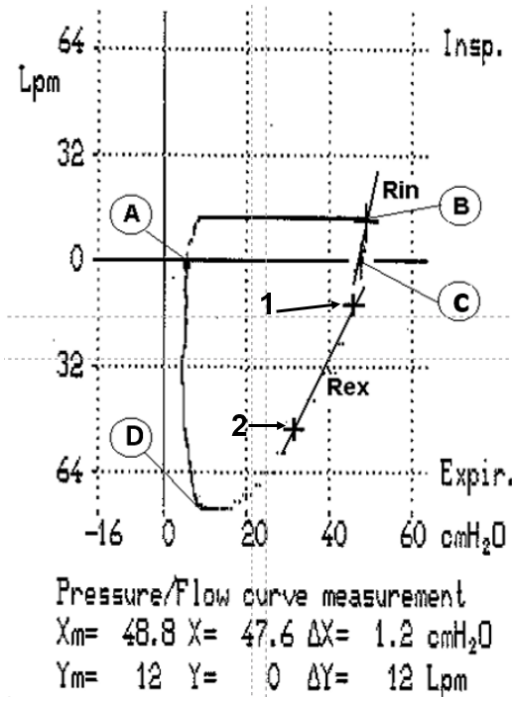

Figure 2. Pressure-flow diagram under controlled mechanical ventilation.

Pressure is depicted on the horizontal axis and flow on the vertical one. Inspiration starts at point A and then at point B the maximum inspiratory flow is observed. From point B, flow starts to decrease and reaches zero at point C, which represents EIP. The line that passes through B and C represents inspiratory resistance and its slope ΔX: ΔY allows its accurate calculation. Pressure decline continues at the expiratory limb of the diagram accompanied by a negative increase of the flow until the point of maximum expiratory flow (point D). Following that, flow decreases and reaches again zero at point A, which is the point of expiratory zero flow. The line that passes through points 1 and 2 represents expiratory resistance and its slope allows its accurate calculation.

Vital signs were recorded throughout the study period. Heart rate and rhythm were monitored by a three-lead ECG device (Cardiocap CCI-104, Datex, Finland) and oxygen saturation by a

pulse oxymeter (Cardiocap CCI-104, Datex, Finland) which was adapted on the ear flap of the animal. Continuous invasive blood pressure measurement (SAPs, SAPd, SAPm) was applied by using a femoral arterial catheter connected to a transducer (Transpac III, Abbot Laboratories LTD, North Chicago, IL, USA) which was connected to the monitor (Cardiocap CCI-104, Datex, Finland). Moreover, a catheter (Swan-Ganz, 8F, 110 cm) was placed in the pulmonary artery for hemodynamic monitoring, which included central venous pressure (CVP), right ventricular pressure (RVP), pulmonary artery pressures (PAP), pulmonary occlusion pressure (PAOP), continuous oxygenation saturation from mixed venous blood and continuous cardiac output (OptiQ SvO_2/CCO Abbott Laboratories North Chicago, IL, USA).

Hemodynamic stability throughout the study period was maintained by intravenous lactated ringer administration (Ringer Lactate).

Measurements were obtained in both groups at baseline and every 20min for 180min (the final measurement was after the release of pneumoperitoneum) (Table 1).

Phases of measurement	Time of measurement (min)	Study settings
0	0	Baseline
1	20	IAP = 25 mmHg
2	40	IAP = 25 mmHg
3	60	IAP = 25 mmHg
4	80	IAP = 25 mmHg + Sepsis in Group B
5	100	IAP = 25 mmHg + Sepsis in Group B
6	120	IAP = 25 mmHg + Sepsis in Group B
7	140	IAP = 25 mmHg + Sepsis in Group B
8	160	IAP = 25 mmHg + Sepsis in Group B
9	180	Release of the pneumoperitoneum

Table 1: Phases of measurement over time and corresponding study settings.

Recorded study parameters included: PIP_{AW}, PIP_{ES}, EIP_{AW}, EIP_{ES}, PEEP, $Pmean_{AW}$, $Pmean_{ES}$, C_{RS}, C_{CW}, C_L, $Rinsp_{RS}$, $Rinsp_{CW}$, $Rexp_{RS}$, $Rexp_{CW}$ and Vexp.After the end of the study period (10 phases of measurement) animals were humanely euthanized by intravenous administration of 500mg thiopental and 20ml KCl 10%.

SPSS 25 was used for the statistical data analysis. Kolmogorov-Smirnov was used to test for normal distribution and after normality was confirmed repeated measures ANOVA test was

used in each group for repeated measures analysis of variance. Statistical significance was tested at the same study phases by using t test for independent samples. All p-values less than 0.05 were considered statistically significant.

RESULTS

PIP_{AW} showed a statistically significant ($p<0.01$) alteration in both groups after pneumoperitoneum induction. In Group B it increased further after LPS administration and remained elevated even after pneumoperitoneum release. On the contrary in Group A it returned to its baseline values after pneumoperitoneum release (Fig. 3). A statistically significant difference ($p<0.01$) between the two groups was recorded only at phase 9.

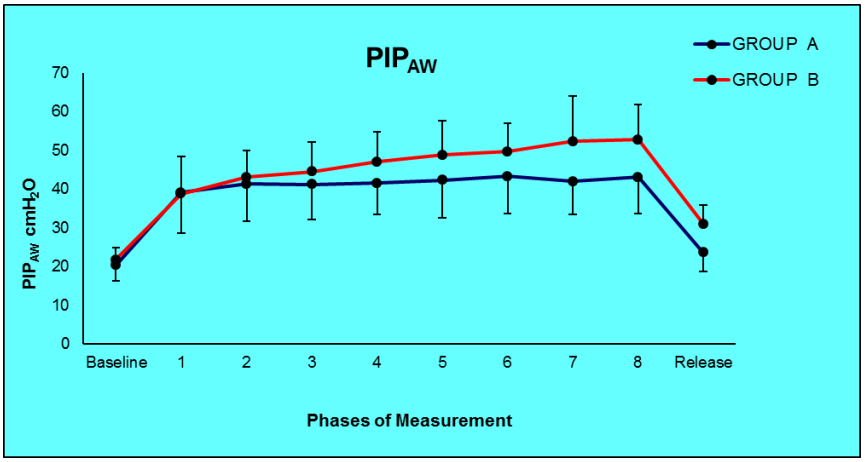

Figure 3: PIP_{AW} alterations during the study period.

PIP_{ES} showed a statistically siginificant ($p<0.01$) alteration in both groups after pneumoperitoneum induction and returned again to its baseline values after pneumoperitoneum release. Comparison between groups did not reveal any statistically significant difference (Fig.4).

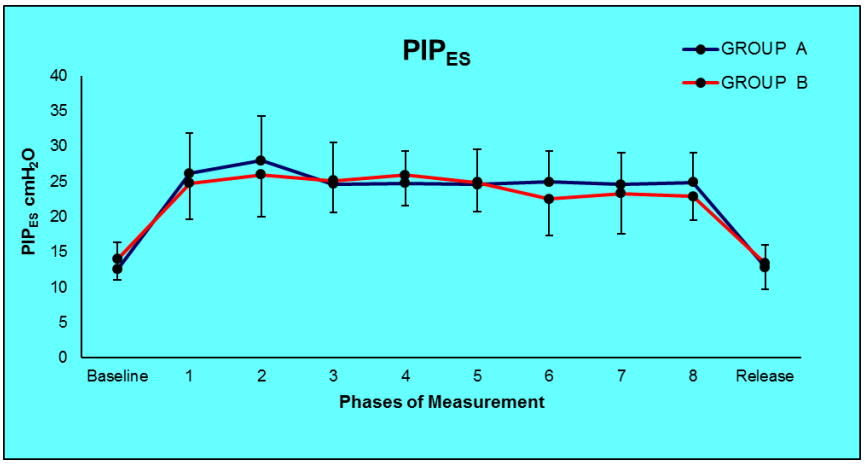

Figure 4: PIP_{ES} alterations during the study period.

EIP_{AW} showed a statistically significant ($p<0.01$) alteration in both groups after pneumoperitoneum induction. After pneumoperitoneum release it returned again to its baseline values only in Group A (Figure 5). Comparison between groups revealed statistically significant differences at Phases 7-9 ($p<0.05$).

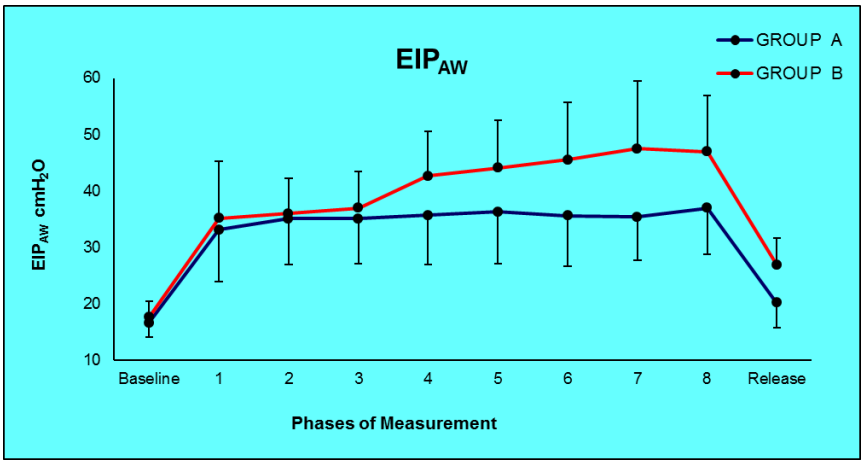

Figure 5: EIP_{AW} alterations during the study period.

EIP_{ES} showed a statistically significant ($p<0.01$) increase in both groups after pneumoperitoneum induction and returned again to its baseline values after pneumoperitoneum release. Comparison between groups did not reveal any statistically significant difference (Fig. 6).

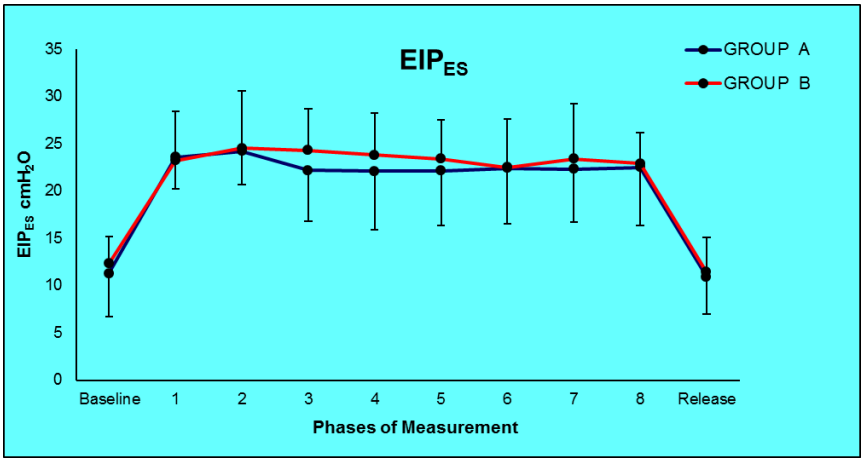

Figure 6: EIP_{ES} alterations during the study period.

$Pmean_{AW}$ showed a statistically significant ($p<0.01$) increase in Group A after pneumoperitoneum induction and returned again to its baseline values after pneumoperitoneum release. In Group B it showed a further increase after phase. However, comparison between groups did not reveal a statistically significant difference (Fig. 7). $Pmean_{ES}$ showed a statistically significant ($p<0.01$) increase in both groups after pneumoperitoneum induction and returned again to its baseline values after pneumoperitoneum release (Fig. 8).

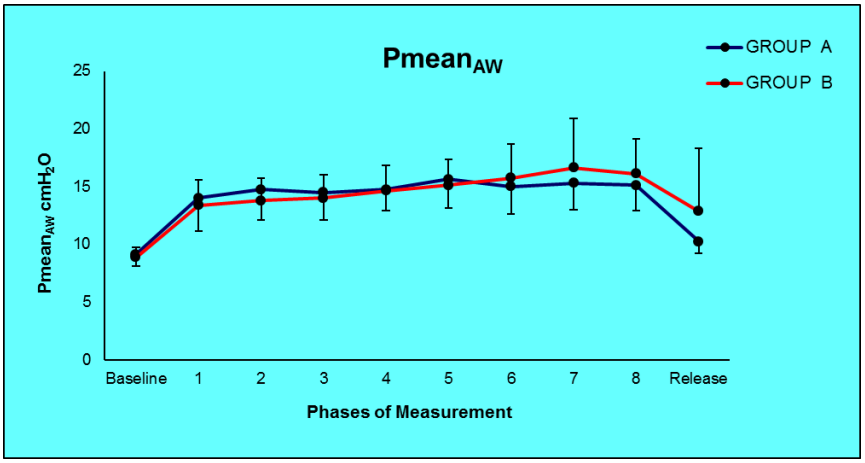

Figure 7: $Pmean_{aw}$ alterations during the study period.

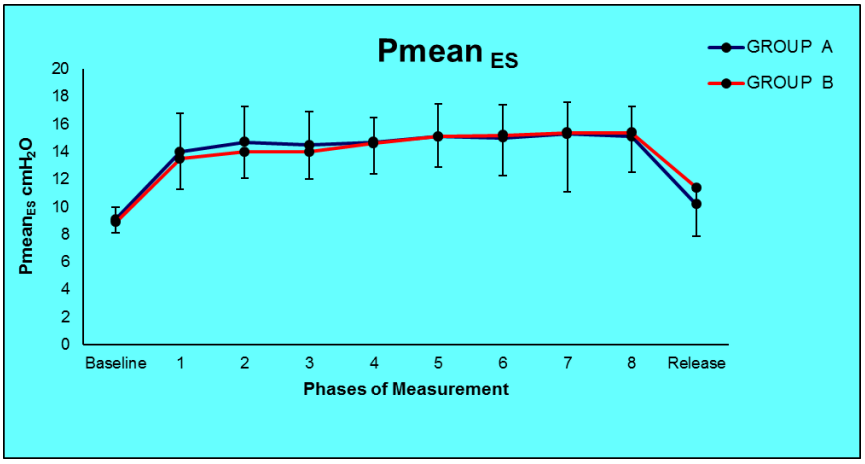

Figure 8: $Pmean_{ES}$ alterations during the study period.

PEEP (both values namely at the port of the Y connector and in the esophagus) remained unchanged in both groups throughout the study period (Fig. 9 & 10).

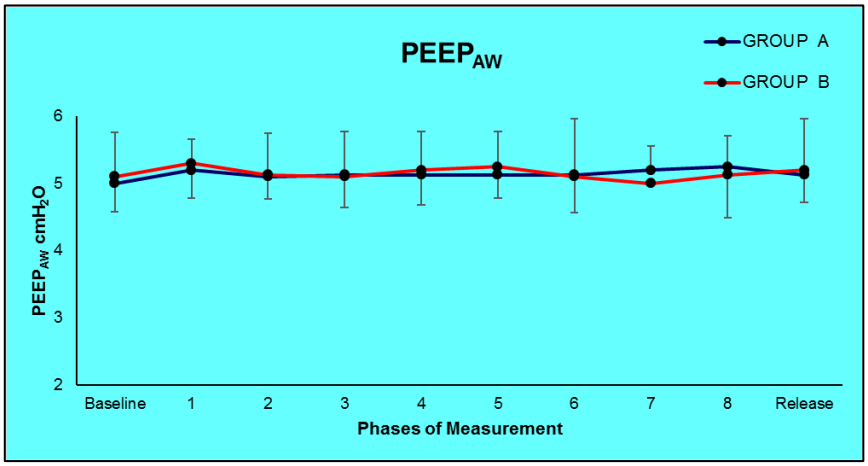

Figure 9: $PEEP_{AW}$ alterations during the study period.

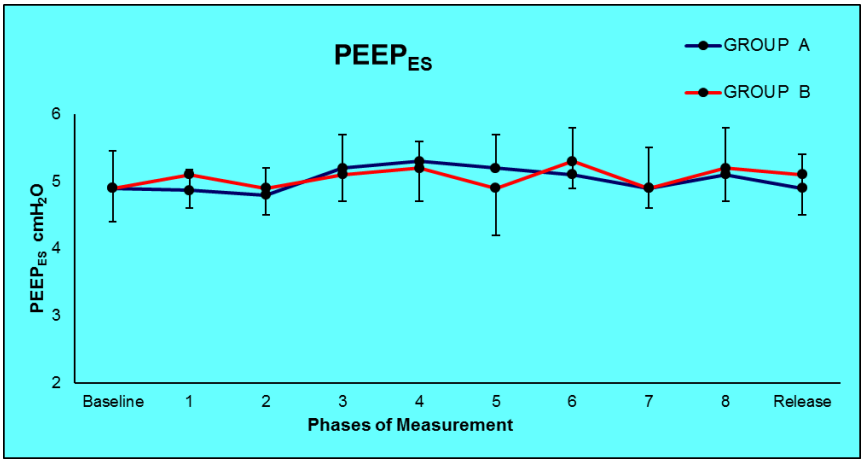

Figure 10: $PEEP_{ES}$ alterations during the study period.

C_{RS} showed a statistically significant ($p<0.01$) decrease in both groups after pneumoperitoneum induction. In Group B it decreased even further after LPS administration and never reached its baseline values. On the contrary in Group A it returned to its baseline values after pneumoperitoneum release. A statistically significant difference (0.01) between the two groups was recorded only at phase 9 (Fig. 11).

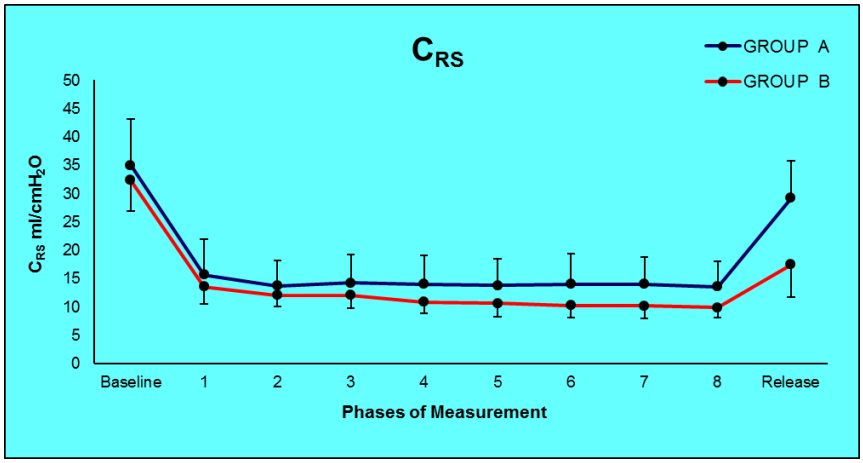

Figure 11: C_{RS} alterations during the study period.

C_{CW} showed a statistically significant ($p<0.01$) decrease in both groups after pneumoperitoneum induction. Comparison between groups revealed a statistically significant difference at Phase 9 ($p<0.05$) (Fig. 12). C_L showed a statistically significant ($p<0.01$) decrease in both groups after pneumoperitoneum induction. Comparison between groups revealed statistically significant differences, which started at phase 4 and remained until the end of the study protocol. In fact, the statistically significant differences became gradually more intense (at phases 4-8 $p<0.005$ and at phase 9 $p<0.001$) (Fig. 13). $Rinsp_{RS}$ did not show any statistically significant alterations in Group A. On the contrary, it showed a moderate increase in Group

B, which reached a statistically significant level (compared to baseline values) at phases 8 & 9. Comparison between groups revealed statistically significant differences ($p<0.05$) at phase 6 and thereafter until the end of the study period (Fig. 14).

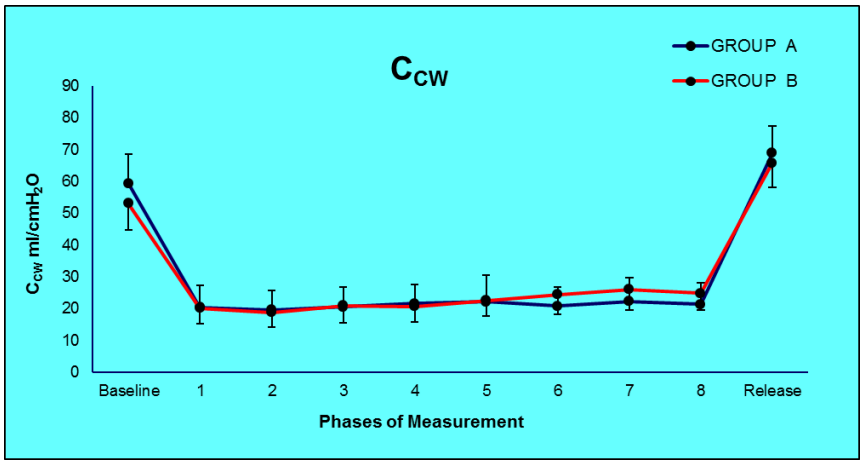

Figure 12: C_{CW} alterations during the study period.

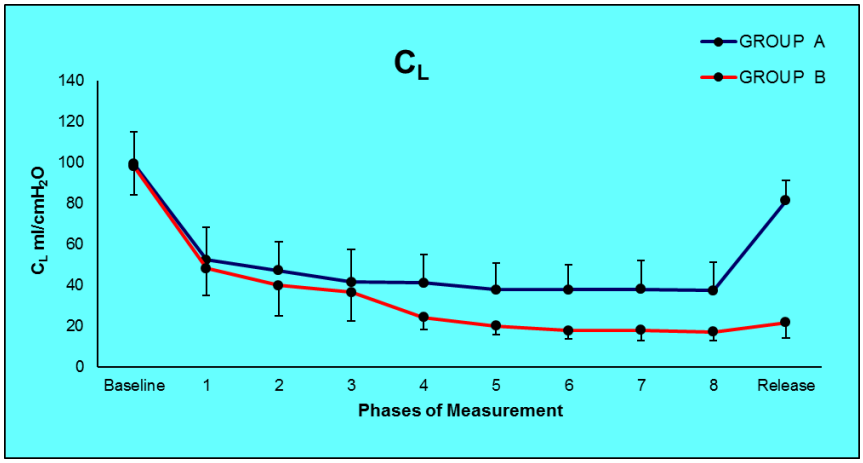

Figure 13: C_L alterations during the study period.

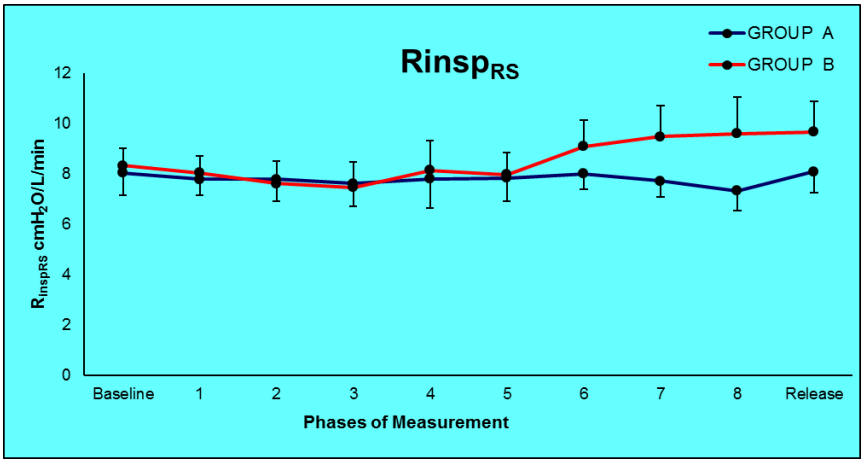

Figure 14: $Rinsp_{RS}$ alterations during the study period.

$Rexp_{RS}$ showed a statistically significant ($p<0,01$) increase in both groups after pneumoperitoneum induction and returned again to its baseline values after pneumoperitoneum release only in Group A. Comparison between groups revealed statistically significant differences ($p<0.05$) at phase 7 and thereafter until the end of the study period (Fig. 15).

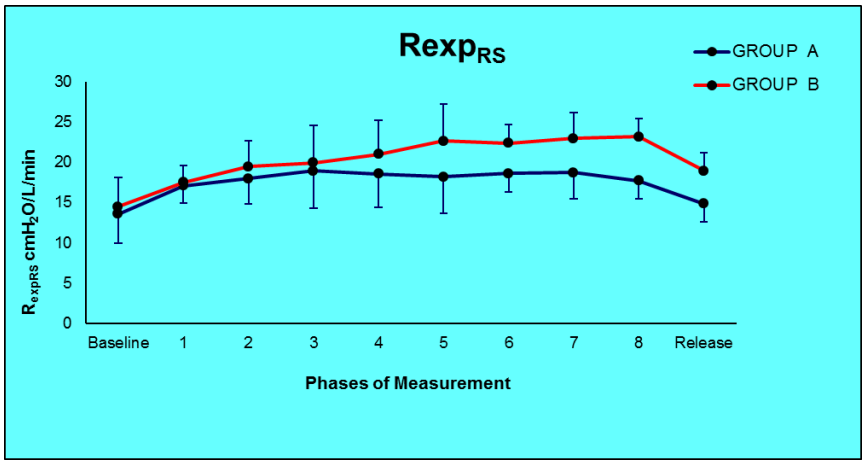

Figure 15: $Rexp_{RS}$ alterations during the study period.

$Rinsp_{CW}$ and $Rexp_{CW}$ remained unchanged in both groups throughout the study period (Fig. 16 & 17). Vexp showed similar alterations in both groups.

It showed a statistically significant ($p<0.01$) increase after pneumoperitoneum induction and returned again to its baseline values after pneumoperitoneum release (Fig. 18).

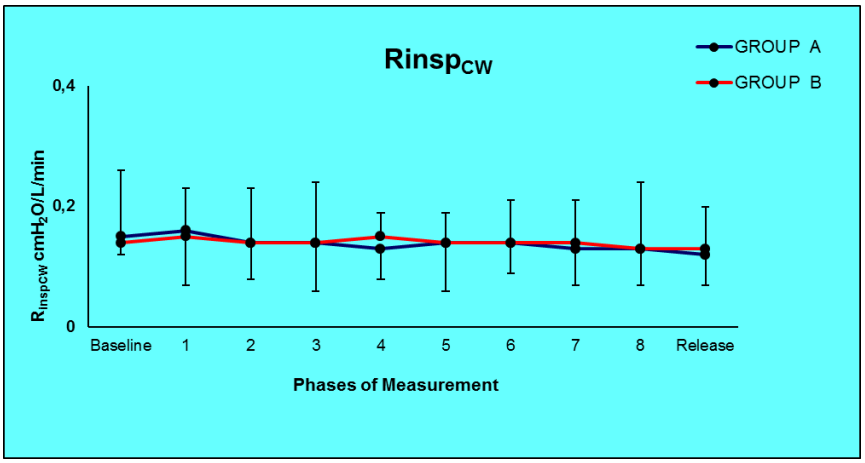

Figure 16: $Rinsp_{CW}$ alterations during the study period. Vexp showed similar alterations in both groups.

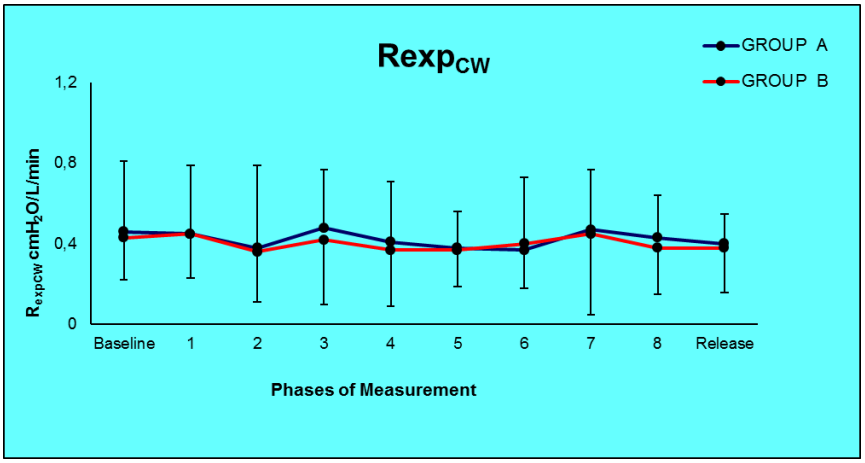

Figure 17: Rexp$_{CW}$ alterations during the study period.

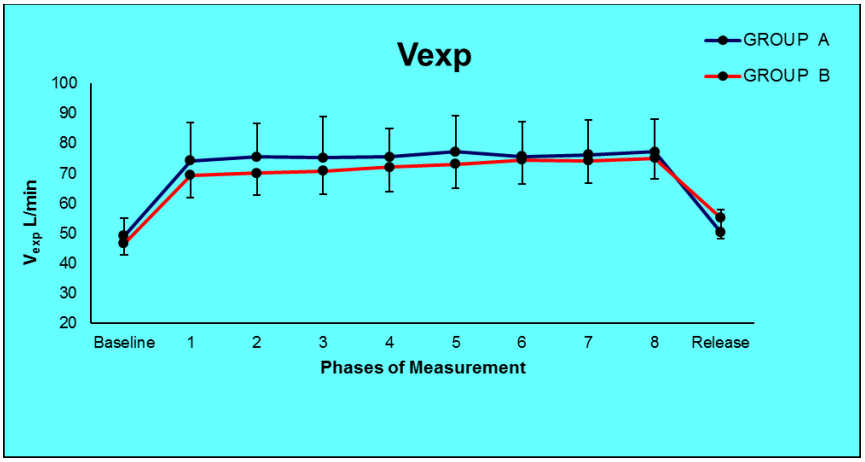

Figure 18: Vexp alterations during the study period.

DISCUSSION

In this experimental study we investigated the effects of IAH and sepsis on respiratory mechanics. The combination of those two clinical conditions was selected because IAH is a cause of sepsis and on the other hand sepsis can cause an increase in IAP.

The level of IAP in our study protocol was set at 25mmHg. This was based on the reports by Malbrain et al[35] who have described that IAP levels of 8-10mmHg induce important but reversible alterations. Similarly, IAP levels of 15-20mmHg have eventually the same impact[12,36]. An IAP value of 25mmHg is considered to be a borderline pressure value to guide the decision making for proceeding to surgical abdominal decompression[10,16,37,38].

Measurements of the esophageal pressure by the use of a specific esophageal balloon catheter allowed us to study into detail mechanics of the different aspects of the respiratory system. This was even more helpful and important since sepsis was induced in one of the two study groups

and esophageal pressure measurements allowed us to evaluate the impact of each factor (IAH and sepsis) individually.We documented a statistically significant increase in PIP_{AW} right after IAH induction (IAP=25mmHg), which was actually doubled compared to baseline. This trend remained throughout the study period and was fully restored only in Group A after pneumoperitoneum release. Sepsis induction in Group B increased PIP_{AW} even further. However, there was no statistically significant difference between the two study groups.

Alterations of PIP_{AW} measured at the port of the Y connector reflect the effects of increased IAP on the respiratory system mechanics.

Several experimental and clinical studies found that elevation of IAP causes increase of intrapleural and airway pressures [9,10] and results in complete respiratory function deterioration in patients with spontaneous ventilation and under mechanical ventilation[39,40].

PIP_{ES} showed a similar statistically significant increase compared to baseline, which was recorded after IAH induction and was fully restored after pneumoperitoneum release in both groups. Those findings have been also confirmed by other investigators[12].

PIP_{ES} measurements were obtained by a specific set up in the esophagus and reflected alterations of respiratory mechanics, which were associated with the chest wall[40-43] . This impact is attributed to IAP transmission to the chest wall and diaphragm translocation. At this point it should be noticed, that sepsis induction does not have any impact on chest wall mechanics since its negative effects are associated with the lungs and not with the chest wall[12,35,36]. This finding should be taken into account when managing ARDS patients, where treatment decisions should be guided and modified according to the underlying pathology, the clinical condition and the role of the abdomen in the pathogenesis pathway[12].

EIP_{AW} reflects alterations associated with the respiratory system under static end - inspiratory conditions. It should be mentioned that in this specific measurement set up, EIP_{AW} reflects relatively accurately the corresponding alveolar pressures[44].

In this study model, EIP_{AW} showed a statistically significant increase in both groups (it was doubled compared to baseline) immediately after IAP increase but returned to baseline values after pneumoperitoneum release only in Group A.

Actually, these alterations reflect the impact of increased IAP on the elastic lung properties, which clinically are presented as respiratory deterioration or failure in IAH patients[39]. Sepsis induction in Group B caused a further EIP_{AW} increase, which was not restored after pneumoperitoneum release. This could be explained by the assumption that sepsis caused a permanent change on lung mechanics

On the other hand EIP_{ES} showed in both groups changes similar to the previously mentioned

PIPes alterations, which confirm the impact of pneumoperitoneum on chest wall mechanics and at the same time the absence of any sepsis effect on chest wall mechanics[12,35,36].

$Pmean_{AW}$ is a derivative parameter and as such it is dependent on the evolution of pressures over time at each breathing cycle. Thereafter, $Pmean_{AW}$ alterations reflect the already described and discussed changes in both groups[45,46].

To be more specific, $Pmean_{AW}$ increased in a statistically significant manner in Group A after pneumoperitoneum induction and was fully restored after its release. In Group B, $Pmean_{AW}$ showed a statistically significant increase after pneumoperitoneum induction but did not return to baseline values after IAP normalization. These alterations are explained by the corresponding PIP_{AW} and EIP_{AW} changes. $Pmean_{AW}$ reflects mean alveolar pressure[40,45,46].

$Pmean_{ES}$ was measured by the esophageal balloon catheter. $Pmean_{ES}$ alterations confirmed the findings which were made by PIP_{ES} and EIP_{ES} changes. Namely, it was found that $Pmean_{ES}$ is affected only by increased IAP. $Pmean_{ES}$ and its alterations in a setting of increased IAP conditions are possibly of great importance especially in patients with the corresponding underlying pathology due to the impact of positive pressures on the cardiovascular system and on pulmonary microcirculation[39].

PEEP did not show any changes in any of the two groups throughout the study period at both measurement points, namely at the port of the Y connector and in the esophagus. In the setting of controlled mechanical ventilation, PEEP is a predetermined parameter that remains constant provided that no dynamic hyperinflation occurs, which could lead to air trapping and auto positive end - expiratory PEEP (auto PEEP)[47].

During the application of occlusion maneuver (occlusion of the expiratory limb of the breathing circuit and suspension of the next insufflation) no auto PEEP was detected at any case in our study.

Study of the respiratory system compliance (C_{RS}) (Fig. 1), as this was calculated by the corresponding graphs and waveforms, clearly depicted the impact of increased IAP and sepsis on the whole respiratory system. It should be noted that C_{RS} describes the elastic properties of the whole respiratory system, including the lungs and the chest wall and therefore those parameters are both taken into account when calculating C_{RS}[48]. In Group A, C_{RS} showed a statistically significant decrease during pneumoperitoneum and was restored after its release. On the other hand, in Group B, C_{RS} did not return to baseline values after pneumoperitoneum release. This is explained due to the fact that C_{RS} reflects mechanics both of the chest wall and of the lungs.

C_{CW} decreased in a statistically significant manner in both groups right after pneumoperitoneum induction. This dramatic decrease is attributed to the increase of chest wall elasticity

because of the cranial translocation of the diaphragm and the direct transmission of IAP to the thoracic cavity[11]. After pneumoperitoneum release C_{CW} returned to baseline values in both groups. Sepsis did not have any additional effect on C_{CW}.

In the present study C_L is a derivative parameter and as such it is depended on C_{RS} and C_{CW} measurements. This specific methodology is considered compulsory in the setting of controlled mechanical ventilation and allows simultaneous measurements[41]. IAP increase had a negative effect on C_L in Group A, which is explained by the fact that lungs and chest wall are connected in parallel. Lungs are included in the thoracic cavity and therefore they are subjected to the before mentioned effects, which refer to the chest wall[12,36].

In Group B, sepsis had a negative impact on lung compliance immediately after the first minutes of LPS administration. Those negative effects were more intense in Group B compared to Group A and remained even after pneumoperitoneum release. This is probably attributed to the impact of sepsis on lung parenchyma, which includes pulmonary hypertension, total lung water increase and the subsequent effects on mechanics.

In a setting of combined ACS and sepsis, we can presume that both the alterations on the chest wall due to abdominal distension and on the lung parenchyma due to the autonomic negative effects of sepsis contribute to the decreased compliance.

Malbrain et al reported similar findings and pointed out that those effects can be reversed by application of positive endexpiratory pressure, which results in airway pressure increase[35]. In an effort to titrate the necessary PEEP, Malbrain et al discovered the relationship between level of IAP and necessary PEEP. Despite the fact that this maneuver might seem opposed to consensus statements, it is demonstrated that it could be necessary and clinically useful. The rationale behind this maneuver is that PEEP can provide protection to lung parenchyma against extrathoracic damaging factors. Therefore, PEEP application in patients with ACS, along with other indicated interventions could be considered as an alternative treatment option for the management of respiratory system disorders and compliance restoration[49].

Clinical management of this particular respiratory system pathophysiology presents huge challenges and cannot be treated just by IAP release or PEEP application[12,36,50].

$Rins_{RS}$ did not show any significant evolution in Group A, whereas $Rins_{RS}$ showed an increase in Group B, which became statistically significant after phase 6. Moreover, in Group B, $Rins_{RS}$ did not return to baseline values at the end of the study period. These findings can be attributed to resistance increase of the distal airways due to the effects of sepsis on the bronchial smooth muscles by bronchoconstriction and to lung pa-

renchyma disorders and altered lung mechanics[52,53].

During expiration $Rexp_{RS}$ increased statistically significant in both groups. In Group A, $Rexp_{RS}$ returned to baseline values after pneumoperitoneum release, whereas in Group B $Rexp_{RS}$ remained increased in a statistically significant manner compared to Group A. $Rexp_{RS}$ increase in the setting of IAH can be explained by the before mentioned rise of expiratory flow, since flow is being taken into account when calculating $Rexp_{RS}$[54]. On the contrary, the more intense increase of $Rexp_{RS}$ in Group B and the fact that $Rexp_{RS}$ did not return to baseline values can be attributed to the before mentioned disorders, which are associated with the lung parenchyma[55].As far as chest wall resistances are concerned, there were no statistically significant findings neither during inspiration nor during expiration in any of the two groups.

In the present study, Vexp evaluation was considered necessary due to the fact that increased IAP facilitates expiration, which is a passive process even under controlled mechanical ventilation[56]. This assumption was confirmed in our study since we observed in both groups a statistically significant Vexp increase compared to baseline, which was restored in Group A after pneumoperitoneum release. In Group B, Vexp did not return to baseline values at the end of the study period. These findings have not been properly and adequately described in the literature expect some scarce reports of patients with severe obstructive lung disease, who were managed effectively regarding expiration by intermittent application of abdominal or chest compressions[57-59].

The limitations in this experimental study concerned the use of pigs as experimental models in which the increase of the IAP was induced by insufflation into the peritoneal cavity and sepsis by intravenous LPS administration. Despite the fact that the methods used for the IAP increase and sepsis induction are considered as acceptable experimental models, it should be noted that the associated underlying pathology, which in clinical practice causes IAH, sepsis or both, was not present. Moreover, it would be useful to study a third group of septic pigs without IAH to investigate and determine the isolated effects of sepsis on respiratory mechanics.

CONCLUSION

IAP increase has detrimental effects on respiratory system mechanics. Those effects are reversible after IAP normalization. The coexistence of sepsis with IAH causes further adverse effects, which remain even after IAP normalization.

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GV drafted the paper and is the lead author. FB contributed to planning and the critical revision of the paper. GS contributed to planning and the critical revision of the paper. ThP contributed to planning and the critical revision of the paper. KG contributed to planning and the critical revision of the paper. KM contributed to planning and the critical revision of the paper. PM contributed to planning and the critical revision of the paper. KK contributed to planning and the critical revision of the paper.

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