Experimental Study

The work of breathing during mechanical ventilation in a porcine model of abdominal hypertension: The impact of sepsis

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ABSTRACT

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The work of breathing (WOB) is the amount of energy, which is consumed by the respiratory muscles, in order to perform one complete respiratory cycle. In several medical conditions, WOB might rise to a critical level which could necessitate initiation of mechanical ventilation (MV) or complicate weaning of the patient from MV. We recorded the alterations of WOB (total value and its components) in a porcine model of increased intraabdominal pressure (IAP) with (Group B) and without sepsis (Group A). IAP

increased by helium insufflation into the peritoneal cavity and sepsis was induced by LPS administration. WOB was calculated by pressure/volume curves based on Capbell's methodology. WOB was affected both by IAP increase and sepsis. WOBinsp RS Resistive increased in both groups in a statistically significant manner. Its alterations were more evident in group B and became statistically significant at specific study phases. However, WOBinsp RS Resistive returned to baseline values in both groups.

WOBexp RS Resistive increased and was restored in both groups. However, WOBexp RS Resistive increase was higher and more persistent in group B. Similarly, WOB_{insp} RS Elastic increased in both groups after IAP increase. Sepsis caused a further statistically significant increase in group B compared to group A, which remained until the end of the study.

WOB_{insp} L Elastic increased significantly after establishment of pneumoperitoneum in both Groups. In Group B, after LPS administration a further increase was recorded, which remained even after pneumoperitoneum release. WOB_{insp} CW Resistive, WOB_{insp} CW Elastic and WOB_{exp} CW Resistive increased in a statistically significant manner after IAP increase and returned to baseline values after its release, without any statistically significant difference between the two study groups. Based on the results of our study it seems that IAP increase causes an increase of the WOB. However, WOB returns to normal values after pneumoperitoneum release. Sepsis results in a further deterioration of respiratory energy balance, which is persistent even after pneumoperitoneum release.

Keywords: Work of Breathing**,** abdominal hypertension, abdominal compartment syndrome.

Abbreviations: *WOB_{insp} RS Resistive: Work of Breathing inspiratory respiratory system resistive, WOB_{insp} RS Elastic: Work of Breathing inspiratory respiratory system elastic, WOB_{insp} CW Resistive: Work of Breathing inspiratory chest wall resistive, WOB_{insp} CW Elastic: Work of Breathing inspiratory chest wall Elastic, WOB_{insp} L Elastic: Work of Breathing inspiratory lung elastic, WOB_{exp} RS Resistive: Work of Breathing expiratory respiratory system resistive, WOB_{exp} CW Resistive: Work of Breathing expiratory chest wall resistive. WOB_{insp} RS Total: Work of Breathing inspiratory respiratory system total, WOB_{exp} RS Total: Work of Breathing expiratory respiratory system total.*

INTRODUCTION

Work of breathing is the amount of energy, which is consumed by the respiratory muscles, in order to perform one complete respiratory cycle[1]. According to physics, work is defined as the product of force and distance and is measured in Joules (1J=1Nx1m). When this formula is applied to respiration the equation converts as follows: Work = Force × Distance,

Force = Pressure× Area, Work = Pressure× ×Area × Distance, Area × Distance = Volume, Work = Pressure× Volume.

Consequently, the formula for calculating WOB is Work=Pressure x Volume and WOB is measured in Joules (Joules=Pascal x m^3) according to the International System of Units (SI)[2]. This formula calculates WOB of one respiratory cycle without taking into account respiratory or flow rate, despite the fact that those parameters have a significant impact on the required amount of consumed energy.

At a resting state the amount of energy which is consumed, is less than 2% of the basal metabolic rate (BMR) and the required oxygen about 2-5% of VO_2 or 3/ml/min. In critically ill patients, WOB might constitute more that 30% of the BMR and could result to respiratory muscle fatigue and respiratory failure.

The components of WOB are elastic work and resistive work. Elastic work is the work required to overcome elastic recoil of the lungs and the chest wall and to expand the lungs, whereas resistive work is the work required to overcome flow resistance. In a normal lung elastic work is 65% of the total WOB and a significant amount of it is used during expiration. In several medical conditions WOB might rise to a critical level, which could necessitate initiation of mechanical ventilation (MV) [3] or complicate weaning of the patient from MV[4].

During the inspiratory phase in mechanically ventilated patients, this work is consumed to overcome flow airway resistance and to change the volume of lungs and chest according to their specific mechanical characteristics[1].

In each respiratory cycle, WOB is calculated by the formula WOB= ∫ Pressure x Volume and this is actually equal to the area under the curve on a pressure/volume loop[1,5]. It is possible to calculate the elastic inspiratory and expiratory work and the resistive inspiratory and expiratory work for each respiratory cycle (inspiration and expiration).

When WOB is calculated by using the pressure measured at the airway opening, this corresponds to the Respiratory System (RS) and refers to the effects distally from the measurement point, namely mechanical interference of airways, lungs and the chest wall. When WOB is calculated by using the esophageal pressure which is determined by an esophageal catheter, this refers to the lungs during spontaneous ventilation and to the chest wall during mechanical ventilation[6].

Campbell et al, described the methodology of WOB calculation and analysis by the use of pressure/volume loops both in the setting of spontaneous ventilation and under positive pressure mechanical ventilation[7].

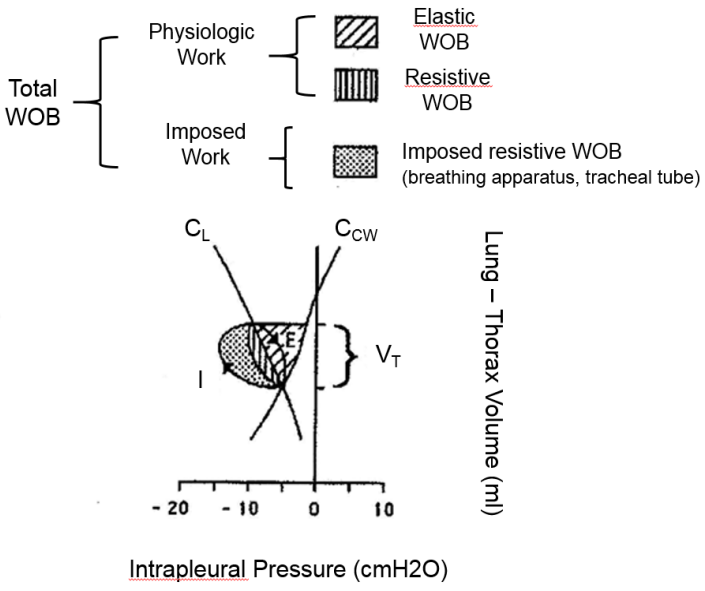
Depending on the measurement point of the pressure and the type of ventilation it is possible to calculate the different values of WOB and to decompose it into its different compo-

nents such as total respiratory system (RS), chest wall and lungs (Table 1 and Figure 1) [7-9].

Table 1: Impact of measurement point of pressure on the calculation of different parameters (from Banner M, modified).

Point of pressure measurement	Area under the curve on the P/V Loop = =Work to Overcome	Slope of the P/V Loop
Esophageal pressure during spontaneous ventilation	Pulmonary inspiratory & expiratory resistance	Lung compliance
Esophageal pressure during mechanical ventilation	Chest Wall inspiratory & expiratory resistance	Chest Wall compliance
Pressure at the end of endotracheal tube during mechanical ventilation	Pulmonary & Chest Wall inspiratory & expiratory resistance	Compliance of the respiratory system
Pressure at airway openingduring mechanical ventilation	Pulmonary & Chest Wall inspiratory & expiratory resistance plus resistance of the endotracheal tube	Compliance of the respiratory system

Figure 1: Calculation and analysis of WOB during spontaneous ventilation (from Banner M, modified).

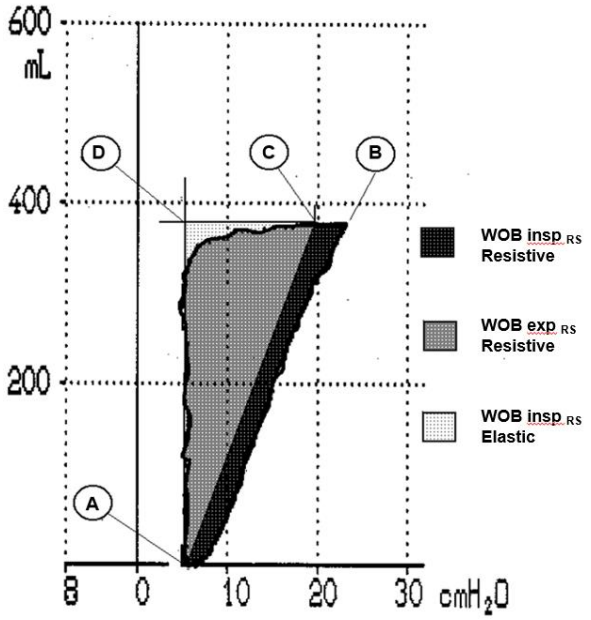


For each component the WOB can be further decomposed into elastic work, resistance work and additional work, as those are defined by the corresponding areas on the pressure/volume diagrams.

Measurement and analysis of WOB of the total RS is depicted on Figure 2. On this airway pressure/volume loop under positive pressure mechanical ventilation, inspiration begins at point A (Positive End Expiratory Pressure/PEEP), runs counterclockwise over point

B (Peak Inspiratory Pressure/PIP) and ends at point C (End Expiratory Pressure/EIP).

Figure 2. Measurement and analysis of WOB of the total RS under mechanical ventilation.

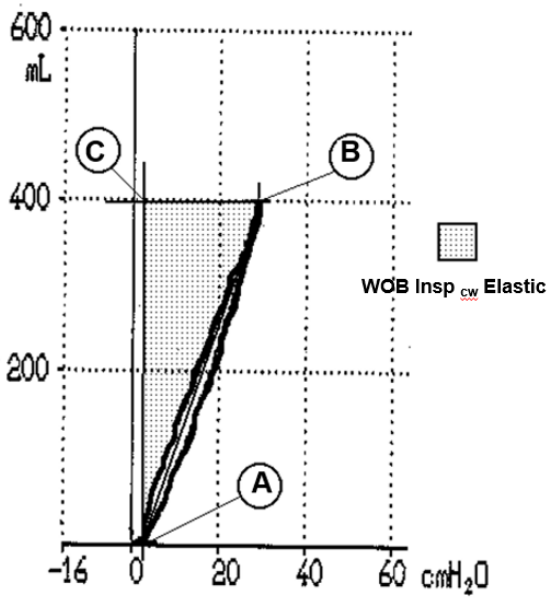


The area defined by the AB curve and the AC line (compliance line) represents the inspiratory resistive WOB (WOB insp RS Resistive). Expiration starts at point C and the curve progresses until expiration ends at point A. The area defined by CA curve and AC line (compliance line) represents the expiratory resistive WOB (WOB exp RS Resistive). The area of the triangle ACD, which is defined by the line AC (compliance line) and the vertical axis AD (equilibrium point at PEEP level) represents the elastic WOB of the RS. Based on the principle of conservation of energy, this value is similar both for inspiration and expiration (WOB insp RS Elastic = WOB exp RS Elastic) since it refers to points of zero flow. The sum of the individual components of WOB is defined as total WOB for each breathing phase (WOB insp RS Total and WOB exp RS Total) and is calculated as follows: WOB insp RS Total = WOB insp RS Resistive + WOB insp RS Elastic, WOB exp RS Total = WOB exp RS Resistive – WOB exp RS Elastic.

On the pressure/volume loop of the chest wall, pressure is measured by an esophageal balloon (Pes) (Figure 3).

Pressure/volume loops under positive pressure mechanical ventilation of the total RS and of the CW are depicted on Figure 4. Starting point of the loop is PEEP and end point EIP.

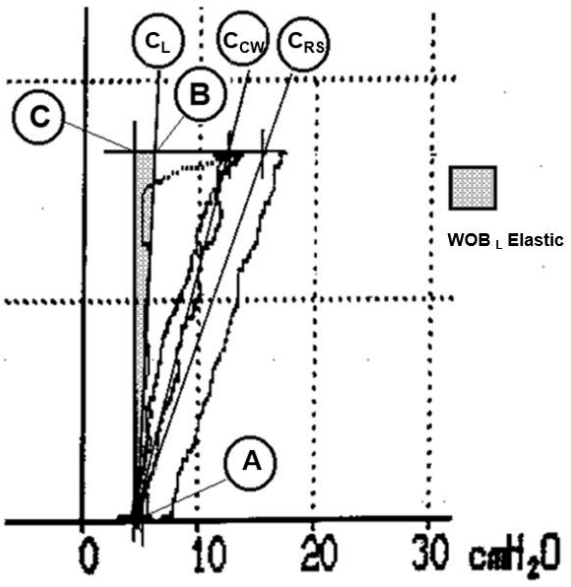
Figure 3. Measurement and analysis of WOB of the chest wall under positive pressure mechanical ventilation.



Inspiration starts at point A (Positive End Expiratory Pressure/PEEP) and ends at point B (Peak Inspiratory Pressure/PIP). Shifts of the AB curve to the right of the compliance line C (defined by the line connecting points A and B) are significant smaller compared to the corresponding ones for the total RS. This area represents inspiratory resistive WOB of the chest wall (WOB insp CW Resistive). Expiration starts at point B and ends at point A. The area defined by the BA curve and the AB line (compliance line C) represents the

expiratory resistive WOB of the chest wall (WOB exp CW Resistive). The area of the triangle ABC, which is defined by the compliance line (line AB) and the vertical axis AC (equilibrium point at PEEP level) represents the elastic WOB of the chest wall. Based on the principle of conservation of energy, this value is similar both for inspiration and expiration (WOB insp CW Elastic = WOB exp CW Elastic) since it refers to points of zero flow. The sum of the individual components of WOB is defined as total WOB for each breathing phase (WOB insp CW Total and WOB exp CW Total) and is calculated as follows: WOB insp CW Total = WOB insp CW Resistive + WOB insp CW Elastic, WOB exp CW Total = WOB exp CW Resistive – WOB exp CW Elastic.

Figure 4. Measurement and analysis of WOB of the lungs under mechanical ventilation.



The lines C_{RS}, C_{CW} and C_L represent compliance of the RS, the CW and the lungs respectively. Lung compliance is the line connecting points A and B and is calculated by the formula $1/C_{RS} = 1/C_{CW} + 1/C_L$. The area of the triangle ABC represents the elastic WOB of the lungs (according to the already mentioned Campbell methodology) both for inspiration and expiration (WOB insp L Elastic = WOB exp L Elastic) using a positive or negative sign depending on the reference point.

MATERIALS AND METHODS

Sixteen female pigs of a mean age of 3-4 months and weight of 25-30kg were used in this study. Animals were provided by the same supplier, in order to have a homogenous group of pigs of similar phylogenetic origin and environmental growth conditions. All experiments took place in the animal laboratory at University Hospital AHEPA Thessaloniki, after submitting all relevant documents regarding research purpose and ethics of animal experimentation and obtaining the official permission of the Direction Office of Veterinary Medicine.

Study animals were divided into two groups of 8 pigs, Group A (control group) and Group B (sepsis group). Intraabdominal pressure increased via Helium insufflation by a pneumoperitoneum creation device used in laparoscopic surgery (Wisap, Semm System, Sauerlach Germany). Helium was administered via a Verres needle and IAP was raised to 25mmHg. Sepsis was induced by intravenous endotoxin administration (Lipopolysaccharides-LPS) via an infusion pump over a period of 30min. LPS was injected at a dose of 100μg/Kg, which was diluted in 60ml of NaCl 0.9%.

After baseline measurements, IAP increased in Group A to 25mmHg and remained at this lev-

el until the end of the study period (3 hours of increased IAP). Similarly, in Group B, IAP increased after baseline measurements and after the first 60min of the study LPS was administered over 30min to induce sepsis.

As it is depicted on Table 2, beside baseline values, measurements were obtained every 20min in both groups. The last one was obtained after pneumoperitoneum release.

Table 2. Study phases over time and corresponding study settings

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

After the end of the study (10 measurements) euthanasia was performed by administration of 500mg thiopental and 20ml KCl 10%. At all study phases, control mechanical ventilation (CMV) was applied under general anesthesia and muscle paralysis. Cuffed tracheostomy tubes (Portex – Blue Line HV) with a diameter of 6.5mm were used for intubation and the breathing circuit was elastic with rings (Taema-Air Liquide). For the measurement of proximal airway pressures (P_{AW}), a straight M/F 22/12 connector with a Luer Lock output was used at the ventilation Y piece of the breathing circuit, which was connected to a rigid F/F extender, connected to the ventilator manometer.

Applied parameters of controlled mechanical ventilation included: fixed inspiratory linear flow rate (Vinsp) of 20L/min, tidal volume (V_{Ti}) of 10-12ml/kg BW, respiratory rate (RR) of 12-15/min, Positive End Expiratory Pressure (PEEP) of 5cmH_2O, inspired oxygen concentration of 50%, inspiration/expiration ratio (T_I/T_E) 1/2, period of zero flow during inspiration set at 10% of total inspiratory time and deactivation of all ventilator alarms. All those parameters were held constant in both Groups throughout the study period.

At each study phase the planimetry method was used for the calculation of WOB by the use of specific software (Image Tool) on the pressure/volume loops and by evaluating the integral ∫P.V according to the Campbell methodology (Table 1).

The various components of WOB were expressed in m Joules:

- WOB_{insp} RS Resistive
- WOB_{insp} RS Elastic
- WOB_{insp} CW Resistive
- WOB_{insp} CW Elastic
- WOB_{insp} L Elastic
- WOB_{insp} RS Total
- WOB_{exp} RS Resistive
- WOB_{exp} CW Resistive
- WOB_{exp} RS Total

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

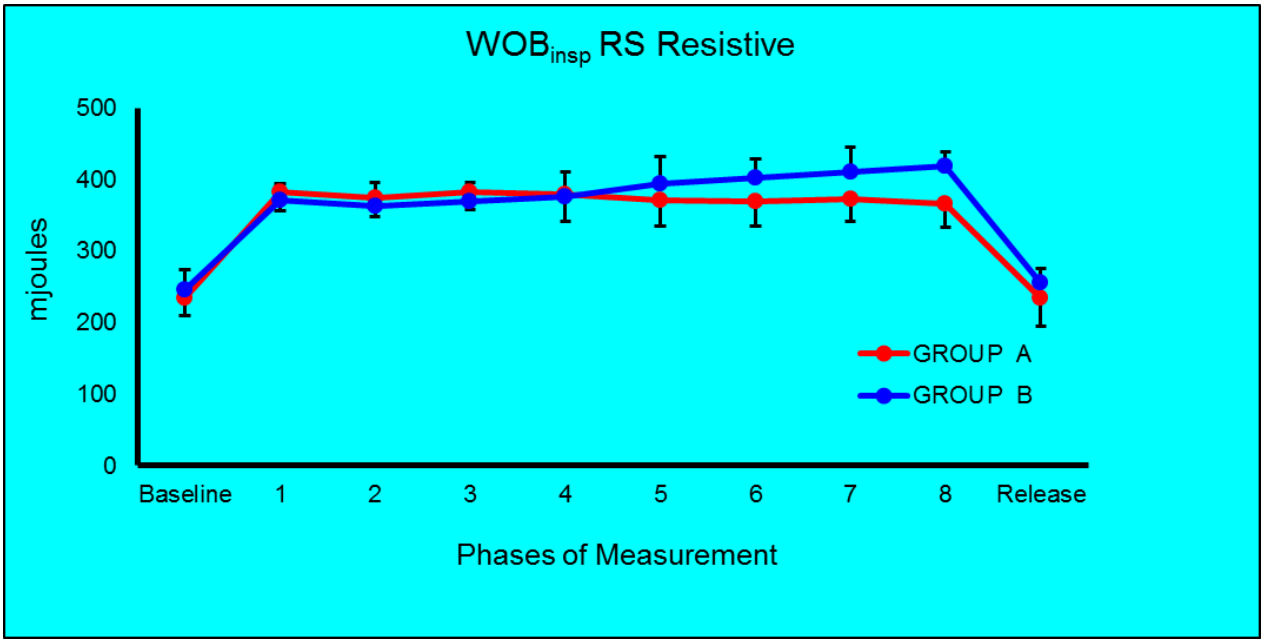
Our result showed that WOB_{insp} RS Resistive increased significantly after establishment of pneumoperitoneum in both Groups and returned to baseline values after its release. Comparison between Groups was statistically significant at 140min ($p<0,05$) and 160min (($p<0,01$) (Table 3 & Figure 5).

Table 3. Statistically significant differences between Group A and Group B at the same study phase.

	Study phases									
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
WOB Inspiratory										
RS Res.	NS	NS	NS	NS	NS	NS	NS	**p<0,05**	**p<0,01**	NS
RS Elas.	NS	NS	NS	NS	NS	NS	NS	NS	NS	**p<0,05**
CW Res.	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
CW Elas.	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Lung Elas.	NS	NS	NS	NS	**p<0,001**	**p<0,001**	**p<0,001**	**p<0,001**	**p<0,001**	**p<0,01**
Total	NS	NS	NS	NS	NS	NS	NS	NS	**p<0,05**	**p<0,05**
WOB Expiratory										
RS Res.	NS	NS	NS	NS	NS	NS	**p<0,05**	**p<0,05**	**p<0,05**	**p<0,05**
CW Res.	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Total	NS	NS	NS	NS	NS	NS	NS	NS	NS	**p<0,05**

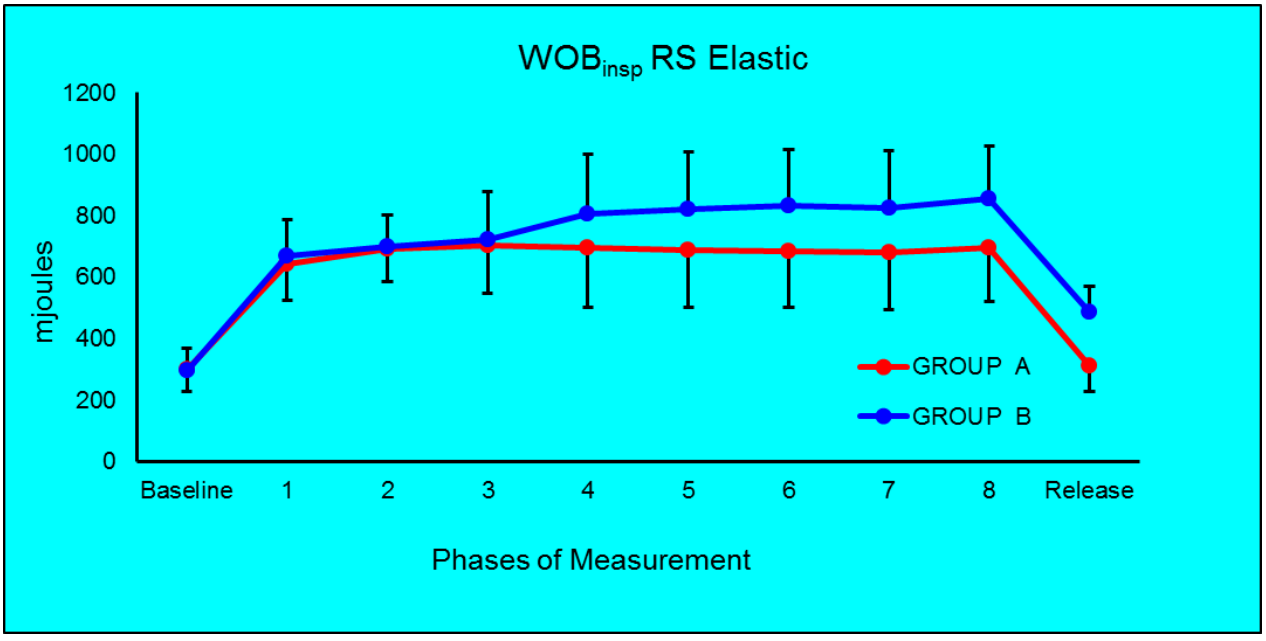
NS: Non significant

Figure 5. WOB_{insp} RS Resistive alterations



Also, WOB_{insp} RS Elastic increased significantly after establishment of pneumoperitoneum in both Groups. Comparison between Groups was statistically significant at180min (release of pneumoperitoneum) ($p < 0,05$) (Table 3 & Figure 6).

Figure 6. WOB_{insp} RS Elastic alterations



WOB_{insp} CW Resistive increased significantly after establishment of pneumoperitoneum in both Groups and returned to baseline values after its release. Comparison between Groups did not reveal any statistically significant differences (Figure 7 & Table 3).

WOB_{insp} CW Elastic increased significantly after establishment of pneumoperitoneum in both Groups and returned to baseline values after its release. Comparison between Groups did not reveal any statistically significant differences (Figure 8 & Table 3).

Figure 7. WOB_{insp} CW Resistive alterations

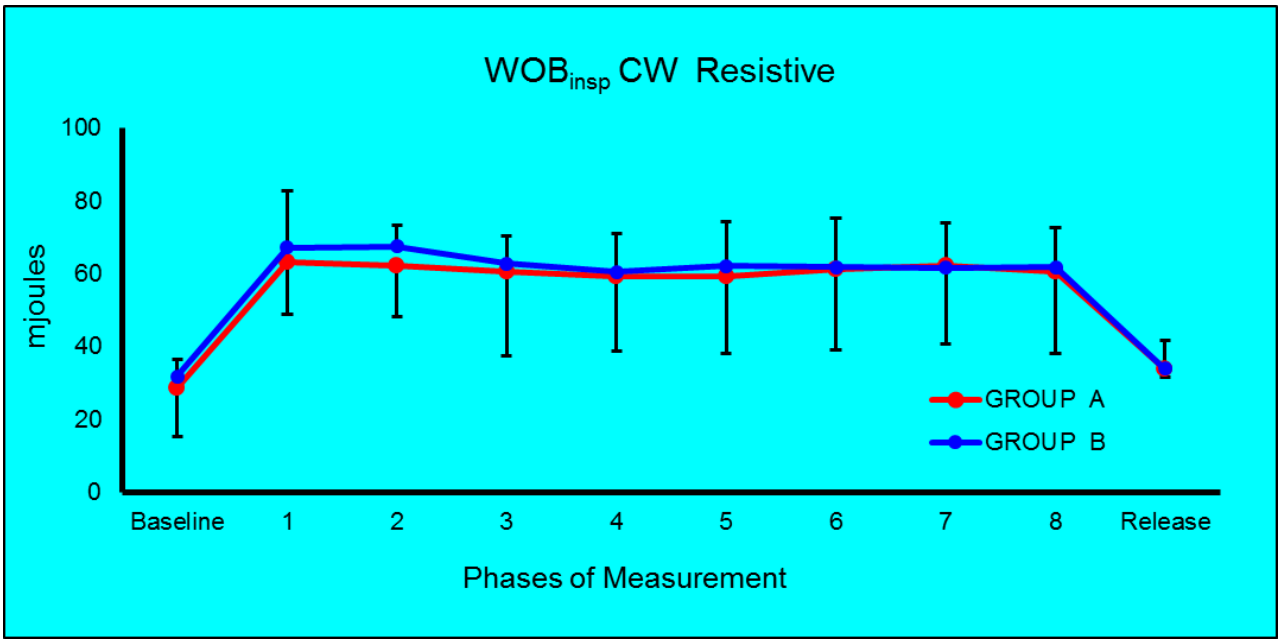
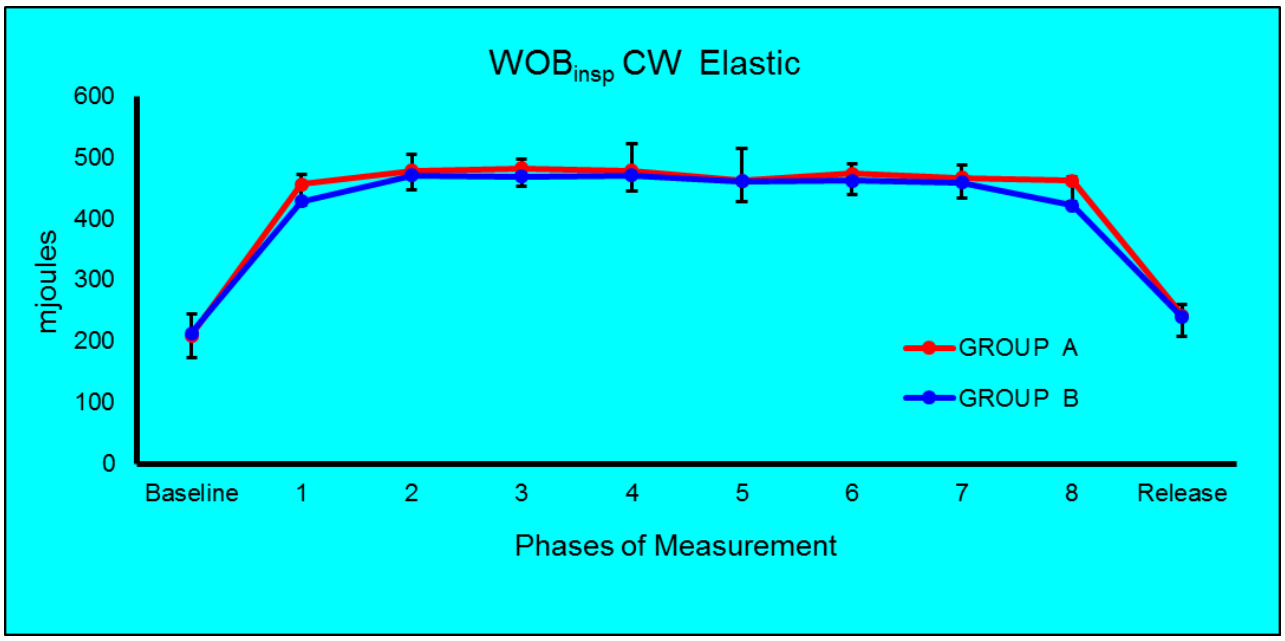


Figure 8. WOB_{insp} CW Elastic alterations.



WOB_{insp} L Elastic increased significantly after establishment of pneumoperitoneum in both groups. In Group B, after LPS administration a further increase was recorded. Comparison

between Groups was statistically significant at 80min and thereafter at all study phases until the end of the study period (Figure 9 & Table 3). WOB_{insp} RS Total increased significantly after establishment of pneumoperitoneum in both Groups. Comparison between Groups was statistically significant at 160min and 180min ($p<0,05$) (Figure 10 & Table 3).

Figure 9. WOB_{insp} L Elastic alterations

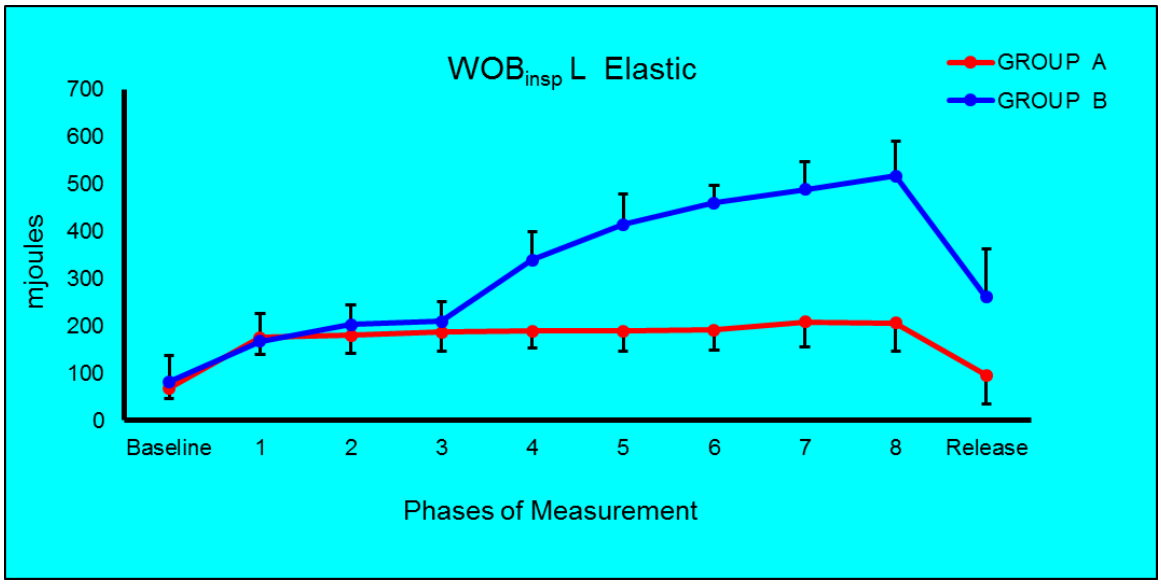


Figure 10. WOB_{insp} RS Total alterations

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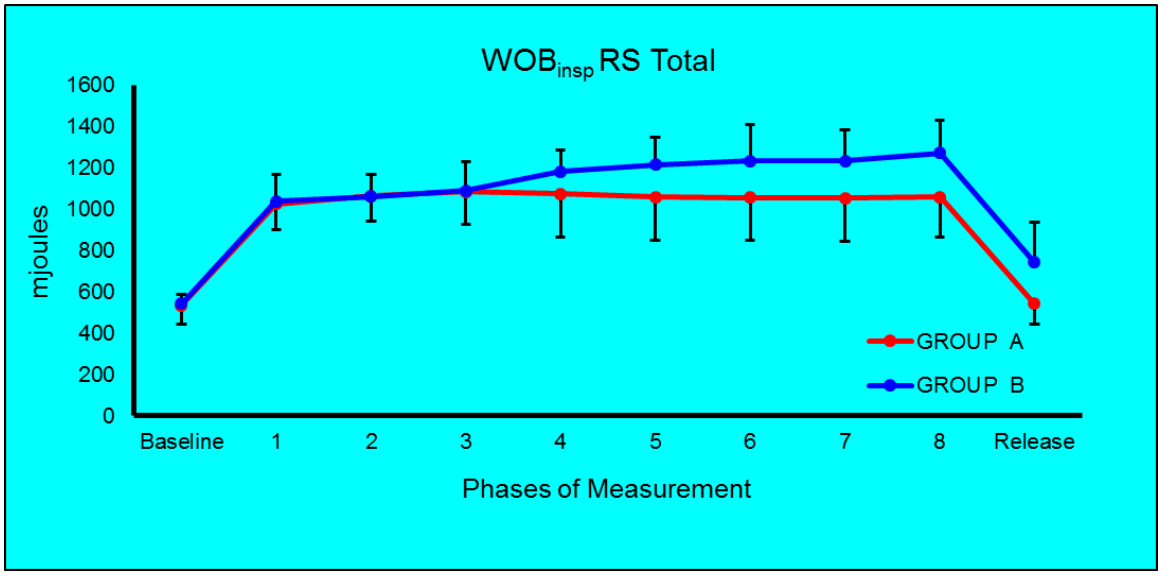


WOB_{exp} RS Resistive increased significantly after establishment of pneumoperitoneum in both Groups and returned to baseline values after its release. Comparison between Groups

was statistically significant at 120min ($p<0.05$) and thereafter at all study phases until the end of the study period (Figure 11 & Table 3).

WOB_{exp} CW Resistive increased significantly after establishment of pneumoperitoneum in both Groups and returned to baseline values after its release. Comparison between Groups did not reveal any statistically significant differences (Figure 12 & Table 3).

Figure 11. WOB_{exp} RS Resistive alterations

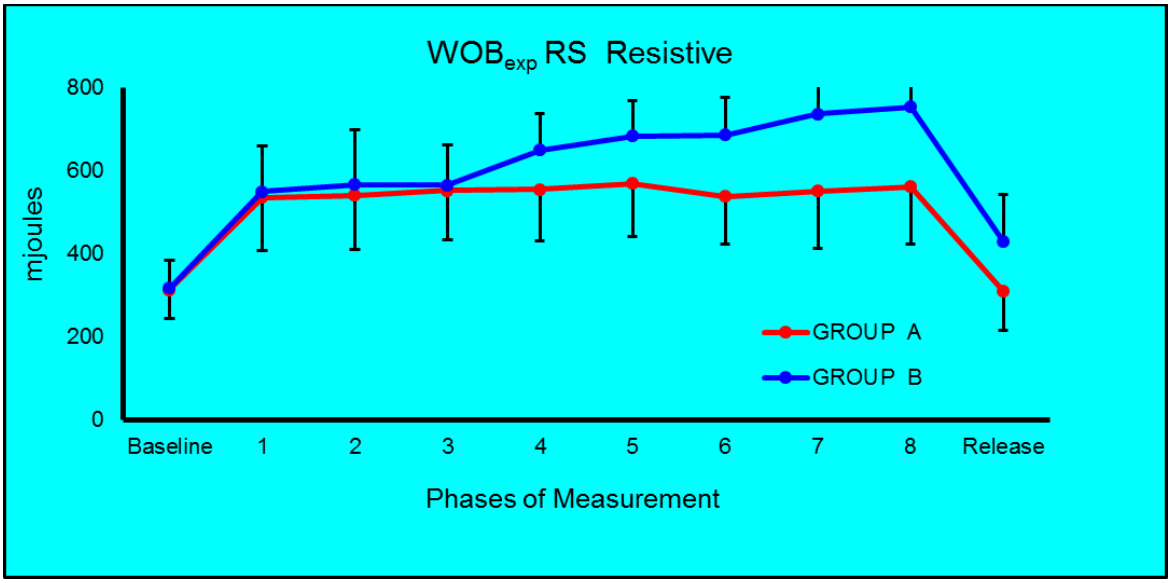
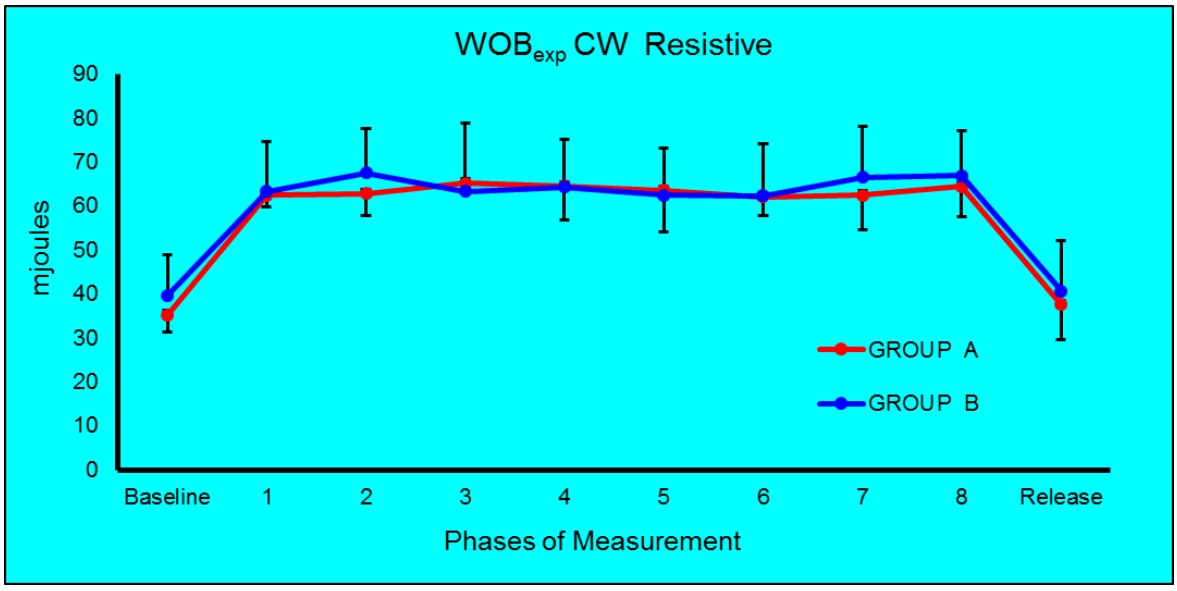
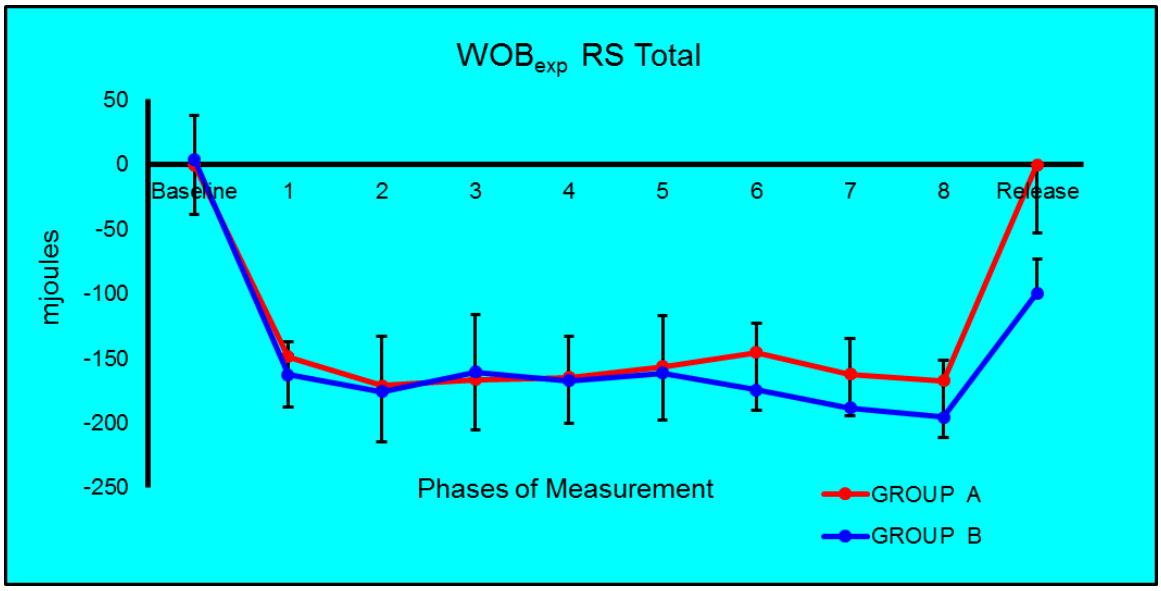


Figure 12. WOB_{exp} CW Resistive alterations



WOB_{exp} RS Total increased significantly after establishment of pneumoperitoneum in both Groups. Comparison between Groups was statistically significant at 180min ($p<0.05$) (Figure 13 & Table 3).

Figure 13. WOB_{exp} RS Total alterations



DISCUSSION

IAP increase is common among critically ill ICU patients, has detrimental effects on organs and systems and could affect the outcome[10,11]. Especially in regard to the mechanics of respiration, IAP increase has a significant impact on them and causes increase of the intrathoracic pressures due to the cephalad shift of the diaphragm, compliance decrease and WOB increase[12]. It is common that such medical conditions might necessitate the need for initiation of MV. Moreover, patients with respiratory failure under mechanical ventilation could have increased IAP.

Since sepsis is a factor causing intraabdominal hypertension (IAH) and vice versa we designed a study to simulate the clinical setting of IAH combined with sepsis. IAP increased via Helium insufflation by a pneumoperitoneaum creation device used in laparoscopic surgery.

Helium was selected in order to avoid the effects of CO_2 on pulmonary circulation. IAP was raised to 25mmHg and sepsis was induced by intravenous LPS administration. Ventilator settings were adjusted to ensure that the lungs remain open and all measurements were obtained under mechanical ventilation[12,13]. WOB of every studied component (RS, CW and L) was calculated based on the Campbell methodology by the use of pressure/volume loops[5,7,14].An esophageal balloon was used for the calculation of WOB of the CW[15,16].

WOB, which was calculated by the planimetry method, was influenced by IAP increase and sepsis. To be more specific, WOBinsp RS Resistive increased statistically significant both in the control and in the sepsis Group. Alterations were more excessive and statistically significant during sepsis, however WOBinsp RS Resistive values were restored in both Groups to

baseline level. Those alterations are attributed to PIP and EIP changes and demonstrate the need for MV in patients with abdominal compartment syndrome.

WOBinsp RS Elastic is significantly affected by the increased IAP. Sepsis causes further deterioration of the energy breathing economy and persistent disorders due to sepsis related alterations in the lung compliance. These findings were confirmed by the fact that there weren't any sepsis associated alterations regarding inspiratory resistive work and CW elasticity since sepsis does not have any impact on the mechanics of the CW.

IAP increase caused a statistically significant alteration in the inspiratory elastic work of the lungs in both groups. However, LPS administration resulted to a further significant increase ($p<0,001$), which confirms that this effect is non-reversible and remains in patients even after pneumoperitoneum release[17-19]. Both clinical and experimental studies have proved that IAP increase causes a rise in airway pressures and has detrimental effects on the mechanics of the respiratory system[12,20,21].

WOBexp RS Resistive values increased in both groups in a similar way and they were restored at the end of the study. However values remained persistently increased at higher levels in sepsis Group. As far as expiratory resistive work of the CW is concerned, it increased and returned to baseline values in both Groups. Increase of the expiratory resistive work is explained by the expiratory flow increase, which was recorded at all study phases due to facilitation of expiration by the increased pressure in the intraabdominal cavity and by resistance deterioration due to sepsis[22.]

All those before mentioned effects of increased IAP and sepsis on the work of breathing were depicted on our results, namely on the calculated values of total inspiratory and expiratory work. IAP increase results to a statistically significant increase of WOB insp RS Total and sepsis causes a further and non-reversible deterioration. This observation is in line with the results of other literature studies, which report the presence of severe respiratory failure in patients with increased IAP, that necessitates intensive care and initiation of MV when indicated[12,23].

In the setting of temporary increased IAP, alterations have a god profile and seem reversible, whereas in cases of sepsis, all disorders are persistent and not easily reversible. Controlled mechanical ventilation under general anesthesia and PEEP application have been already described in the literature and are considered as appropriate management techniques[12,13]. Coexistence of sepsis in patients with inrtaabdominal compartment syndrome makes management more difficult and worsens outcome. This is the reason why this clinical entity is considered to be an acute respiratory condition of dual localization and pathogenesis, namely both of the intraabdominal cavity and

of the chest wall and the lungs[24-26].

In an effort to estimate the effects of abdominal compartment syndrome and sepsis on expiratory work, we concluded that during pneumoperitoneum even statistically significant alterations are reversible, whereas during sepsis alterations are more excessive and persistent. IAP increase facilitates expiration as this is depicted by the negative sign of the corresponding calculated work. This finding could be useful in the clinical setting of patients with obstructive lung disorders. Sepsis has been previously associated with expiratory work increase due to a rise in the resistance of the respiratory tract and deterioration of lung mechanics[26-28].

According to experimental and clinical studies it has been proven that IAP increase has detrimental effects on respiratory mechanics and causes airway pressure increase and volume decrease[12,29]. All those alterations are successfully managed by a decompressive laparotomy, which is aiming at reducing IAP[12,30].

WOB alterations play a major clinical role in patients under mechanical ventilation since they can influence the chances of successful weaning[31-34].

Coexisting pathophysiological variables may cause more excessive and non-reversible alterations[26,35,36].

Limitations of the study

A model of increased IAP combined with sepsis was used in this experimental study. IAP increase was acute and controlled and sepsis was induced by LPS administration. In most clinical settings, ICU patients suffer from several comorbidities and IAP increase is neither acute nor controlled. Controlled mechanical ventilation under general anesthesia was applied to all study animals. Thereafter, WOB in our study has been taken over by the ventilator. The addition of one more study group with animals in sepsis without any other confounding factor would enlighten further the impact of each parameter on the WOB.

CONCLUSION

The findings of the present study confirm the detrimental effects of IAH and sepsis on the respiratory system. Alterations which are related to IAH have a good profile and are reversible, when IAP is restored. On the contrary, coexistence of sepsis triggers several internal processes, which on the one hand result to a deranged functional homeostasis and on the other hand cause persistent and more excessive alterations, which are not restored by simple release of the mechanical or biological factor.

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