Elias Ferreira Porto¹, Antonio Adolfo Matos de Castro², José Renato de Oliveira Leite³, Saul Vitoriano Miranda⁴, Auristela Lancauth⁴, Claudia Kumpel⁵

1.Master, Physiotherapist from the Physiotherapy Course of the Centro Universitário Adventista de São Paulo -UNASP, São Paulo (SP), Brazil and from the Research Group for Upper Limbs and Pulmonary Hyperinsuflation in COPD from the Universidade Federal de São Paulo - UNIFESP, São Paulo (SP), Brazil. 2. Master, Professor from the Post-Graduate Course in Intensive Care Therapy of the Centro Universitário Adventista de São Paulo - UNASP, São Paulo (SP), Brazil, Physiotherapist from the Heart Intitute (InCor) of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – USP, São Paulo (SP), Brazil; Researcher of the Pulmonary Rehabilitation Center of Universidade Federal de São Paulo - UNIFESP, São Paulo (SP), Brazil. 3. Professor from the Physiotherapy Course of Centro Universitário Adventista de São Paulo - UNASP, São Paulo (SP), Brazil and Physiotherapist from the Heart Institute (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – USP, São Paulo (SP), Brazil 4. Student from the Physiotherapy Specialization Course of Intensive Therapy of Centro Universitário Adventista de São Paulo – UNASP, São Paulo (SP), Brazil; 5. Master, Professor from the Physiotherapy Course at Centro Universitário Adventista de São Paulo - UNASP, São Paulo (SP), Brazil

Received from the Universidade Federal - UNIFESP, São Paulo (SP), Brazil.

Submitted on February 20, 2008 Accepted on August 6, 2008

Address for correspondence:

Elias Ferreira Porto
R. Almirante Luiz Penido Burnier 47/24
Jardim Sandra
05860-000 São Paulo (SP), Brazil.
E-mail: eliasfporto@gmail.com

Comparative analysis of respiratory system compliance in three different positions (lateral, supine and sitting) of patients on long-term invasive mechanical ventilation

Análise comparativa da complacência do sistema respiratório em três diferentes posições no leito (lateral, sentada e dorsal) em pacientes submetidos à ventilação mecânica invasiva prolongada

ABSTRACT

Objectives: This study is justified due to in clinical practice, positioning of the bedfast patient is constantly changed during stay in the intensive care unity. A better understanding is needed to acertain the possible adverse effects that such changes might cause, mainly in the respiratory system condition. The objective of this study was to evaluate if patient's positioning in bed may interfere with pulmonary compliance.

Methods: All patients included were submitted to mechanical ventilation and were sedated and curarized. Respiratory system compliance was assessed in three different positions: lateral, dorsal and sitting. After an alveolar recruitment maneuver, patients were placed in a position for two hours, and during the last five minutes data was collected from the mechanical ventilator display.

Results: Twenty eight patients were prospectively assessed. Values of

the respiratory system compliance in lateral decubitus were 37.07 ± 12.9 in dorsal decubitus were 39.2 ± 10.5 and in the sitting position were 43.4 ± 9.6 mL/cmH2O. There was a statistical difference when the sitting and dorsal positions was compared with the lateral for respiratory system compliance (p = 0.0052) and tidal volume (p <0.001). There was a negative correlation between mean values of positive end expiratory pressure and respiratory system compliance (r = 0.59, p = 0.002). The FIO₂ administered was 0.6 for the lateral decubitus and 0.5for the supine and sitting positions (p

Conclusions: Positioning of bedfast patients submitted to invasive mechanical ventilation induces oscillations of pulmonary compliance, tidal volume and SpO₂. Pulmonary compliance is higher in the sitting position than in the others.

Keywords: Pulmonary compliance; Artificial respiration

INTRODUCTION

An important aspect that must be assessed before ventilator weaning is compliance of the respiratory system, because mechanical ventilation weaning may be impaired by the patient's poor pulmonary condition.^{1,2} Compliance of the respiratory system is defined as the slope of the pressure-volume curve or the volume variation per unit of pressure change. The lungs and chest are formed by tissue with elastic properties, therefore compliance of the respiratory system is a measure of its elasticity and resistance to deformation by any force represented by variable degrees of effort.³

Compliance of the respiratory system may be measured with the patient

under mechanical ventilation and sedation⁴ and its measurement is expressed by dividing tidal volume by peak pressure less the positive end expiratory pressure (PEEP). To carry out measurement of the respiratory system's compliance with a patient under mechanical ventilation a previous alveolar recruitment maneuver is recommended, aiming to homogenize all pulmonary areas.³

One of the factors that may interfere, reducing or increasing compliance of the respiratory system is the patient's positioning in bed.⁴ Currently, it is recommended that positions be changed every two hours for patients in an intensive care unit (ICU).⁵

Studies show that compliance of the respiratory system undergoes significant changes between the sitting position and lateral decubitus, as well as increase in the inspiratory peak pressure. This same group showed that compliance of the respiratory system changes when the patient remains on mechanical ventilation for a prolonged period and increases the patient's risk of reintubation. ^{1,6}.

The purpose of this study was to evaluate the patient's positioning in the hospital bed that offers better pulmonary compliance in patients under invasive mechanical ventilation aiming at successful ventilator weaning.

METHODS

After approval by the Teaching and Research Commission of the hospitals, this study was carried out in two private hospitals in the city of São Paulo, from February to December of 2006.

Patients admitted at the ICU, submitted to prolonged mechanical ventilation, with ages varying from 18 to 81 years, hemodynamically stable and with no previous diagnosis of acute respiratory distress syndrome (ARDS) and pulmonary fibrosis were included.

Data collected were: age, clinical diagnosis of the patient, ventilatory and hemodynamic parameters. Ventilation data were collected from the display of the mechanical ventilator Raphel - Hamilton Medical*.

The medical team was asked to provide sedation and analgesia to inhibit the patients' respiratory drive. All patients were being ventilated in the pressure controlled ventilation (PCV) mode where all ventilation cycles were generated and controlled by the mechanical ventilator; precluding any alternative cycling mechanism.

Data collection was carried out in three positions:

lateral decubitus (LD), sitting position (SP) and dorsal decubitus (DD). The sequence of the positions was randomized.

After randomization, the patient was comfortably positioned in bed. Two hours thereafter the inspired fraction of oxygen (FiO₂) was set at 100% and a pulmonary homogenization was performed by increasing PEEP 2 by 2 cmH₂O up to 20 cmH₂O and maintained for 2 minutes. Afterwards, PEEP was reduced 2 by 2 cmH2O until the initial PEEP level was reached. After homogenization, data was collected. Patients remained in the recommended position for 5 minutes more with the minimal FiO₂ to keep arterial oxygen saturation (SaO₂) above 93%. After two hours in the next position, performance of pulmonary homogenization and data collection, SaO₂ should remain the same, but if the patient presented a dessaturation higher than 3% or SaO₂ lower than 90%, the FiO₂ would be increased.

Values of the tidal volume, inspiratory peak pressure, inspiratory flow, minute-volume, respiratory rate, inspiratory plateau pressure, PEEP, inspiratory flow, mean airways pressure, dead space/tidal volume ratio were obtained directly from the ventilator display. These values were monitored breath by breath for one minute. For assessment of the respiratory mechanics, the respiratory circuit humidifier was removed and statistical compliance of the respiratory system (mL/cm-H₂O) lung resistance (cmH₂O/L/m) and dead space/tidal volume ratio were measured.

An analysis of static compliance was achieved dividing tidal-volume by the plateau pressure from which PEEP value was subtracted. Total airways resistance was calculated dividing the difference between inspiratory peak pressure and plateau pressure by inspiratory flow.

Mechanical ventilation software allowed indirect calculation of pleural and alveolar pressure data. This data was monitored breath by breath on the mechanical ventilator display. Transpulmonary pressure was calculated subtracting alveolar pressure from pleural pressure. Dynamic compliance of the respiratory system was measured by the formula: tidal-volume/inspiratory peak pressure subtracted from the PEEP value.² Respiratory rate, PEEP and FiO₂ were maintained during the entire procedure. For statistical analysis the maximum value obtained for each parameter was considered.

After data collection, patient was placed in the next adopted position and the procedures were repeated.

Statistical Analysis

Data are expressed as mean,± standard deviation,

minimum and maximum. Analysis of variables in three moments was carried out using variance analysis of repeated measurements (ANOVA RM) with the Bonferroni post-test. For analysis of associative strength among variables, Pearson's correlation was used. A p< 0.05 value was considered as statistically significant.

RESULTS

This study had the participation of 28 patients, 17 of the male gender, with a mean age of 51.1 ± 17.4 years (18 and 81). The most frequent diagnosis was intestinal neoplasia found in 28.5% of patients while the most frequent complication was respiratory failure in 60.7% of them. There were no side effects during data collection procedure, except for five patients who had a SaO₂ lower than 90% in lateral decubitus and one

in the dorsal.

All patients in the study were under invasive mechanical ventilation in PCV. Data are shown in Chart 1.

Mean values of respiratory system compliance in LD were $37.07 \pm 12.9 \text{ mL/cmH}_2\text{O}$, in DD $39.2 \pm 10.5 \text{ mL/cmH}_2\text{O}$ and in the SP $43.4 \pm 9.6 \text{ mL/cmH}_2\text{O}$, respectively. Statistically significant differences were found in the mean values of the respiratory system compliance, when comparing the sitting position and the dorsal decubitus to the lateral decubitus (p=0.0052 (Figure 1). Regarding pulmonary compliance, no statistically significant differences were found for the three positions (Figure 2).

Mean values of exhaled tidal volume in LD was 670 ± 202 mL, in DD was 690 ± 229 mL in SP 705 ± 269 mL. There was a statistical significance between DD and SP in relation to LD (p < 0.001) (Figure 3).

Chart 1 – Demographic characteristics, diagnosis and clinical complications in the patients studied (n = 28)

Gender	Age	Diagnosis	Complications
M	59	Ischemic stroke + hepatic failure	Pneumonia, ARF
F	61	Colon neoplasia, medullar aplasia	Septic shock, ARF
F	59	Endometrial neoplasia	Septic shock
M	74	Acute pulmonary edema , CHF	ARF shock, ARF pneumonia,
M	64	CHF	Pleural effusion
M	65	Cardiomegaly, Chagas	AReF, sepsis
F	26	Cranioencephalic traumatism, polytrauma	Hemothorax, ARF
M	74	Daibetic ketoacidosis	Sepsis
M	22	Cranioencephalic trauma	Pneumonia
M	47	Polytrauma	Septic shock
F	30	Intestinal cancer	Pleural effusion
F	18	High thoracic medullary injury	Pneumonia
M	53	Acute myocardial infraction	Cardiogenic shock
F	60	Renal failure	Pulmonary edema
F	31	Sepsis	Septic shock
M	70	Cardiogenic shock	ARF
M	55	Cranioencephalic trauma	Pneumothorax
M	81	Lung neoplasia	ARF
M	52	Rectum resection due to neoplasia	None
M	41	Pulmonary thromboembolism	ARF
M	61	Choledochoplasty due to neoplasia	Sepsis
M	69	Rectosimoydectomy	None
M	63	Antero-lateral acute myocardial infraction	Cardiogenic shock
M	45	Renal failure, metastatic neoplasia in the left lung	ARF
F	35	Sepsis	Septic shock
F	30	Respiratory failure	None
F	31	Respiratory failure	None
F	55	Respiratory failure	None

CHF- cardiac heart failure, ARF - acute renal failure, AReF - acute respiratory failure

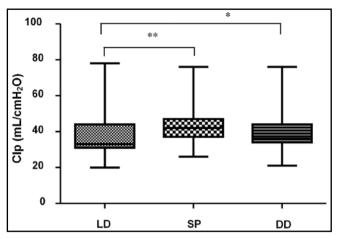


Figure 1 – Values of the respiratory system compliance in the three positions studied. Clp – compliance, LD – lateral decubitus, SP – sitting position, DD – dorsal decubitus. * p < 0.01, ** p < 0.001

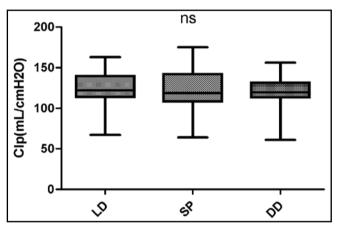


Figure 2 – Values of pulmonary compliance in the three positions studied. Clp – compliance, LD – lateral decubitus, SP – sitting position, DD – dorsal decubitus, NS – not significant

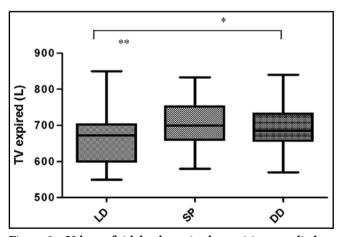


Figure 3 – Values of tidal volume in the positions studied. TV – expired tidal volume, LD – lateral decubitus, SP – sitting position, DD – dorsal decubitus. * p < 0.01, ** p < 0.001

Mean peak pressure in LD was 24.6 ± 4.5 (14 to 31); in DD mean was 24.6 ± 4.7 (14 to 30) cmH₂O. While in SP mean was 25.3 ± 4.7 (16 to 35) cmH₂O. Therefore no difference was found in the peak pressure in the different positioning (p = 0.81).

Alveolar pressure was significantly higher in SP (21 cm H_2O) in relation to LD (18 cm H_2O) p = 0.0067, but no difference was found between DD, SP and LD. Transpulmonary pressure was higher in SP (p<0.001) and DD (p < 0.01) than in LD (Figure 4).

Mean values of airways pressure in LD and DD respectively were 15.9 ± 5.7 and 16.4 ± 6.6 ; and in SP was of 16.9 ± 7.3 , with no statistical difference among them (p = 0.34). Mean PEEP values in the three positions were similar, with no statistical difference (p=0.99). There was a negative correlation between the mean values of PEEP and pulmonary compliance (r = -0.59, p = 0.002).

Mean values of respiratory rate in the three positions were similar, with no statistically significant difference (p=0.99).

Mean values of inspiratory flow in LD and DD were 65.8 ± 21.3 and 63 ± 19 L/s, respectively; in SP was 65.7 ± 6.8 L/s. A statistically significant difference was found when LD was compared with the other positions (p=0.044).

There was a statistically significant difference (p=0.049) regarding mean values of the FiO_2 in the sitting and dorsal positions in relation to LD, considering that the given FIO2 would be minimally sufficient to keep a SpO_2 higher or equal to 93%. For LD, FIO2 was 0.6; for DD and SP it was 0.5.

Figure 5 shows results achieved in the three positions in relation to mean values of minute-volume. It was verified that minute-volume was lower in the lateral decubitus when compared with dorsal decubitus and the sitting position (p< 0.0002).

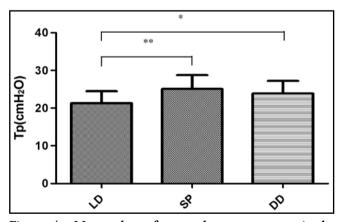


Figure 4 – Mean values of transpulmonary pressure in the positions studied. TP – transpulmonary pressure, LD – lateral decubitus, SP – sitting position, DD – dorsal decubitus. * p < 0,01, ** p < 0,001

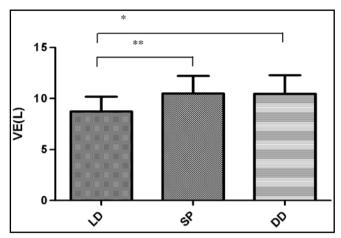


Figure 5 – Mean values of minute-ventilation in the positions studied. VE – minute volume, LD – lateral decubitus, SP – sitting position, DD – dorsal decubitus. * p < 0,01, ** p < 0,001

DISCUSSION

As a priority, the present study analyzed the influence of body positioning on the physiological changes of pulmonary pressures, volumes and flows. The essential finding is that the sitting position provided the highest value of compliance of the respiratory system, although the same situation was not found for pulmonary compliance, higher tidal volume and consequently minute-volume. However, it did present a lower pulmonary inspiratory flow.

Some authors report that under normal conditions the lower regions of the lungs ventilate better that the upper. The However, it was noted that in patients in LD during controlled mechanical ventilation, the contralateral lung ventilated better, as its alveolar units are more distensible and less resistant to the air flow than the homolateral lung (dependent pulmonary zone).

Pulmonary functions may be affected by position changes.⁷ The importance of position change in specified periods (at each 2 hours) is not only to avoid dermatological lesions, but also to improve respiratory and vascular functions.¹⁰

In this study it was observed that patient positioning in the bed greatly interferes with compliance of the respiratory system, as well as with the PEEP level to be used. It was noted that the higher the PEEP value used, the worse was the pulmonary compliance found. Since PEEP fosters oxygenation by increasing the cross-sectional area of the alveolus, a situation of pulmonary hyperinsuflation is ensured. This situation allows a modest volume increase due to pressure generated by the respiratory muscles, that is to say, a small increase of pulmonary compliance; on the

other hand, the highest force vector generated is that of elastic recoil, that is, of greater elastance.

Some studies showed a greater compliance of the respiratory system in lateral decubitus and established that in this position, the weight of the mediastinum and the displacement of the abdominal content contributed to the gradient of vertical pleural pressure¹¹⁻¹³, therefore suggested that only LD provides greater compliance to the respiratory system. As a counterpart, another study showed that compliance of the respiratory system is greater in the SP and DD when compared to LD; possibly because alveolar units are less distensible and offer greater resistance to the airflow due to the mechanical disadvantage presented by the patient when in LD.⁹

In this study, greater compliance of the respiratory system was observed in the sitting position in relation to the lateral and dorsal decubitus (p=0.0052). This was ascribed to the dependent zone in the sitting position, which is the area of the pulmonary base. Indeed, this is smaller than the areas of the dependent regions in the other positions. Therefore this allows the remaining non dependent zones to be more compliant. Time constant may also be altered by change of position causing discrepancies in the distribution of ventilation, the lower compliance units fill more quickly than the others. Pulmonary units with high compliance and normal resistance of the airways have a large expansion, while those with poor compliance have a shorter filling time.¹⁴

It was further observed that tidal volume was greater in the sitting position than in the dorsal and lateral decubitus (p=0.001). This was related to compliance of the respiratory system, which is a measure of elasticity and resistance to deformation when facing any force represented by varied degrees of effort. ^{15,16} It was also seen that the pulmonary flow is lesser in dorsal decubitus than in the lateral and sitting position (p=0.044). This is probably due to a greater mechanical compression in the chest when in dorsal decubitus, thereby reducing respiratory flow.

Specifically regarding the sitting position, inspiratory flow was smaller, probably because of increased resistance of the airway. This position is the same one that assured greater compliance of the respiratory system when compared to the other positions and therefore greater pulmonary ventilation. In general, this may have taken place due to the great distensibility that took place because of the large quantity of air filling the alveoli and bringing about a decrease of the inspiratory flow, that is to say close to the maximum alveolar capacitance.

Consequently, there is an exponential increase in the

resistance of the airway and in the pulmonary parenchyma. Resistance is expressed by the amount of intrathoracic pressure produced, divided by the pulmonary flow. Therefore, in this condition, a large increase of muscular pressure would be needed to generate a minimum inspiratory flow, because of the large alveolar distensibility and resistance. 17,18

Limitations of this study are due to the fact that data were not collected in a continuous manner, for two hours as suggested by the studies; that changes in decubitus must be carried out every two hours, and thus changes in pulmonary compliance in the different positions could have been much better quantified, as well as reading of pleural and alveolar pressure by an indirect method, which would be more reliable if obtained by introducing an esophageal balloon which is a reliable method.

We concluded that body positioning of patients submitted to invasive mechanical ventilation produces variation in the compliance of the respiratory system. In the sitting position compliance of the respiratory system is greater when compared to the dorsal and lateral decubitus.

In the sitting position a lower inspiratory flow than in lateral and dorsal decubitus takes place. And, not-withstanding the body positioning there is progressive reduction of pulmonary compliance when a progressive increase of the positive pressure at the end of expiration takes place.

These conclusions lead us to suggest that when changing the positioning of patients in bed, alterations of the patient's ventilatory mechanics must be carefully assessed.

RESUMO

Objetivos: A realização deste estudo se justifica pelo fato que na prática clinica ocorrem constantes mudanças de decúbito do paciente no leito durante a hospitalização na terapia intensiva, sendo que necessita melhor entendimento sobre possíveis efeitos adversos principalmente sobre as condições do sistema respiratório que tais mudanças podem ocasionar. O objetivo deste estudo foi avaliar se o posicionamento do paciente no leito pode interferir na complacência pulmonar.

Métodos: Todos os pacientes incluídos neste estudo estavam em ventilação mecânica, e foram sedados e curarizados. Verificou-se a complacência do sistema respiratório de todos os pacientes em três diferentes posicionamentos: decúbito lateral (DL), decúbito dorsal (DD) e sentado (PS), para tanto, após a manobra de recrutamento alveolar os pacientes ficavam no posicionamento definido por 2 horas e nos últimos 5 min os dados eram colhidos do *display* do ventilador mecânico.

Resultados: Vinte e oito pacientes foram prospectivamente analisados, Os valores de complacência do sistema respiratório no DL foram 37.07 ± 12.9 no DD 39.2 ± 10.5 e na PS 43.4 ± 9.6 mL/cmH $_2$ O Houve diferença estatisticamente significativa quando a PS e a DD foram comparadas com a DL para complacência o sistema respiratório (p = 0.0052) e volume corrente (p < 0.001). Houve correlação negativa entre os valores médios de pressão expiratória final positiva e complacência do sistema respiratório (r = 0.59, p = 0.002). Para o DL a FIO $_2$ foi 0,6, para o DD e posição sentada foi 0,5. (p = 0,049).

Conclusões: O posicionamento dos pacientes no leito, em ventilação mecânica invasiva, ocasiona variação na complacência do sistema respiratório, volume corrente e saturação de oxigênio. Na posição sentada a complacência do sistema respiratório é maior quando comparada aos decúbitos dorsal e lateral.

Descritores: Complacência pulmonar; Respiração artificial

REFERENCES

- 01. Meade M, Guyatt G, Cook D et al Predicting success in weaning from mechanical ventilation. Chest, 2001;120:(Suppl6):400S-424S.
- 02. Azevedo JRA. Ventilação mecânica prolongada e desmame do respirador na insuficiência respiratória aguda do paciente com DPOC. J Pneumol. 1985; 11(4):185-9.
- 03. West JB Fisiologia respiratória. 6a ed. São Paulo: Manole;
- 04. Jolliet P, Bulpa P, Chevrolet JC. Effects of the prone position on gas exchange and hemodynamics in severe acute respiratory distress syndrome. Crit Care Med. 1998; 26(12):1977-85. Comment in: Crit Care Med. 1998; 26(12):1934-5.
- 05. Blanes L, Duarte IS, Calil JA, Ferreira LM. Avaliação clí-

- nica e epidemiológica das úlceras por pressão em pacientes internados no Hospital São Paulo. Rev Assoc Med Bras (1992). 2004; 50(2):182-7.
- 06. Porto EF, Coelho AF. Estudo comparativo da PEEP ideal X PEEP fisiológica em pacientes cardiopatas hemodinamicamente estáveis quando submetidos à Ventilação Mecânica. Rev Soc Cardiol Estado de Sao Paulo. 2003; 13:(Supl):114
- 07. Zanotti E, Rubini F, Iotti G, Braschi A, Palo A, Bruschi C, et al. Elevated static compliance of the total respiratory system: early predictor of weaning unsuccess in severed COPD patients mechanically ventilated. Intensive Care Med. 1995; 21(5):399-405.
- 08. Auler JO Jr, Carmona MJ, Barbas CV, Saldiva PH, Malbouisson LM. The effects of positive end-expiratory pressure on respiratory system mechanics and hemodynamics

- in postoperative cardiac surgery patients. Braz J Med Biol Res. 2000; 33(1):31-42.
- 09. Blanch L, Mancebo J, Perez M, Martinez M, Mas A, Betbese AJ, et al. Short-term effects of prone position in critically ill patients with acute respiratory distress syndrome. Intensive Care Med. 1997; 23(10):1033-9.
- Gentilello L, Thompson DA, Tonnesen AS, Hernandez D, Kapadia AS, Allen SJ, et al - Effect of a rotating bed on the incidence of pulmonary complications in critically ill patients. Crit Care Med. 1988; 16(8):783-6.
- 11. Numa AH, Hammer J, Newth CJ. Effect of prone and supine positions on functional residual capacity, oxygenation, and respiratory mechanics in ventilated infants and children. Am J Respir Crit Care Med. 1997;156(4 Pt 1):1185-9.
- 12. Kenyon CM, Pedley TJ, Higenbottam TW. Adaptive modeling of the human rib cage in median sternotomy. J Appl Physiol. 1991; 70(5):2287-302.
- 13. Pelosi P, Bottino N, Chiumello D, Caironi P, Panigada M, Gamberoni C, et al. Sigh in supine and prone position

- during acute respiratory distress syndrome. Am J Respir Crit Care Med. 2003; 167(4):521-7.
- 14. Jandre FC, Pino AV, Ascoli A, Giannella-Neto A. Controlador automático da ventilação pulmonary mecânica: projeto e simulação. Rev Bras Eng Biomed. 2002; 18(2):99-110.
- 15. Servillo G, Roupie E, De Robertis E, Rossano F, Brochard L, Lemaire F, Tufano R. Effects of ventilation in ventral decubitus position on respiratory mechanics in adult respiratory distress syndrome. Intensive Care Med. 1997; 23(12):1219-24.
- 16. Avanzolini G, Barbini P, Cappello A, Cevenini G. Influence of flow pattern on the parameter estimates of a simple breathing mechanics model. IEEE Trans Biomed Eng. 1995; 42(4):394-402.
- 17. 17 Manco JC. Fisiologia e fisiopatologia respiratórias. Medicina (Ribeirao Preto). 1998; 31(2):177-90.
- Green M, Pride NB. Normal respiratory mechanics. In: Scadding JG, Cumming G, Thurlbeck WM. Scientific foundations of respiratory medicine. Philadelphia: W.B. Saunders; 1981. p. 113-29.