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Original Article

# PRESSÃO POSITIVA NA VENTILAÇÃO MECÂNICA INVASIVA E IMPLICAÇÕES RENAIS EM PACIENTES CRÍTICOS

# POSITIVE PRESSURE ON INVASIVE MECHANICAL VENTILATION AND RENAL IMPLICATIONS IN CRITICAL PATIENTS

# PRESIÓN POSITIVA SOBRE VENTILACIÓN MECÁNICA INVASIVA E IMPLICACIONES RENALES EN PACIENTES CRÍTICOS

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## RESUMO

**Objetivo:** Verificar se há influência da ventilação mecânica com pressão positiva, ao final da expiração, na função renal de pacientes internados em unidade de terapia intensiva. **Método:** Estudo prospectivo e quantitativo realizado, em unidade de terapia intensiva, especializada em trauma ortopédico e medular. A amostra foi não probabilística, composta por 31 pacientes em ventilação mecânica invasiva que desenvolveram lesão renal aguda na internação. Os pacientes foram alocados em grupos, conforme valor da pressão positiva, ao final da expiração, e os dados coletados por questionário estruturado. Para a análise das variáveis, realizaram-se testes não paramétricos. Resultados com p ≤ 0,05 foram considerados significativos. **Resultados:** A idade média foi 46,94±24,2 anos com predominância do sexo masculino (61,3%). A disfunção renal (70,97%), no estágio 1(risco) (35,5%), predominou. Pacientes com maior pressão positiva, ao final da expiração, evoluíram com disfunção renal (p=0,04). Além disso, para aqueles com pressão positiva, ao final da expiração≥ 10cmH2O, a idade (p=0,05) e a disfunção renal (p=0,04) mostraram-se associados significativamente. **Conclusão:** Pacientes críticos em ventilação mecânica invasiva com pressão positiva, ao final da expiração mais elevada, mostraram reunir maior predisposição para a lesão renal aguda.
**Descritores:** Lesão Renal Aguda; Respiração Artificial; Unidades de Terapia Intensiva.

## ABSTRACT

**Objective:** To verify if there is influence of positive end-expiratory pressure (PEEP) used in invasive mechanical ventilation (IMV) on renal function in ICU patients. **Method:** Prospective and quantitative study conducted in an intensive care unit specialized in orthopedic and spinal cord trauma. The sample was non-probabilistic, consisting of 31 patients on invasive mechanical ventilation who developed acute kidney injury during hospitalization. Patients were allocated to groups according to positive end-expiratory pressure and data collected by a structured questionnaire. For the analysis of the variables, nonparametric tests were performed using SPSS software (version 23). Results with p ≤ 0.05 were considered significant. **Results:** The mean age was 46.94 ± 24.2 years old, with male predominance (61.3%). Renal dysfunction (70.97%) in stage 1 (risk) (35.5%) predominated. Patients with higher positive end-expiratory pressure developed renal dysfunction (p = 0.04). In addition for those with positive end-expiratory pressure ≥ 10cmH2O, age (p = 0.05) and renal dysfunction (p = 0.04) were significantly associated. **Conclusion:** Critical patients on invasive mechanical ventilation with positive end-expiratory pressure were shown to have a greater predisposition to acute kidney injury.
**Descriptors:** Acute Kidney Injury; Respiration, Artificial; Intensive Care Units.

## RESUMEN

**Objetivo:** Para verificar si hay influencia de la presión positiva al final de la espiración (PEEP) utilizada en la ventilación mecánica invasiva (IMV) en la función renal en pacientes de la UCI. **Método:** Estudio prospectivo y cuantitativo realizado en una unidad de cuidados intensivos especializada en traumatismos ortopédicos y de médula espinal. La muestra no fue probabilística, consistió en 31 pacientes con ventilación mecánica invasiva que desarrollaron lesión renal aguda durante la hospitalización. Los pacientes fueron asignados a grupos de acuerdo con la presión positiva al final de la espiración y los datos recopilados mediante un cuestionario estructurado. Para el análisis de variables, se realizaron pruebas no paramétricas en SPSS versión 23. Los resultados con p ≤ 0.05 se consideraron significativos. **Resultados:** La edad media fue de 46,94 ± 24,2 años con mayoria masculina (61,3%). Predominó la disfunción renal (70.97%) en la etapa 1 (riesgo) (35.5%). Los pacientes con mayor presión positiva al final de la espiración desarrollaron disfunción renal (p = 0.04). Además, para aquellos con presión positiva al final de la espiración ≥ 10cmH2O, la edad (p = 0.05) y la disfunción renal (p = 0.04) se asociaron significativamente. **Conclusion:** Los pacientes críticos con ventilación mecánica invasiva y con presión positiva al final de la espiración mostraron una mayor predisposición a la lesión renal aguda.
**Descriptores:** Lesión Renal Aguda; Respiración Artificial; Unidades de Cuidados Intensivos.

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## INTRODUCTION

Positive end-expiratory pressure (PEEP) on invasive mechanical ventilation (IMV) may cause neuro-hormonal changes in critically ill patients due to activation of the sympathetic neuro-vegetative system, renin-angiotensin, and suppression of atrial natriuretic peptide release, inducing fluid retention and decreased renal blood flow, potential causes of acute kidney injury (AKI)[(1)]. Thus, the identification of mechanisms and / or modifiable factors may be useful to better manage management, as well as the process of systematizing care and safety of critically ill patients with AKI[(1-2)].

Invasive mechanical ventilation associated with high intrathoracic pressures resulting from the ventilator-lung interaction may reduce cardiac output, predisposing to inadequate renal perfusion, gas exchange abnormalities that determine hypoxemia, hypercarbia, and systemic acidosis, which in turn may influence renal vascular resistance, altering renal perfusion pressures, culminating in AKI[(3)].

AKI is a potentially reversible syndrome defined as an abrupt reduction in renal function associated with the accumulation of nitrogen solutes. Serum creatinine level and urine output were assessed over a period of up to seven days, with potential reversibility within 48 hours of the insult onset[(4)].

The etiology of AKI is multi-factorial[(5)] hospitalization (10% to 18%), especially in developing countries. Studies have shown an association between the occurrence of AKI and IMV in Brazil and worldwide[(6-8)]. The relationship between lungs and kidneys is clinically important in the health-disease process, considering that IMV causes hemodynamic abnormalities associated with reduced cardiac output, compromising renal perfusion, as well as like hormonal stimulation and the sympathetic pathways[(8-9)].

Early prediction of the risk of complications and mortality for AKI patients can contribute and direct decision-making in time for appropriate action to be taken, considering that AKI is a heterogeneous disease and its cause is complex, which makes these predictions a challenging task[(10)]. AKI is therefore a condition that developing countries cannot ignore, and an appreciation of its local standard can contribute and underpin policies for its prevention and management[(11)]. Regarding the importance of this theme, the aim of this study was to verify if there is influence of positive end-expiratory pressure (PEEP) used on invasive mechanical ventilation (IMV), renal function in ICU patients.

## METHODS

Observational, longitudinal, prospective and quantitative study conducted at the Intensive Care Unit, specialized in orthopedic and spinal cord trauma, from a public hospital in the Federal District, Brazil, from December 2015 to December 2016.

The sample was non-probabilistic (convenience), consisting of 31 ICU patients for at least seven days and, at the end of this period, the outcome (AKI and death) was verified.

Inclusion criteria were patients aged 18 years or older, with serum creatinine alteration for more than 24 hours after ICU admission. Patients with a history of prior renal injury, according to electronic medical records and chronic renal failure (stages 4 and 5) were excluded by the Kidney Disease Improving Global Outcomes (KDIGO) classification[(4)].

The baseline creatinine serum level was that recorded up to one month before ICU admission. For data collection, a questionnaire consisting of patient demographics, clinical history (comorbidities, length of stay, time on mechanical ventilation, ventilatory parameters), hemodynamic variables (blood pressure, oximetry, respiratory rate, heart rate, temperature), laboratory parameters (serum creatinine, potassium and urea) recorded daily.

To evaluate laboratory parameters, the reference value assumed by the study hospital was adopted: Creatinine (mg / dL): 0.80 - 1.40; Potassium (mEq / L): 3.60 - 5.0; Sodium (mEq / L): 135.0 - 148.0; Urea (mg / dL): 10.0 - 50.0; Hemoglobin (g / dL): 13.0 - 17.0; and Hematocrit (%): 42.0 - 50.0.

Data collection followed the protocol:

Step 1: Patient allocation in a given group according to the programmed PEEP value on the mechanical ventilator, as follows: (1) group 1 - IMV with PEEP ≤ 5cmH2O; (2) group 2 - IMV with PEEP> 5cmH2O and <10cmH2O; (3) group 3 - IMV with PEEP ≥ 10cmH2O.

Step 2: Daily patient follow-up for seven days through medical records.

Stage 3: Staging the severity of renal impairment, based on serum creatinine values, according to the KDIGO classification [(4)].

Stage 4: analysis of the outcome of participants, at the end of ICU stay (discharge, death).

The assessment of renal function was based on the KDIGO classification[4] – which allows the staging of renal function based on the variation of serum creatinine value in relation to basal creatinine and urinary output. The severity of impairment is determined by stages distributed as follows: (1) stage 1 (lower severity), when there is a 1.5 to 1.9 fold increase or 0.3 mg / dL in basal creatinine and urinary output less than 0.5 mL / kg / h for 6 to 12 hours; (2) stage 2 (moderate severity), when there is a 2.0 to 2.9-fold increase in basal creatinine or urinary output less than 0.5 mL / kg / h for 12 hours or more, and finally (3), stage 3 (greater severity) is a 3.0-fold increase in basal creatinine or an increase of 4.0 mg / dL or initiation of dialysis therapy in children under 18 years of age with a creatinine clearance of less than 35 mL / min / 1.73 m² and / or urinary output less than 0.3 mL / kg / h for a time greater than or equal to 24 hours or anuria for a time greater than or equal to 12 hours.

Data was expressed as absolute frequency (n), relative frequency (%), mean and standard deviation for the normal distribution of the sample. For asymmetric distribution, verified after normality test, the median and the 25th and 75th percentiles were calculated and Fisher's Exact and Mann-Whitney non-parametric tests were applied. Results with p values ≤ 0.05 were considered significant.

## RESULTS AND DISCUSSION

Of the 31 patients, most were male (61.3%) with median age and body mass index of 43 (27-64) years and 23 (21-25) kg / m2, respectively. The length of stay was 10.5 ± 37.2 days. Most used antibiotics (96.8%), noradrenaline (83.9%) and furosemide (67.7%). Mortality affected 9.7% of patients (Table 1).

Table 1 - Distribution of patients (n = 31) according to sociodemographic and clinical characteristics. Brasilia, DF, Brazil, 2016.

| Variable | n (%) | Average±SD | Median (25-75) |
|---|---|---|---|
| **Sex** | | | |
| Male | 19 (61.3) | - | - |
| Female | 12 (38.7) | - | - |
| Age | - | 46.94±24.2 | 43 (27-64) |
| Height | - | 164.3±9.7 | 164 (155-172) |
| BMI | - | 23.5±4.0 | 23 (21-25) |
| Weight | - | 63.1±10.3 | 59 (57-70) |
| Death | 3 (9.7) | - | - |
| **Number of days** | | | |
| Hospitalization | - | 10.5±37.2 | |
| IMV | - | 22.0±55 | 7 (7-11) |
| **Number of days** | | | |
| Noradrenaline | - | 4.0±2.5 | - |
| Furosemide | - | 3.0±2.8 | - |
| Antibiotics | - | 5.7±2.0 | - |
| Bladder catheter | - | 6.0±2.0 | - |
| **Use of medication** | | | |
| Noradrenaline | 26 (83.9) | - | - |
| Dobutamine | 2 (6.4) | - | - |
| Furosemide | 21 (67.7) | - | - |
| Antibiotics | 30 (96.8) | - | - |

BMI = Body Mass Index. IMV = Invasive Mechanical Ventilation.

The results showed preservation of the hemodynamic profile and some changes in biological variables, such as serum urea elevation (59.3 ± 35mg / dL), hemoglobin reduction (10.7 ± 9.1g / dL) and hematocrit (31.3 ± 6.6%). There was a tendency to maintain acid blood pH (7.3 ± 0.09) (Table 2).

Table 2 - Distribution of hemodynamic and biological variables of patients (n = 31) admitted to the Intensive Care Unit. Brasilia, DF, Brazil, 2016.

| Variable | Average±SD |
|---|---|
| **Hemodynamics** | |
| SBP (mmHg) | 133.0±23 |
| DBP(mmHg) | 70.0±16 |
| HR (bpm) | 85±22 |
| RF (rpm) | 17±3 |
| SpO2 (%) | 97±7 |
| **Biological** | |
| Creatinine (mg/dL) | 1.05±0.6 |
| Potassium (mEq/L) | 3.8±0.7 |
| Sodium (mEq/L) | 140±11 |
| Ureia (mg/dL) | 59.3±35 |
| Hemoglobin (g/dL) | 10.7±9.1 |
| Hematocrit (%) | 31.3±6.6 |
| pH | 7.3±0.09 |

SBP = systolic blood pressure. DBP = diastolic blood pressure. HR = heart rate. RR = respiratory rate. SpO2 = peripheral oxygen saturation.

Most patients under positive pressure invasive mechanical ventilation developed stage 1 renal dysfunction, ie, less severe (35.5%) and a lower percentage in stage 2, of moderate severity (16.1%). according to KDIGO classification (Table 3).

Table 3 - Distribution of patients (n = 31), in stages of renal dysfunction, according to the KDIGO classification. Brasilia, DF, Brazil, 2016.

| Stage | n (%) |
|---|---|
| Stage 1 (risk) | 11 (35.5) |
| Stage 2 (injury) | 5 (16.1) |
| Stage 3 (failure) | 6 (19.4) |

Patients with acute respiratory failure (ARF) (31.8%) and pneumonia (50%) were more likely to develop renal dysfunction. Patients with higher PEEPs evolved with renal dysfunction (p = 0.04). There were no patients classified in Group 1 (PEEP≤5cm / H2O) (Table 4).

Table 4 - Univariate analysis of the clinical characteristics, in relation to the renal function of the hospitalized participants, in the Intensive Care Unit. Brasilia, DF, Brazil, 2016.

| **Characteristics** | **No renal dysfunction (n = 9)** | | **With renal dysfunction (n = 22)** | | **p** |
|---|---|---|---|---|---|
| | **n (%)** | **Median (25-75)** | **n (%)** | **Median (25-75)** | |
| Male sex | 5 (55.6) | | 14 (63.6) | | 0.5‡ |
| Age (years) | | 35 (31 – 51) | | 46 (25 – 67) | 0.7† |
| BMI (kg/m²) | | 24.2 (22.1 – 25.6) | | 22.5 (20.0 – 23.9) | 0.2† |
| Noradrenaline Time (days) | | 4 (3 – 6) | | 5 (4 - 7) | 0.3† |
| Furosemide time (days) | | 2 (1 - 6) | | 4 (4 - 7) | 0.2† |
| ATB time (days) | | 7 (3 - 7) | | 7 (6 - 7) | 0.5† |
| MV Time (days) | | 7 (5 - 7) | | 7 (7 - 12) | 0.3† |
| Death | 1 (11.1) | | 2 (9.1) | | 0.7‡ |
| ARF | 5 (55.6) | | 11 (50.0) | | 0.5‡ |
| PEEP – Group 2 | 9 (100.0) | | 14 (63.6) | | 0.04‡ |
| PEEP – Group 3 | 0 (0.0) | | 8 (36.4) | | 0.04‡ |
| **Current diagnosis** | | | | | |
| Septic shock | 2 (22.2) | | 5 (22.7) | | 0.7‡ |
| Pneumonia | 5 (55.6) | | 11 (50.0) | | 0.5‡ |
| Sepsis pulmonary origin | 2 (22.2) | | 2 (9.1) | | 0.3‡ |
| ARF | 5 (55.6) | | 7 (31.8) | | 0.2‡ |
| Transtrochanteric fracture IPO | 1 (11.1) | | 6 (27.3) | | 0.3‡ |
| **Comorbidities** | | | | | |
| SAH | 2 (22.2) | | 3 (13.6) | | 0.5‡ |
| DM | 2 (22.2) | | 2 (9.1) | | 0.3‡ |
| **Drugs in use** | | | | | |
| Noradrenaline | 7 (77.8) | | 19 (86.4) | | 0.5‡ |
| Furosemide | 5 (55.6) | | 16 (72.7) | | 0.3‡ |

† Mann-Whitney test; ‡ Fisher's test; BMI = body mass index; ATB = antibiotic; MV = mechanical ventilation; ARF = acute respiratory failure; PEEP = positive end-expiratory pressure; PEEP Group 2 = PEEP> 5 and ≤10cmH2O; PEEP Group 3- PEEP> 10 cmH2O; IPO = immediate postoperative period; SAH = systemic arterial hypertension; DM = diabetes mellitus.

Having a younger median age [27 (22 - 38) years] significantly interfered with the need for mechanical ventilation with higher PEEP (> 10 cmH2O) (p = 0.05). Obesity and gender did not influence the value of PEEP employed in the ventilatory strategy (p> 0.05). Patients with PEEP> 5 and ≤10cmH2O died more frequently (13%), although without statistical significance (Table 5).

Table 5 - Relationship between clinical characteristics and positive end-expiratory pressure (PEEP) value of inpatients in the Intensive Care Unit. Brasilia, DF, Brazil, 2016.

| **Characteristics** | **PEEP – Group 2 (n = 23)** | | **PEEP – Group 3 (n = 8)** | | **p** |
|---|---|---|---|---|---|
| | **n(%)** | **Median (25-75)** | **n(%)** | **Median (25-75)** | |
| Male sex | 13 (56.5) | | 6 (75.0) | | 0.3‡ |
| Age (years) | | 49 (34 – 66) | | 27 (22 – 38) | 0.05† |
| BMI ($kg/m^2$) | | 23.6 (21.5 – 25.8) | | 22.2 (19.6 – 23.9) | 0.4† |
| Noradrenaline Time (days) | | 5 (4 – 7) | | 6 (3 – 6.5) | 0.9† |
| Furosemide time (days) | | 4 (3.5 – 6.5) | | 5 (3 - 7) | 0.8† |
| ATB time (days) | | 7 (5 - 7) | | 7 (5 - 7) | 0.8† |
| MV Time (days) | | 7 (5 - 7) | | 7 (7 - 12) | 0.7† |
| Death | 3 (13.0) | | 0 (0.0) | | 0.4‡ |
| **Clinical history** | | | | | |
| Spinal cord trauma | 7 (30.4) | | 3 (37.5) | | 0.5‡ |
| Non spec. Pneumonia. | 13 (56.6) | | 3 (37.5) | | 0.3‡ |
| Dyspnea | 6 (26.1) | | 1 (12.5) | | 0.4‡ |
| ARF | 13 (56.5) | | 3 (37.5) | | 0.3‡ |
| Renal disfunction | 14 (60.9) | | 8 (100.0) | | 0.04‡ |
| **Comorbidities** | | | | | |
| SAH | 5 (21.7) | | 0 (0.0) | | 0.2‡ |
| DM | 3 (13.0) | | 1 (12.5) | | 0.7‡ |
| **Drugs in use** | | | | | |
| Noradrenaline | 19 (82.6) | | 7 (87.5) | | 0.6‡ |
| Furosemide | 16 (69.6) | | 5 (62.5) | | 0.5‡ |

† Mann-Whitney test; ‡ Fisher's test; BMI = body mass index; ATB = antibiotic; MV = mechanical ventilation; ARF = acute respiratory failure; SAH = systemic arterial hypertension; DM = diabetes mellitus.

IMV is usually considered a risk factor for AKI in critically ill patients. The results of this study showed that the use of PEEP with higher values during IMV tends to induce AKI (p = 0.04). This relationship can be attributed to hemodynamic factors that, when altered, influence renal perfusion by determining vasoconstriction, a condition that predisposes to reduced urinary output, urinary sodium excretion and creatinine clearance [(8)].

PEEP, as a positive pressure established from IMV, causes an increase in intrathoracic pressure and, as a consequence, alteration of hemodynamic function, reduction of systemic vascular resistance, compression of the superior and inferior vena cava, decrease of ventricular filling, as well as left atrium and ultimately reduction in cardiac output and blood pressure[(12)]. Hemodynamic instability was a condition identified in the present study by the need for norepinephrine, a vasoconstrictor drug that promotes elevated blood pressure[(13)], in the group of patients on IMV with PEEP elevation.

In intensive care patients, the instability of physiological systems, recognized by fluctuations in blood pressure, conditions that determine the need for vasoactive drugs, is common. These drugs act directly on the cardiovascular system, and norepinephrine is often selected and administered for its adrenergic agonist action, responsible for the elevation and stabilization of blood pressure[13].

The invasive ventilatory strategy is a resource adopted for the recovery of breathing pattern during hospitalization and its use is considered effective in the treatment of different pathologies[14], favoring the survival of patients for a longer period, as identified in this investigation, in which mortality affected 9.7% of patients. Younger individuals also made up the group with higher PEEP compared to older individuals. AKI is a complex condition underlying different etiologies and pathophysiological mechanisms; is commonly diagnosed in hospitalized patients and contributes to increased morbidity, mortality as well as health care costs[15] Biomarkers have been adopted to predict AKI outcomes[16-17]; however, the clinical history of patients with spinal cord injury supports the understanding of mortality, in a relatively low percentage of AKI, predominantly in young male patients, when compared to a study conducted in Spain with 279 patients showing a 22% mortality rate[18]. Large retrospective AKI studies also show higher mortality than that identified in the present study (14 and 36%)[19].

From this perspective, it was possible to identify that even demographic characteristics, such as gender, can influence the occurrence of AKI in patients with IMV. Males were predominant in this and another study[20], confirming the existence of female hormonal protection, described by the lower risk of estrogen inhibition and androgen activation[21]. It is noteworthy that estrogen affects the kidney by decreasing mesangial cell proliferation, increased metalloproteinase enzyme activity and nitric oxide synthesis, changes in inflammation, decreased renin-angiotensin system activity. In renal disease, the presence of other intervening mechanisms, different from gender, such as renal hemodynamics, diet, renal / glomerular size and genetic polymorphisms is highlighted[22].

In the clinical context of critically ill patients, the use of diuretics has been associated with a higher risk of AKI. The theory of preserving diuretic-induced renal medullary oxygenation to prevent AKI has not been proven. The issue of forced/triggered euvolemic diuresis to prevent AKI is controversial. Diuretics do not shorten the duration of this syndrome and do not reduce the need for renal replacement therapy. They matter in volume management in kidney injury[23]. Our findings suggest that most patients who required furosemide tended to develop renal dysfunction.

It is noted that AKI management has gained uniqueness from the Kidney Disease Improving Global Guidelines (KDIGO)[4], clinical practice guideline for AKI, which, in this context, when adopted, allowed the predominant identification of mildly severe renal dysfunction (stage 1) in most patients. In addition, although lower, an important percentage also evolved at the most severe stage (renal failure). A retrospective cohort study conducted in a Mexican ICU showed that most patients evolved in stage 1, followed by stages 3 and 2, a result similar to the findings in this study[24].

The limitations can be described by the fact that the study was developed in a single center specialized in orthopedic and spinal cord trauma, in addition to the small sample size. It is worth noting that effective AKI treatment and prevention strategies may be possible in the future, but for the time being, efforts should focus on early identification of patients with aggravated AKI and, at the outset of designed care packages, to mitigate modifiable risk factors and provide intensive supportive care in the ICU. Future studies should focus on the implementation of AKI care package interventions based on active surveillance and workflow interventions that provide clinical decision support to help healthcare professionals more effectively manage this syndrome. The ability to diagnose and detect AKI early may reduce negative outcome in intensive care patients.

## CONCLUSION

The results of this study showed that critically ill patients with higher PEEP have a higher predisposition to AKI. In addition, age proved to be a variable that may influence the determination of the PEEP value during the ventilatory strategy.

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