Original Article

Acute kidney injury in critically ill patients on positive pressure mechanical ventilation

Lesão renal aguda em pacientes críticos em ventilação mecânica com pressão positiva

Lesión renal aguda en pacientes críticos en ventilación mecánica con presión positiva

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Abstract

Objective: To assess the effect of using mechanical ventilation with positive end-expiratory pressure (PEEP) on the renal function of patients admitted to the Intensive Care Unit (ICU).

Methods: This is a quantitative retrospective cohort study developed in the ICU of a public hospital in Brasília, Distrito Federal. The sample consisted of 52 medical records of patients admitted to the ICU from November 2016 to December 2018. Data collection was performed through a questionnaire with demographic, clinical and laboratory data. Patients were allocated in two groups: (1) PEEP ≤ 5 cmH2O, (2) PEEP > 5 cmH2O and < 10 cmH2O, and (3) PEEP ≥ 10 cmH2O.

Results: The mean age of patients was 59 years and 50% of them were over 63 years. It was found that 63.16% of patients who were on mechanical ventilation with positive end-expiratory pressure ≥ 10 cmH2O evolved in stage 1 (less severe acute kidney injury (AKI)) and 21.5% in stage 2 (moderate gravity). Even so, a small percentage (5.8%) of patients died. Patients who were unsuccessful in weaning from mechanical ventilation had a 10.24-fold chance of developing AKI.

Conclusion: mechanical ventilation use can cause damage to the renal function of patients hospitalized in the intensive care unit and that those with greater need to offer PEEP evolved with different severities and persistence of AKI.

Resumo

Objetivo: Avaliar o efeito do uso de ventilação mecânica com pressão positiva expiratória final (PEEP) na função renal dos pacientes internados em Unidade de Terapia Intensiva (UTI).

Métodos: Estudo de coorte retrospectivo, quantitativo, desenvolvido na UTI de um hospital público de Brasília, Distrito Federal. A amostra foi constituída de 52 prontuários de pacientes internados na UTI de novembro de 2016 a dezembro de 2018. A coleta dos dados foi realizada por meio de um questionário com dados demográficos, clínicos e laboratoriais. Os pacientes foram alocados em grupos: (1) PEEP ≤ 5 cmH2O, (2) PEEP > 5 cmH2O e < 10 cmH2O e (3) PEEP ≥ 10 cmH2O.

Resultados: A média de idade dos pacientes foi de 59 anos e 50% deles tinha mais de 63 anos. Constatou-se que 63,16% dos pacientes que estavam em ventilação mecânica com pressão positiva ao final da expiração ≥ 10 cmH2O evoluíram no estágio 1 (menor gravidade de lesão renal aguda (LRA)) e 21,5% no estágio 2 (moderada gravidade). Ainda assim, um pequeno percentual (5,8%) de pacientes evoluiu a óbito. Pacientes sem sucesso no desmame da ventilação mecânica apresentaram 10,24 vezes a chance de evoluir com LRA.

Conclusão: o emprego da ventilação mecânica pode determinar danos à função renal dos pacientes internados em unidade de terapia intensiva e que aqueles com maior necessidade de oferta de PEEP evoluíram com diferentes gravidades e persistência da LRA.

Keywords
Acute kidney injury; Respiration, artificial; Positive-pressure respiration; Intensive care units

Descritores
Injuria renal aguda; Respiração artificial; Respiração por pressão positiva intrínseca; Unidades de terapia intensiva

Descriptores
Lesión renal aguda; Respiración artificial; Respiración con presión positiva; Unidades de cuidados intensivos

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Conflicts of interest: nothing to declare.

Resumen

Objetivo: Evaluar el efecto del uso de la ventilación mecánica con presión positiva espiratoria final (PEEP) en la función renal de los pacientes internados en Unidad de Cuidados Intensivos (UTI).

Métodos: Estudio de corte retrospectivo, cuantitativo, desarrollado en la UCI de un hospital público de Brasília, Distrito Federal. La amuestra estuvo constituida por 52 prontuarios de pacientes internados en la UCI de noviembre de 2016 a diciembre de 2018. La recolección de los datos se realizó por medio de un cuestionario con datos demográficos, clínicos y laboratoriales. Los pacientes fueron distribuidos en grupos: (1) PEEP ≤ 5 cmH2O, (2) PEEP > 5 cmH2O y < 10 cmH2O y (3) PEEP ≥ 10 cmH2O.

Resultados: El promedio de edad de los pacientes era de 59 años y el 50 % de ellos tenía más de 63 años. Se constató que el 63,16 % de los pacientes que estaban en ventilación mecánica con presión positiva al final de la expiración ≥ 10 cmH2O evolucionaron en la etapa 1 (menor gravedad de lesión renal aguda (LRA)) y 21,5 % en la etapa 2 (moderada gravedad). Aun así, un pequeño porcentaje (5,8 %) de pacientes falleció. Pacientes sin éxito en la descontinuación de la ventilación mecánica presentaron 10,24 veces la posibilidad de evolucionar con LRA.

Conclusión: el uso de la ventilación mecánica puede determinar daños a la función renal de los pacientes internados en una unidad de cuidados intensivos y que los que tengan una mayor necesidad de oferta de PEEP evolucionaron con distintas gravedades y persistencia de la LRA.

Introduction

Acute kidney injury (AKI), in the critical patient scenario due to its multifactorial etiology, frequently impacts mortality and morbidity, even though there have been so many scientific advances in recent decades. AKI affects more than 13 million people a year and globally results in 1.7 million deaths.[1] Its diagnosis can result in a greater need for vasoactive drugs, mechanical ventilation, renal replacement therapy, increased hospitalization days and the possibility of progression to chronic kidney disease, conditions that contribute to a high mortality rate, which, although worrisome, proves to be a trigger for measures that encourage the early detection of risk factors and the prevention of potential complications. [2,3]

More recently, the persistence of AKI for more than seven to 90 days has been called acute renal insufficiency (ARI). Chronic conditions, on the other hand, exceed this period and are recognized as chronic renal failure (CRF).[4]

In critical care, these pathologies are often diagnosed due to their multifactorial origin, with mechanical ventilation being one of the potential risk factors for AKI. The relationship between the kidneys and the lung, although vital, can manifest itself as a clinical challenge in critically ill patients, given the intrinsic mechanisms present between these organs, which sometimes due to complications and comorbidities can induce malfunctions resulting in damage.[5,6]

Mechanical ventilation represents one of the main life support resources used in the Intensive Care Unit (ICU), although its use is frequent, the evolutionary follow-up of critically ill patients dependent on this support should not be underestimated, given that changes in the diagnostic picture, such as neurological, nutritional, hemodynamic, metabolic and renal changes, are recurrent and can generate irreparable damage.[7]

In the context of invasive mechanical ventilation (IMV), positive end-expiratory pressure (PEEP) use has been shown to be frequent, especially in critically ill patients due to the need to prevent small airway collapse during the respiratory cycle and reduce airway possibility of atelectasis and alveolar collapse.[8] However, high PEEP value use is associated with a decrease in cardiac output by increasing intrathoracic pressure and reducing right and left ventricular venous return.[9]

This scenario seems to favor the impairment of renal function and the occurrence of AKI becomes predictable. It is believed that mechanical ventilation-induced AKI will occur not only due to damage to renal perfusion arising from hemodynamic and neurohormonal changes, determinants of intrarenal blood flow changes, but also due to the inflammatory mediators generated by lung injuries induced by mechanical ventilators.[10]

Although some scientific evidence links IMV use to a three-fold increase in the chance of developing AKI in critically ill patients, there is still ambiguity as to whether this type of ventilatory support would really determine AKI.[5,11]

Given the high frequency of patients on mechanical ventilation and AKI in the intensive care setting, understanding this relationship implies a better management of the impacts and complications arising from this association, such as increased length of hospital stay and overload of the health system. Paying attention to the clinical picture of patients and findings of kidney injury can contribute to determining the early etiology and prevention of its complications,[2,12] increasing the possibility of survival.

Therefore, this study aimed to assess the effect of mechanical ventilation use with PEEP on the renal function of patients admitted to the ICU.

Methods

This is a historical, retrospective, quantitative cohort developed in an ICU for clinical and surgical care of adult patients of a tertiary public hospital in the Federal District, Brazil.

The medical records of selected patients were divided into groups according to the worst PEEP value programmed on mechanical ventilator during ICU stay, as follows: Group 1 – patients with PEEP ≤ 5 cmH2O; Group 2 – patients with PEEP > 5 cmH2O and < 10 cmH2O; Group 3 – patients with PEEP ≥ 10 cmH2O. When the occurrence of AKI or ARI was identified, its severity was assessed as follows: stage 1 (risk for kidney damage), stage 2 (kidney damage) or stage 3 (kidney failure), according to the rating Kidney Disease Improving Global Outcomes (KDIGO). Those with persistence of AKI for a period longer than seven days up to 90 days were identified with ARI.[4]

A total of 387 medical records were consulted and 52 patients' records were consecutively included. Losses resulted from incomplete records of the study data of interest, death in less than 7 days, spontaneous breathing, or non-invasive ventilatory support device use.

The medical records of patients admitted to ICU from November 2016 to December 2018, aged over 18 years, invasive mechanical ventilation support, intubation prior to admission to ICU of up to seven days, PEEP and creatinine clearance greater than or equal to 30 mL/min/1.73 m^2 were included, i.e., according to classification (KDIGO)[13] on admission to ICU. The medical records of patients with a medical diagnosis of CRF (stage 4 and 5 according to KDIGO classification),[14] history of death within a period of less than seven days during ICU stay, kidney transplantation, palliative care and trauma.

The collected data were registered in a structured questionnaire with items related to patients' demographic, clinical and laboratory characteristics. Independent variables were age, sex, serum creatinine level, invasive mechanical ventilation, PEEP. Dependent variables included worsening renal function, AKI, ARI, mortality (death), failure in ventilatory weaning.

AKI was defined as the patient who presented an increase in serum creatinine greater than 0.3 mg/dL (≥ 26.5 µmol/l) in 48 hours or an increase in serum creatinine ≥ 1.5 of the baseline value, according to the creatinine criterion of the KDIGO classification.[13] The urinary output was not assessed due to the absence or inadequacy of records in the medical record in the different shift periods. Thus, AKI was assessed exclusively by the serum creatinine criterion.

Access to the data record was obtained through the internal communication system (intranet) and physical records of the medical file. The evolution of patients during hospitalization in the ICU for a period of 14 consecutive days was verified from the medical records, with follow-up to assess the primary outcome: injury and acute kidney disease and secondary outcome: mortality and failure in ventilatory weaning.

In the descriptive analysis of qualitative variables, absolute and relative frequencies were calculated and measures of central tendency and dispersion were taken for quantitative variables. To compare the quantitative variables according to sex, the Mann-Whitney test was used and, to compare the qualitative variables, Fisher's exact test or the chi-square test was used. The Stagewise method was used to select the variables. For missing data, a sensitivity analysis was performed to assess differences in demographic and clinical characteristics, in the rate of injury and acute kidney disease, and in secondary outcomes when mortality was not available. The software used in the analyzes was the R (version

3.1.5) and the p-value adopted was ≤ 0.05, with a significance level of 5%.

This study met the national standards for research involving human beings and was submitted to the Institutional Review Board of the *Universidade de Brasília*, Distrito Federal, CAAE (*Certificado de Apresentação para Apreciação Ética* - Certificate of Presentation for Ethical Consideration) 97920718.9.0000.0030. Opinion 3,267,654.

Results

In this study, 52 patient records were followed up. The mean age of patients was 59 years and 50% of them were over 63 years. Records showed that patients remained hospitalized for a period of 13.64 ± 1.1 days. With regard to biological variables, patients' renal profile was slightly altered (creatinine of 1.56 ± 1.56 mg/dL and urea of 110.84 ± 62.1 mg/dL).

In Table 1, it is observed that there was a predominance of males (63.5%). It is noteworthy that a small percentage (5.8%) of patients died. Among the most administered drugs, norepinephrine (73.1%) stood out. Regarding the severity of AKI according to the KDIGO classification, most patients evolved in stage 1 (risk), less severe (25%), 7.7% in stage 2 (injury) and 3.8% in stage 3 (bankruptcy), greater severity. It is noteworthy that 5 patients (9.6%) evolved with acute kidney disease.

It is observed in Table 2 that an increase of 1 mg/dL in creatinine tended to increase 17.37 times the chance of patients developing AKI. So, there was a significant influence (p-value=0.001) of creatinine on AKI. The increase of 1 mg/dl in urea tended to increase the chance of a patient developing AKI by 2% (p-value=0.003).

In Table 3, it is observed that of the total of 52 patients, only 19 evolved with acute impairment of renal function after IMV during the follow-up period. In the group of 19 patients, the most serious condition (kidney failure) was identified in groups 2 and 3, i.e., PEEP above 5 cmH2O (5.26%), respectively. Less severe renal impairment (Stage 1) predominated especially in group 3 with PEEP ≥ 10 cmH2O (63.16%), although (1) 5.26% of patients evolved with renal failure (Stage 3).

In Table 4, the multivariate analysis shows that patients who were unsuccessful in weaning from mechanical ventilation had 10.24 times the chance

Table 1. Descriptive distribution of quantitative and qualitative variables

Variables	Mean ± SD	Median (25 - 75)	n(%)
Age (years)	59 ± 18.42	63 (43.5 - 74.5)	-
Hospitalization days followed up (days)	13.64 ± 1.1	14 (14 - 14)	-
ICU length of stay (days)	6.69 ± 8.97	4 (1 - 8)	-
Time on MV	15.12 ± 4.57	14 (12 - 16.5)	-
Mechanical ventilation (number of follow-up days)	12.31 ± 2.39	14 (10 - 14)	-
PEEP (cmH2O)	12.15 ± 2.89	12 (10 - 14)	-
Tidal volume (ml)	641.33 ± 149.96	612.5 (520 - 783)	-
Noradrenaline use (days)	4.89 ± 4.92	3 (0 - 8.5)	-
Baseline serum creatinine (mg/dL)	1.56 ± 1.56	1.2 (0.7 - 1.7)	-
Serum urea (mg/dL)	110.87 ± 62.1	101 (61 - 150)	-
Male	-	-	33(63.50)
Female	-	-	19(36.50)
Noradrenaline use	-	-	38(73.10)
Dobutamine use	-	-	2(3.80)
KDIGO (Stage 1)	-	-	13(25.00)
KDIGO (Stage 2)	-	-	4(7.7)
KDIGO (Stage 3)	-	-	2(3.8)
ARI	-	-	5(9.6)
Death	-	-	3(5.80)
Outcome successful patient in MV weaning	-	-	19(33.50)
Outcome patient who remains on MV	-	-	33(63.5)

ICU - Intensive Care Unit; PEEP - positive end-expiratory pressure; NA – noradrenaline; MV - mechanical ventilation; ARI - acute renal insufficiency; KDIGO - Kidney Disease Improving Global Outcomes

Table 2. Univariate analysis of clinical variables and acute kidney injury

Variables	OR	95% CI	p-value
Female	0.32	[0.08; 1.10]	0.085
Age	1.00	[0.97; 1.04]	0.776
Weight	0.99	[0.96; 1.02]	0.582
ICU stay length	1.01	[0.94; 1.08]	0.803
Hospitalization days followed up	0.44	[0.12; 0.87]	0.074
MV time (days)	1.12	[0.88; 1.47]	0.387
Noradrenaline	0.21	[0.03; 0.89]	0.057
Follow-up days in NA use	1.08	[0.96; 1.21]	0.215
Sepsis	0.69	[0.20; 2.50]	0.567
Septic shock	0.62	[0.16; 2.50]	0.491
Diuretics	0.86	[0.04; 9.61]	0.906
Creatinine	17.37	[4.37; 121.17]	0.001
Urea	1.02	[1.01; 1.04]	0.003
Potassium	1.23	[0.90; 1.69]	0.195
Sodium	1.02	[0.98; 1.07]	0.262
Hemoglobin	0.73	[0.49; 0.99]	0.075
Hematocrit	0.91	[0.82; 0.99]	0.059
Leukocytes	1.04	[0.99; 1.11]	0.135

NA-noradrenaline; ICU – Intensive Care Unit; MV - mechanical ventilation

Table 3. Distribution of patients in stages of acute kidney injury according to the value of positive end-expiratory pressure

PEEP Group	KDIGO classification (n=19)		
	Risk (Stage 1) n(%)	Kidney injury (Stage 2) n(%)	Kidney failure (Stage 3) n(%)
Group 1	0(0.00)	0(0.00)	0(0.00)
Group 2	1(5.26)	0(0.00)	1(5.26)
Group 3	12(63.16)	4(21.05)	1(5.26)

PEEP - positive end-expiratory pressure; Group 1 - patients with PEEP ≤ 5 cmH20; Group 2 - patients with PEEP > 5 cmH20 and < 10 cmH20; Group 3 patients with PEEP ≥ 10 cmH20

of developing AKI. The increase of 1 mg/dL in urea tended to increase by 3% the chance of patients developing AKI (p-value=0.007).

Table 4. Multivariate analysis between clinical variables and acute kidney injury

Variables	Initial model			Final model		
	OR	95% CI	p-value	OR	95% CI	p-value
Outcome = weaning failure	45.85	[1.90; 8390.35]	0.063	10.24	[1.59; 122.98]	0.030
PEEP (cmH20)	0.72	[0.37; 1.20]	0.253	-	-	-
Urea (mg/dL) (max. 1 - 14 day)	1.03	[1.01; 1.08]	0.041	1.03	[1.01; 1.05]	0.007

PEEP - positive end-expiratory pressure; max – maximum; OR – Odds Ratio; CI - confidence interval

Discussion

The limitations of this study are related to the retrospective analysis and to the single-center study. The absence or incompleteness of the records made it impossible to properly assess urinary volume and determined the exclusive serum creatinine use for AKI analysis. The absence of these records in patients' medical records added to the set of limitations, as observed in a multicenter prospective cohort study, which did not include urinary output due to record heterogeneity and data unavailability.[15]

On the other hand, the study adds an underexplored arm related to restrictions on mechanical ventilation use and its effects on renal function.

The social impact of this study points to the possibility of better targeting specific interventions, considering the surveillance and monitoring of factors directly related to impaired renal function in critically ill patients on mechanical ventilation by health professionals such as nurses.

Nurses specializing in AKI play a fundamental role in the implementation of interventions and efforts for early detection of this syndrome, such as water and urinary volume control, preparation and administration of drugs.[16]

The findings of this study show that successful weaning from mechanical ventilation predisposes to normalization/recovery of renal function, but differently, the presence of failure can increase the chance of AKI by 10.24 times (p=0.030). Mechanical ventilation use culminates in the expression of circulating mediators, such as pro-inflammatory cytokines, adhesion molecules and chemokines, in addition to causing hemodynamic imbalances with a decrease in cardiac output and, thus, changes in renal perfusion.[17]

In a systematic review and meta-analysis of 31 studies carried out in the Netherlands, an association between invasive mechanical ventilation and AKI was observed, however the expected interference of the ventilatory parameter settings such as tidal volume and PEEP were not identified.[5] Despite this, a study carried out in a public ICU showed a higher incidence of kidney damage in patients with PEEP between 5 and 10 cmH20. to the detriment of those with PEEP ≥ 10 cmH2O,[18] which demonstrates the lack of consensus regarding the influence of mechanical ventilation in relation to AKI occurrence. The hypotheses regarding the induction of local and systemic inflammatory responses are related to systemic inflammatory mediators, specifically in the kidneys, with microcirculation alterations, molecular interactions and a decrease in the glomerular filtration rate (GFR).[17] It is noteworthy that the present investigation shows a trend of patients with higher PEEP need to evolve with AKI of different severities, although without significant association.

A study showed a clear and inverse relationship between the level of continuous positive pressure applied in the airways and renal function and concluded that mechanical ventilation induced a "circulatory stress" that could be identified by the reduction in renal function.[10] In fact, an experimental study with animals showed that positive pressure ventilation causes a reduction in cardiac output by preventing venous return[19] and consequently predisposes to AKI. Although it is known that mechanical ventilation is necessary as a life-saving intervention in critically ill patients, its installation has generated repercussions in the renal system, increasing the risk of AKI by three times.[10]

The present study showed a higher prevalence of AKI defined by the creatinine criterion of the KDIGO classification in the ICU population in stage 1 (25%), 7.7% in stage 2 (kidney injury) and 3.8% in stage 3 (failure renal). This finding is consistent with that found in the multicenter prospective cohort study, with 3206 patients from 32 countries, in which the lowest severity (stage 1) of AKI predominated, followed by stages 2 and 3 (highest severity).[20]

AKI is characterized by a reversible increase in creatinine and urea resulting in reduced renal perfusion and a drop in GFR. The use of these markers in the clinic can even help to distinguish acute tubular necrosis from prerenal AKI.[21] In general, small increases in serum creatinine may be associated with adverse outcomes, such as longer hospital stay and in-hospital mortality rate[22] as well as urea.[21] The increase of 1 mg/dL in urea tended to increase by 3% the chance of patients to develop AKI (p=0.007), as well as the increase of 1 mg/dL in serum creatinine increased by 3% 17.37 times the chance of patients developing AKI in the present study.

As an aggravating factor of risk for AKI, the age group of patients was advanced, with a median above 60 years. The inversion of the age pyramid in contemporary society has manifested itself as a characteristic and can significantly influence society's quality of health, vitality and economy, imposing the need for greater attention to health policies and research.[23] It is known that the advanced age group is related to renal aging, which leads to physiological and structural changes, such as a reduction in the number and size of nephrons, interstitial tubule fibrosis, glomerulosclerosis, insufficiency microvascular, decline in GFR.[24] Thus, nursing interventions such as hydroelectrolytic, acid-base, infection, hypovolemia, cardiac controls, precautions against embolisms, respiratory monitoring and hemodynamic regulation stand out.[25]

Instability of physiological systems is frequent in critically ill patients and, therefore, leads to fluctuations, for example in blood pressure. The correction of these variations is related to the need to use vasoactive drugs, among which norepinephrine has been a frequent choice, given its adrenergic agonist action. A national scientific study also highlights the predominance of norepinephrine use in these situations, reaching about 73.1% of frequency of use in relation to other drugs,[7] a finding consistent with what was found in the present investigation.

It was identified through the KDIGO classification that ARI affected 9.6% of patients with AKI, which shows the persistence of AKI for a long time in the intensive care setting. A study highlights that there is still a gap in the management of this condition (ARI) after kidney injury.[26] The scope of AKI care should be continuous, from risk assessment and prevention in a community setting, prevention of AKI in a hospital setting, improvement of management and surveillance of recurrent AKI and progression to ARI.[27]

Identifying the severity and persistence of AKI may contribute to indicate patients at higher risk of progression to CRF, which favors the reduction or attenuation of progression to advanced and chronic conditions of impaired renal function.

Conclusion

Mechanical ventilation use can cause damage to the renal function of patients admitted to the intensive care unit and that those with greater need for PEEP offer evolved with different severities and persistence of AKI.

Collaborations

Cunha NV and Magro MC contributed to study design, data analysis and interpretation, article writing, relevant critical review of intellectual content and approval of the final version to be published.

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