

INFLUENCE OF POSITIVE PRESSURE VARIATIONS ON RENAL FUNCTION

INFLUÊNCIA DAS VARIAÇÕES DA PRESSÃO POSITIVA SOBRE A FUNÇÃO RENAL

INFLUENCIA DE LAS VARIACIONES DE PRESIÓN POSITIVA EN LA FUNCIÓN RENAL

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Funding: No funding.

Submitted on: 2019/11/02

Approved on: 2020/02/01

ABSTRACT

Objective: to verify whether the use of invasive mechanical ventilation (IMV) with positive pressure predisposes to the appearance of acute kidney injury (AKI) in critically ill patients. **Method:** prospective cohort of quantitative approach developed in intensive care unit (ICU) of a public hospital. Eligible patients were selected by convenience sampling. For data collection, a questionnaire consisting of items on clinical and laboratory variables was applied. The information was extracted from the medical records during a period of 15 days. Data analysis was descriptive and inferential. Significant results with $p \leq 0.05$ were considered significant. **Results:** hypertension was among the most incident comorbidities (29.1%) of the 79 patients evaluated. Among the patients analyzed, 59.5% required IMV with PEEP ≥ 10 cmH₂O. Of the total number of patients, 91.1% evolved with renal dysfunction, according to the KDIGO classification. As an outcome, 34.2% of patients died. Patients who used PEEP >5 cmH₂O showed significant predisposition to renal dysfunction ($p \leq 0.05$). **Conclusion:** invasive mechanical ventilation with positive pressure (PEEP) was a factor that contributed to aggravate renal function in different gradations. It was found that patients receiving IMV with PEEP >5 cmH₂O are more predisposed to the onset of AKI in the ICU, due to the tendency to advanced age, overweight, long time of mechanical ventilation and also hypertension.

Keywords: Acute Kidney Injury; Intensive Care Units; Respiration, Artificial; Health Evaluation; Positive-Pressure Respiration.

RESUMO

Objetivo: verificar se o emprego de ventilação mecânica invasiva (VMI) com pressão positiva predispõe o aparecimento de lesão renal aguda (LRA) em pacientes críticos. **Método:** coorte prospectiva de abordagem quantitativa desenvolvido em Unidade de Terapia Intensiva (UTI) de um hospital público. Os pacientes elegíveis foram selecionados por conveniência. Para a coleta de dados aplicou-se questionário constituído de itens sobre variáveis clínicas e laboratoriais. As informações foram extraídas do prontuário durante o período de 15 dias. A análise dos dados foi descritiva e inferencial. Consideraram-se significativos resultados com $p \leq 0,05$. **Resultados:** dos 79 pacientes avaliados, a hipertensão arterial esteve entre as comorbidades mais incidentes (29,1%). Entre os pacientes analisados, 59,5% necessitaram de VMI com PEEP ≥ 10 cmH₂O. Do total de pacientes, 91,1% evoluíram com disfunção renal, segundo a classificação KDIGO. Como desfecho, 34,2% dos pacientes evoluíram a óbito. Pacientes que usaram PEEP >5 cmH₂O mostraram significativa predisposição à disfunção renal ($p \leq 0,05$). **Conclusão:** a ventilação mecânica invasiva com pressão positiva (PEEP) foi um fator que contribuiu para o agravamento da função renal em diferentes gradações. Constatou-se que pacientes em VMI com PEEP >5 cmH₂O estão mais predispostos ao aparecimento da LRA em UTI, em razão da tendência à idade avançada, a sobrepeso, tempo prolongado de ventilação mecânica e ainda hipertensão arterial.

Palavras-chave: Lesão Renal Aguda; Unidades de Terapia Intensiva; Ventilação Mecânica; Avaliação em Saúde; Respiração com Pressão Positiva.

How to cite this article:

Silva KGN, Félix JPB, Moreira VR, Magro MCS. Influence of positive pressure variations on renal function. REME – Rev Min Enferm. 2020[cited _____];24:e-1287. Available from: _____ DOI: 10.5935/1415-2762.20200016

RESUMEN

Objetivo: comprobar si el uso de ventilación mecánica invasiva (VMI) con presión positiva predispone a la lesión renal aguda (LRA) en pacientes críticos. **Método:** cohorte prospectiva con enfoque cuantitativo desarrollado en la unidad de cuidados intensivos (UCI) de un hospital público. Los pacientes elegibles fueron seleccionados mediante muestreo por conveniencia. La recogida de datos fue realizada por medio de una encuesta de preguntas sobre las variables clínicas y de laboratorio. La información fue extraída del registro médico durante el período de 15 días. El análisis de datos fue descriptivo e inferencial. Los resultados con $p \leq 0.05$ fueron considerados significativos. **Resultados:** de los 79 pacientes evaluados, la hipertensión arterial se encontraba entre las comorbilidades más incidentes (29,1%). Entre los pacientes analizados, el 59,5% requirió VMI con PEEP ≥ 10 cmH₂O. Del número total de pacientes, el 91,1% tuvo disfunción renal, según la clasificación KDIGO. Como resultado, el 34,2% de los pacientes falleció. Los pacientes que usaron PEEP > 5 cmH₂O mostraron predisposición significativa a la disfunción renal ($p \leq 0.05$). **Conclusión:** la ventilación mecánica invasiva con presión positiva (PEEP) fue un factor que contribuyó al empeoramiento de la función renal en diferentes grados. Se encontró que los pacientes en IMV con PEEP > 5 cmH₂O están más predispuestos a la LRA en la UCI, debido a la edad, al sobrepeso, al tiempo prolongado de ventilación mecánica e incluso a la hipertensión arterial.

Palabras clave: Lesión Renal Aguda; Unidades de Cuidados Intensivos; Respiración Artificial; Evaluación en Salud; Respiración con Presión Positiva.

INTRODUCTION

Invasive mechanical ventilation (IMV) represents a therapeutic strategy indicated in cases of acute or chronic acute respiratory failure, which totally or partly replaces spontaneous ventilation for recovery of most patients critically ill.^{1,2}

Despite being an important intervention for patients with respiratory failure, a study has shown that it may increase the risk of acute kidney injury (AKI).³ Patients in IMV may develop important consequences arising from AKI, but regardless of this syndrome, mortality in the intensive care unit (ICU) goes from 30 to 50%.^{4,5} In patients with combined respiratory failure, AKI rises and goes from 60 to 80%, but depending on its definition, severity and geographical area, it can still be modified.^{6,7}

Although scientific evidence shows different definitions of AKI, just over a decade ago began to appear attempts to standardize these concepts and currently Diseases Kidney: Improving Global Outcomes (KDIGO) has been the criteria adopted for assessments of renal function. In it, AKI was defined as an increase in serum creatinine ≥ 0.3 mg/dL in 48 hours or an increase of 1.5 times in relation to its baseline value (known or pre-established) or reduced urinary output < 0.5 mL/kg/hour in six hours.^{7,8}

The identification of patients at increased risk of AKI is the first step in improving and directing intervention strategies.

The comorbidities inherent to the patient, such as diabetes mellitus, predispose patients to AKI, especially when associated with etiological factors such as dehydration, sepsis and the use of mechanical ventilation.⁹ In this direction, early recognition of AKI is essential to ensure rapid and adequate management and prevent progression to more lethal stages of the disease.^{10,11}

Abnormalities from ineffective gas exchange resulting in hypoxemia, hypercarbia and systemic acidosis may influence renal vascular resistance by altering renal perfusion pressures, and resulting in AKI.^{12,13} Knowing more about the potential consequences to the renal system and the health system, resulting from the permanence of critically ill patients in invasive ventilator strategy, motivated this study and can direct the goals and signal health indicators, given the lack of studies and lack of consensus on the repercussions of mechanical ventilation on renal function.

Thus, this study aims to verify whether the use of IMV with positive pressure predisposes to the onset of AKI in critically ill patients.

METHOD

This is a prospective cohort of quantitative approach, developed in a general intensive care unit of a large public hospital of the *Distrito Federal*.

The population consisted of 108 patients, but due to mortality and transfers to other units, the sample consisted of 79 patients by convenience, aged over 18 years old, without previous renal dysfunction (KDIGO Classification - stage 1 or risk), in IMV for more than 48 hours and who signed the Informed Consent Form (IFC). We excluded patients with a history of chronic kidney disease (stage 4 and 5 of the KDIGO classification)⁸ diagnosed with terminal disease, readmitted to the ICU, using nephrotoxic drugs or undergoing contrast tests.

In the absence of AKI on ICU admission, every patient under mechanical ventilation was followed-up through data in electronic medical records and data collection occurred for 15 days, mediated by the use of a semi-structured questionnaire with items on characterization of renal function, demographic profile, clinical and laboratory parameters. Patients were allocated in groups according to the positive end-expiratory pressure value (PEEP), group 1 – patients with PEEP ≤ 5 cmH₂O; group 2 - patients with 5 cmH₂O $<$ PEEP $<$ 10 cmH₂O; group 3 - patients with PEEP ≥ 10 cmH₂O.

For each patient, regardless of the PEEP group, renal function impairment was performed by observing urinary output and serum creatinine, KDIGO classification criteria⁸. Thus, patients stratified in stage 1 of this classification were considered at risk when there was an increase of 1.5 to 1.9 times or 0.3 mg/dL in basal creatinine for 48 consecutive hours and/

or reduction of urinary output less than 0.5 mL/kg/h for six to 12 hours. In stage 2, the patient was identified with kidney injury when the value of basal creatinine increased 2.0 to 2.9 times and/or urinary output remained below 0.5 mL/kg/h for 12 hours or more. And in stage 3, renal failure was considered when there was: a) an increase of 3.0 times in the value of basal serum creatinine or an increase of 4.0 mg/dL; b) or beginning of dialysis therapy in children under 18 years old with creatinine clearance of less than 35 mL/min/1.73 m²; c) and/or urinary output with a value of less than 0.3 mL/kg/h for 24 hours or more; d) or anuria for a time equal to or greater than 12 hours.⁸

In the first 24 hours after ICU admission, there was no renal impairment combined with the use of mechanical ventilation. After evaluating these criteria, the patients were followed daily and at the end of 15 days, the outcome was evaluated. The data was recorded in a Microsoft Excel spreadsheet for further analysis.

The lowest value obtained on the day of hospitalization or the week before hospital admission was considered as initial creatinine/baseline, but when absent, the lowest serum creatinine considered was the lowest creatinine obtained in the first week after hospitalization.

The data were expressed by means of measures of central trend (mean and median) and dispersion (standard deviation and percentiles 25 and 75). Absolute frequency (n) and relative frequency (%) were also calculated. Continuous variable analysis was performed using nonparametric tests: chi-square and, where appropriate, Fisher's exact test. Odds Ratio (OR) and their 95% confidence interval (95% CI) were also calculated for comparing the risk between groups by the Statistical Package for the Social Sciences (SPSS) version 23 software. Values of $p \leq 0.05$ were considered significant.

This study was approved by the Research Ethics Committee, according to Resolution 466 of 2012 with CAAE 18021313.5.0000.5553.

RESULTS

It was found that of all the 79 patients on mechanical ventilation, males were predominant (42, 53.2%). The mean age of the patients was 55 ± 20 years old and body mass index was 25.2 ± 6.8 kg/m², signaling overweight. Hypertension was the most frequent comorbidity (23, 29.1%), followed by diabetes mellitus (16, 20.3%). More than half of the patients used noradrenaline (48, 60.8%) and required prolonged mechanical ventilation time (17 ± 11 days). Still, the majority evolved in stage 3 of renal dysfunction (more severity) according to the KDIGO classification (Table 1), conditions that sustain the severity evidenced by APACHE II of 18.7 ± 5.5 . No patient used positive end-expiratory pressure (PEEP) ≤ 5 cmH₂O. Most (n=47) used

PEEP ≥ 10 cmH₂O (59.5%) and in 32 (40.5%) 5 cmH₂O < PEEP < 10 cmH₂O was adopted. Of the patients, 27 (34.2%), on the whole, died, however those with PEEP between 5 and 10 cmH₂O, had higher mortality (45.1%) in relation to those with PEEP ≥ 10 cmH₂O (Table 2).

Table 1 - Distribution of patients (n=79) in stages of renal dysfunction according to the KDIGO classification. *Distrito Federal, 2017*

Stage	Creatinine Criterion	Urine Output Criterion
Stage 1	25 (31.6%)	9 (11.4%)
Stage 2	16 (20.3%)	28 (35.4%)
Stage 3	7 (8.9%)	33 (41.1%)

Stage 1: Risk; Stage 2: Injury; Stage 3: Renal failure.

The results show that, regardless of PEEP, the age and severity of the patients were similar. In contrast, the obesity condition was significantly more frequent in the group PEEP 3 when compared to group PEEP 2 ($p=0.03$), as well as mechanical ventilation time ($p=0.04$). Among comorbidities, arterial hypertension predominated significantly in patients in the group PEEP 3 ($p=0.001$) (Table 2).

The results showed that PEEP was a variable that influenced the significant worsening of renal function ($p=0.05$) (Table 3). It was possible to verify that using IMV with PEEP ≥ 10 cm/H₂O (group 3) the chance of renal failure decrease when compared to the use of PEEP >5 cmH₂O and <10 cmH₂O (group 2) during hospitalization in an intensive care unit [OR (failure/risk or kidney injury) = 0.38 (95% CI: 0.14 – 0.98), $p= 0.05$].

DISCUSSION

This study showed that the use of IMV with positive pressure contributed to the occurrence of different stages of AKI severity in those patients under critical condition. Mechanical ventilation causes hemodynamic abnormalities, which can cause changes in renal perfusion by reducing cardiac output.¹⁴ In our study, using PEEP between 5 and 10 cm/H₂O proved to be a risk factor for renal failure. In this perspective, scientific evidence highlights that mechanical ventilation with PEEP > 5 cm/H₂O remains an independent risk factor for AKI, although it is clear that even with the implementation of protocols directed to ventilator strategy¹⁵, there is still no consensus whether modern mechanical ventilation is in fact a "cause" of AKI or whether its association with comorbidities and therapies such as sedation and antibiotics are determining conditions. This potential causality is strongly suggested by the fact that amounts, even modest, of positive pressure when applied to canines or previously healthy humans result in urine production the decrease^{4,5}, although the exact mechanisms

Table 2 - Relationship between clinical characteristics and the use of positive end-expiratory pressure (PEEP) in patients admitted to an intensive care unit. *Distrito Federal, 2017*

Characteristics	Group PEEP 2 (n = 32)		Group PEEP 3 (n = 47)		p
	n (%)	Median (25-75)	n (%)	Median (25-75)	
Age (years old)	-	57.0 (33.5 – 71.5)	-	56.0 (45.5 – 68.5)	0.8*
Male	16 (50.0)	-	26 (55.3)	-	0.5*
BMI (kg/m ²)	-	23.4 (22.0 – 26.1)	-	24.0 (20.9 – 29.2)	0.7*
Obese	2 (6.5)	-	11 (23.4)	-	0.03*†
Overweight or obese	8 (25.8)	-	19 (40.4)	-	0.2†
Noradrenaline	17 (54.8)	-	30 (63.8)	-	0.4†
APACHE II	-	18 (15 - 21)	-	18 (15 - 23)	0.7*
Ventilation time (days) ^c	-	11 (7 - 19)	-	16 (11 - 23)	0.04*
Comorbidities					
Hypertension	3 (9.7)	-	20 (42.7)	-	0.001†
Diabetes Mellitus	5 (16.1)	-	11 (23.4)	-	0.4†
Deaths	14 (45.1)	-	13 (27.7)	-	0.1†

*Fisher Test; †Chi-square test; PEEP = positive end-expiratory pressure; Group 2: PEEP >5 cmH₂O and <10 cmH₂O; Group 3: PEEP ≥10 cmH₂O; *BMI = body mass index; APACHE = Acute Physiology and Chronic Health Disease Classification System II.

Table 3 - Relationship of invasive mechanical ventilation (IMV) with positive end-expiratory pressure (PEEP) and stages of renal dysfunction according to KDIGO classification. *Distrito Federal, 2017*

PEEP	KDIGO Classification		P
	Risk or kidney injury (n=34)	Renal failure (n=37)	
Group 2	9 (26.5%)	18 (48.6%)	0.05
Group 3	25 (73.5%)	19 (51.4%)	

Chi-square test; PEEP = positive end-expiratory pressure; group 2: PEEP >5 cmH₂O and <10 cmH₂O; group 3: PEEP ≥10 cmH₂O.

involved have not yet been fully elucidated. However, more research in this area is clearly necessary to prove causality and identify potentially modifiable therapeutic targets.¹⁴

As an aggravating factor, epidemiological studies with adults, as well as this study, highlighted that AKI was associated with increased mortality, prolonged mechanical ventilation and long of stay in intensive care units.^{16,17}

Scientific evidence conducted in a single center involving adults revealed that mortality and morbidity rates were high when concomitant evaluation of serum creatinine level and urinary output to diagnose AKI than when both criteria were used alone.¹⁸ In the current study, the high incidence and severity of AKI were identified from the concomitant evaluation of serum creatinine and urinary output. Nevertheless, it is important to highlight that, when considering the isolated evaluation of renal function by urinary output, the incidence of AKI remained high.

In humans, scientific evidence showed that the use of PEEP may relate to the reduction of cardiac output, mean blood pressure, sodium excretion rate and glomerular filtration

rate after 30 minutes of its use.^{19,20} From this perspective, our study identified that elevated PEEP (>5 and 10 cmH₂O) was associated with renal failure (p=0.05). Studies describe that neurohumoral mediators, when released during mechanical ventilation, also alter renal blood flow from the cortex to the spinal cord, which leads to sodium resorption and reduced glomerular filtration rate. Resorption of sodium by the kidney requires high oxygen use. Thus, IMV can decrease the supply of oxygen from systemic hemodynamic effects and to some extent predispose to renal dysfunction.⁶

In this study, obese and overweight patients were hypertensive (p=0.004) and evolved to kidney risk or injury. Recent publications are attributing the association between obesity and increased risk of developing kidney injury to increased risk factors, diabetes and hypertension, compensatory mechanism of glomerular hyperfiltration to meet the needs of the body, related to high metabolic demands associated with increased body weight.^{2,21}

The limitations of the study are related to the reduced sample size, also associated with the fact that it was developed

in a single institution, and to the insufficient data in medical records, restricting access to information. We do not have detailed information on interventions (e.g. use of diuretics) that may increase urinary output and thus alter the observed incidence of AKI. On the other hand, the study provides evidence on the relationship between mechanical ventilation use and the occurrence of AKI, stimulating the construction of targeted strategies that can minimize undesirable effects of the use of invasive ventilator strategy with positive pressure.

The study also warns about the need to provide or direct care for obtaining conditions for early ventilator weaning, however, critical care scenario portrays the severity and complexity of the clinical picture of patients as indicators of mechanical ventilation time. Thus, the results obtained support the relevance of providing better-directed care and portray the importance of a health care system that implies the direction and elaboration of standardized measures and protocols from the moment the patient enters the health system, recognized by the primary health care model.

The occurrence of AKI of different levels of severity reinforces the need for systematic surveillance of this syndrome when the patient arrives to the ICU. Early identification of modifiable risk factors for AKI, such as nephrotoxic drugs and ventilator strategies, has the potential to reduce morbidity and mortality.

Improvements in this scenario can be achieved by reducing the turnover of health team professionals, especially nurses, physiotherapists, among others, who continuously act for the patients' recovery and severity evaluation. Therefore, health re-establishment measures, strategies or packages will be effective and sufficient for reassuming activities of daily living, reducing the social impact and promoting the reintegration of the individual into society.

CONCLUSION

Invasive mechanical ventilation with positive pressure (PEEP) was a factor that contributed to the worsening of renal function in different degrees. It was found that patients in IMV with PEEP > 5 cmH₂O are more predisposed to the onset of AKI in the ICU, since they tend to have an advanced age, overweight, prolonged time of mechanical ventilation and hypertension.

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