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Journal of Critical Care 59 (2020) 191–193

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Limiting positive end-expiratory pressure to protect renal function in SARS-CoV-2 critically ill patients

Dear Editor,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) related pneumonia is a risk factor for acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI) [1,2]. While the mechanisms of AKI in this context are not yet elucidated, it is likely that providing a lung protective mechanical ventilation with high levels of positive end-expiratory pressure (PEEP) may worsen renal function [2-5]. Accordingly, strategies of PEEP titration [6] and hemodynamic management in SARS-CoV-2 related ARDS are still open to discussion. Herein, we report our experience in SARS-CoV-2 critically ill patients before and after having modified our practices in the view of the high occurrence of AKI that needed renal replacement therapy (RRT) in the first cases we managed. Our hypothesis was that limiting the level of PEEP (<12 cmH_2O) while targeting upward mean arterial pressure (>75 mm Hg) during the first 48 h after the intubation would decrease the need for RRT.

1. Methods

During "period 1" (between 04 and 15 March 2020), all mechanically ventilated patients with confirmed SARS-CoV-2 admitted to our intensive care unit received volume-controlled ventilation with a tidal volume of 6 $mL.kg^{-1}$ of ideal body weight and PEEP stepwise increased to reach a plateau pressure below 28 cmH_2O. A conservative fluid strategy (i.e. fluid expansion based on bedside evaluation of the cardiac preload dependence) was applied and norepinephrine infusion targeted a mean arterial pressure >65 mm Hg. During "period 2" (from 16 March to 06 April 2020), the following changes were applied: 1) PEEP was limited to 10–12 cmH_2O; 2) liberal fluid strategy was applied (no systematic preload dependence evaluation) and 3) norepinephrine was administrated to achieve a mean arterial pressure >75 mm Hg. We collected baseline patient's characteristics, ventilatory and hemodynamic management, daily clinical and biological data and the need for RRT until day 14. The Lung Injury Score (so called Murray score), which is a four-category scale including: 1, chest roentgenogram score; 2, hypoxemia score; 3, PEEP score; 4, respiratory system compliance score was also collected at admission [7]. During the two periods, the management of RRT was similar and followed our local guidelines based on the delayed RRT strategy group of the AKIKI study [8]. The primary endpoint was the proportion of patients requiring RRT at day 14. The statistical analysis compared patient's baseline characteristics, therapeutic management and the proportion of patients with AKI. Our local ethics committee approved the study (CER Sorbonne University, N°2020 – CER-2020-32). Patients or their family gave their oral consent.

2. Results

Seventy-three patients were included, 20 during "period 1" and 53 during "period 2". Baseline characteristics were not different between periods (Table 1). All patients had AKI at day 14 according to the Kidney Disease: Improving Global Outcomes (KDIGO) definition (Table 1) [9]:

Table 1
Characteristics of patients on admission, therapeutic management and study endpoints.

	Period 1	Period 2	*p* value
	n = 20	*n* = 53	
Patient's characteristics			
Age, year	58 (48–67)	57 (53–67)	0.742
Male gender, *n* (%)	15 (75)	45 (85)	0.327
Body mass index, $kg.m^{-2}$	30 (28–33)	28 (26–32)	0.862
Simplified Acute Physiology Score 2	35 (29–50)	33 (27–41)	0.256
Sequential Organ Failure Assessment	9 (6–10)	7 (5–9)	0.399
Chronic hypertension, *n* (%)	10 (50)	20 (32)	0.426
Diabetes, *n* (%)	7 (35)	14 (17)	0.565
Chronic renal failure, *n* (%)	1 (5)	8 (17)	0.429
Hemodynamic, ventilatory and renal function at admission			
Mean arterial pressure, mm Hg	64 (59–73)	65 (57–77)	0.958
PaO_2/FiO_2	165 (111–218)	116 (88–156)	0.007
Lung Injury score (Murray)	11 (9–12)	11 (10—12)	0.087
Creatinine, $\mu mol.L^{-1}$	78 (67–107)	87 (66–130)	0.457
Hemodynamic management within first 48 h			
Norepinephrine administration, *n* (%)	16 (80)	49 (92)	0.203
Maximal dose of norepinephrine, $\mu g.kg^{-1}.min^{-1}$	0.20 (0.1–1.0)	0.30 (0.2–0.6)	0.555
Fluid expansion, mL	1000 (125–2100)	2000 (1500–2750)	0.021
Averaged mean arterial pressure, mm Hg	87 (82–92)	91 (86–99)	0.095
Mean arterial pressure ≥ 75 mm Hg, *n* (%)	6 (30%)	35 (66%)	0.008
Ventilatory management within first 48 h			
Tidal volume, $mL.kg^{-1}$	4.8 (4.4–5.1)	4.8 (4.2–5.3)	0.343
Averaged Positive end expiratory pressure, mm Hg	14 (14–15)	12 (10–12)	0.001
Peak airway pressure, mm Hg	64 (48–70)	52 (42–60)	0.100
Study endpoints at day 14			
KDIGO 1, *n* (%)	1 (5)	10 (19)	0.139
KDIGO 2, *n* (%)	4 (20)	22 (41)	0.087
KDIGO 3, *n* (%)	15 (75)	21 (40)	0.007
Renal replacement therapy, *n* (%)	9 (45)	11 (21)	0.038
Extracorporeal membrane oxygenation, *n* (%)	4 (20)	11 (21)	0.999
Extubation, *n* (%)	5 (25)	12 (23)	0.999
Intensive care unit mortality, *n* (%)	7 (35)	14 (26)	0.469

KDIGO: Kidney Disease Improving Global Outcomes.
Lung Injury score (Murray score) is a four-category scale consisted of the following categories: 1, chest roentgenogram score; 2, hypoxemia score; 3, positive end-expiratory score; 4, respiratory system compliance score.

https://doi.org/10.1016/j.jcrc.2020.07.008

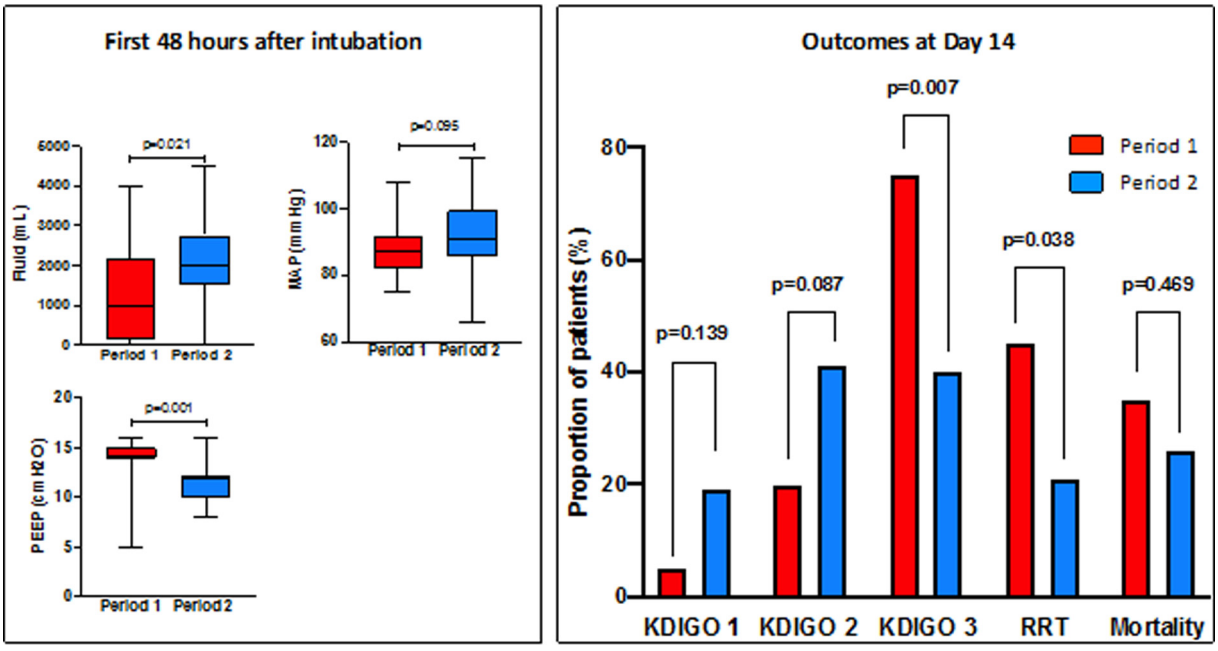

Fig. 1. Proportion of patients with acute kidney injury, need for renal replacement therapy and mortality in the ICU according to the period of the study. Period 1 was characterized by high level of positive end expiratory pressure and conservative fluid strategy. Period 2 was characterized by limited positive end expiratory pressure, liberal fluid strategy and higher mean arterial pressure. KDIGO: Kidney Disease Improving Global Outcomes; RRT: renal replacement therapy; MAP: mean arterial pressure; PEEP: positive and expiratory pressure.

11 patients were classified AKI KDIGO 1 (four patients with creatinine criteria and seven patients with low urine output criteria), 26 patients were classified AKI KDIGO 2 (four patients with creatinine criteria and 22 with low urine output criteria) and 36 patients were classified AKI KDIGO 3 (27 patients with creatinine criteria and nine with urine output criteria).

The proportion of patients requiring RRT and those with AKI KDIGO 3 at day 14 was significantly lower during "period 2", 11 (21%) vs. 9 (45%) $p = .038$ and 21 (40%) vs. 15 (75%) $p = .007$ respectively (Table 1, Fig. 1). The proportion of patients with AKI KDIGO 3 was significantly lower on day 2 and on day 7 during "period 2", 11 patients (21%) vs. 10 (50%) $p = .015$ and 17 patients (38%) vs. 13 (76%) $p = .007$ respectively. The timeline of AKI onset was one day (1–2) after intubation, without significant difference between the two periods ($p = .192$).

As compared to their counterparts, patients admitted during "period 2" received more fluids (2000 mL [IQR 1500–2750] vs. 1000 mL [IQR 125–2100] $p = .021$), had a lower PEEP level (12 [IQR 10–12] vs. 14 [IQR 14–15] $p < .001$) and a majority of patients had higher mean arterial pressure during the first 48 h (35 patients (66%) vs. 6 (30%) $p = .008$) (Table 1, Fig. 1). The peak airway pressure was similar in the two groups (Table 1). Despite a lower PEEP level during "period 2", the Lung Injury Score was similar between the two groups, as well as the mortality (Table 1).

3. Discussion

Our findings suggest that changing our practices was associated with a decreased need for RRT and a lower proportion of patients with AKI KDIGO 3. This might not be a causal relationship and further confirmation is warranted. Several factors may contribute to AKI onset, as comorbidities such as hypertension or diabetes mellitus. These factors are well-known factors of renal vulnerability and have been recently identified as risk factors for AKI in patients with ARDS [2,10]. In patients with SARS-CoV-2 related ARDS, impairment of gas exchange and severe hypoxemia has been recognized as others risk factors [2]. The association between PEEP and AKI has been suggested in physiological studies [2,4,5] but recently, Panitchone et al. have suggested an association between peak airway pressure and AKI [10]. This association was not found in our patients. However, in the early phase of SARS-CoV-2 related ARDS, pulmonary mechanics may be different from traditional ARDS, with different phenotypes characterized by low lung recruitability, normal compliance and without need for very high PEEP or even deleterious effects of the latter [6]. The timeline of AKI onset is another issue. In our patients, we have found that AKI occurred most commonly within 24 h of intubation, as Hirsch et al. have already suggested [11].

The main limitation of our study is the retrospective design that limits the causal relationship of our findings. In addition, the significant proportion (20%) of patients with extra-corporeal membrane oxygenation could have influence our findings but this case mix was inherent to our activity as expert-center. Nevertheless, our experience suggests the existence of a critical cross-talk between lungs and kidney function [2,12] in SARS-CoV-2 critically ill patients. Careful monitoring of lung and kidney interaction is required in these patients. High levels of PEEP may not be required in the early phase of SARS-CoV-2 related ARDS.

Declaration of Competing Interest

Martin Dres received fees from Lungpacer (expertise, lectures). Other authors had no conflict of interest to declare.

References

[1] Wang Y, Lu X, Chen H, et al. Clinical course and outcomes of 344 intensive care patients with COVID-19. Am J Respir Crit Care Med 2020 Jun 1;201(11):1430–4. https://doi.org/10.1164/rccm.202003-0736LE.
[2] Gabarre P, Dumas G, Dupont T, et al. Acute kidney injury in critically ill patients with COVID-19. Intensive Care Med 2020 Jun 12:1–10. https://doi.org/10.1007/s00134-020-06153-9.
[3] Jacob LP, Chazalet JJ, Payen DM, et al. Renal hemodynamic and functional effect of PEEP ventilation in human renal transplantations. Am J Respir Crit Care Med 1995 Jul 152:103–7. https://doi.org/10.1164/ajrccm.152.1.7599806.
[4] Annat G, Viale JP, Xuan BB, et al. Effect of PEEP ventilation on renal function, plasma renin, aldosterone, neurophysins and urinary ADH, and prostaglandins. Anesthesiology 1983 Feb;58:136–41. https://doi.org/10.1097/00000542-198302000-00006.
[5] Husain-Syed F, Slutsky AS, Ronco C. Lung-kidney cross-talk in the critically ill patient. Am J Respir Crit Care Med 2016 Aug 194:402–14. https://doi.org/10.1164/rccm.201602-0420CP.

[6] Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med 2020 Jun;46(6):1099–102. https://doi.org/10.1007/s00134-020-06033-2.
[7] Murray JF, Matthay MA, Luce JM, et al. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988 Sep 138:720–3. https://doi.org/10.1164/ajrccm/138.3.720.
[8] Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med 2016 Jul;375:122–33. https://doi.org/10.1056/NEJMoa1603017.
[9] Kellum JA, Lameire N, KDIGO AKI, Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (part 1). Crit Care 2013 Feb 17:204. https://doi.org/10.1186/cc11454.
[10] Panitchote A, Mehkri O, Hastings A, et al. Factors associated with acute kidney injury in acute respiratory distress syndrome. Ann Intensive Care 2019 Jul 1;9(1):74. https://doi.org/10.1186/s13613-019-0552-5.
[11] Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 2020 Jul;98(1):209–18. https://doi.org/10.1016/j.kint.2020.05.006.
[12] Darmon M, Legrand M, Terzi N, et al. Understanding the kidney during acute respiratory failure. Intensive Care Med 2017 Aug 43:1144–7. https://doi.org/10.1007/s00134-016-4532-z.

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