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Impact of mild hypoxemia on renal function and renal resistive index during mechanical ventilation

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Abstract *Rationale:* Short-term hypoxemia affects diuresis and natriuresis in healthy individuals. No data are available on the impact of the mild hypoxemia levels usually tolerated in critically ill patients receiving mechanical ventilation. *Objectives:* To assess the renal effects of mild hypoxemia during mechanical ventilation for acute lung injury (ALI). *Methods:* Prospective, physiological study in 12 mechanically ventilated patients with ALI. Patients were studied at baseline with an arterial saturation (SaO_2) of 96% [94–98] then a comparison was performed between SaO_2 values of 88–90% (mild hypoxemia) and 98–99% (high oxygenation). *Main results:* FiO_2 was set at 0.25 [0.23–0.32] and 0.7 [0.63–0.8], respectively, to obtain SaO_2 of 89 [89–90] and 99% [98–99]. Hemodynamic or respiratory parameters were not significantly affected by FiO_2 levels. Compared with high oxygenation level, mild hypoxemia using low FiO_2 was associated with increase in diuresis (median [interquartile range], 67 [55–105] vs. 55 [45–60] ml/h; $P = 0.003$) and in doppler-based renal resistive index (RI) (0.78 [0.66–0.85] vs. 0.72 [0.60–0.78]; $P = 0.003$). The 2-h calculated creatinine clearance also increased (63 [46–103] vs. 35 [30–85] ml/min; $P = 0.005$) without change in urinary creatinine ($P = 0.13$). No significant change in natriuresis was observed. Half of the patients were under norepinephrine infusion and the renal response did not differ according to the presence of vasopressors. *Conclusion:* In patients with ALI, mild hypoxemia related to short-term low FiO_2 induce increases in diuresis and in renal RI. This latter point suggests intra-renal mechanisms that need to be further investigated.

Keywords Intensive care unit · Respiratory distress syndrome, adult · Urinary tract physiology · Renal failure, acute · Doppler ultrasonography

Abbreviations

RI	Resistive index
ARDS	Adult respiratory distress syndrome
ALI	Acute lung injury
IQR	Interquartile ranges
ICU	Intensive care unit
PEEP	Positive end-expiratory pressure
Vt	Tidal volume
FENa	Excreted fraction of sodium

Introduction

In mechanically ventilated patients, the inspired oxygen fraction (FiO_2) is set to reach "normal" levels of oxygenation in arterial blood. The recommended values for arterial saturation vary over a relatively large range, however, and the possible consequences on tissue oxygenation are not well understood. For instance, ventilation strategies have been developed to limit lung injury induced by mechanical ventilation in patients treated for acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) [1–3]. These strategies usually seek to maintain the arterial oxyhemoglobin saturation (SaO_2, measured by pulse oximetry) between 88 and 95%. Values at the lower end of this range may help to minimize the adverse effects of oxygen, including denitrogenation atelectasis [1, 3–5], but no comparison of the effects of different targets on tissue oxygenation has been performed.

Tissue oxygenation in the kidney is not uniform. Normally, the partial pressure of oxygen is about 50 mmHg in the cortex and 10–20 mmHg in the medulla [6, 7]. This pattern results from both glomerular filtration and urine concentration processes, as the parsimonious blood flow to the renal medulla preserves the osmotic gradients. In healthy humans and in animals, short-term hypoxemia (20 min to 3 h) of variable intensity (PaO_2 between 30 and 60 mmHg) increases urinary output and natriuresis [8–11]. In contrast, chronic hypoxemia related to chronic respiratory failure is associated with a decrease in urinary output [12–15]. In addition, both hypoxemia and hypercapnia are associated with increased renal resistance, their effects being synergistic [16–19].

In ICU patients, acute renal failure is a major prognostic factor [20], but the effect of mild hypoxemia on renal function has not been studied. Because of the prognostic impact of acute kidney injury in ICU patients [20, 21], it may be important to know whether the range of recommended SaO_2 values has an influence on kidney function in critically ill patients. Therefore, this preliminary study was designed to evaluate whether increase in diuresis, natriuresis and renal resistive index (RI) previously reported in healthy subjects in response to mild hypoxemia, at levels usually tolerated during mechanical ventilation, could be also observed in critically ill patients.

The results of this study have been presented, in part, at the Congress of the European Society for Intensive Care Medicine, Berlin, Germany, 2007 [22].

Patients and methods

Patients

The study was approved by the ethics committee of the French Society for Intensive Care Medicine (SRLF-CE 06-132) and took place between April and December 2006. A printed information sheet was given to each patient's next of kin. In the 13-bed ICU of our teaching hospital, patients were enrolled if they received mechanical ventilation for ALI or ARDS meeting the definition of the American-European International Consensus Conference [23]. At the time of the study, all patients were in stable clinical condition, under continuous intravenous sedation with midazolam and fentanyl with a Ramsay score at 4 and ventilated in assist-control mode whose settings were chosen based on the clinical criteria by the attending physician before study initiation, with an FiO_2 not higher than 0.8. No neuromuscular blocking agent was given for the purpose of the study and sedation was not modified during the study. The SAPSII score was determined at 24 h of ICU admission and the LOD score was calculated at the time of study inclusion [24, 25].

Noninclusion and exclusion criteria

Patients were not included when under 18-year-old, had pregnancy, need for long-term oxygen therapy for chronic obstructive pulmonary disease, or sickle cell disease. They were excluded if, at the time of screening or later, they presented any of the followings: acute ischemic heart disease, hemodynamic instability (defined as a need for fluid resuscitation within the last 6 h or for epinephrine or norepinephrine in doses higher than 1 mg/h), arrhythmia, and renal failure, either acute according to the RIFLE definition, whatever the stage, or chronic with a basal creatinine clearance below 30 ml/min as calculated using the Cockroft and Gault formulae [26, 27], and when diuretics had been given within the last 6 h. Patients who had developed an acute renal failure prior to screening were included only 48 h after full recovery of the renal function.

Protocol

The primary objective of the study was to detect variations in renal function, assessed by diuresis, natriuresis, and doppler-based renal RI, as response to mild hypoxemia. The secondary objective was to evaluate cardiovascular and respiratory physiological response to mild hypoxemia. Each patient was assessed first at baseline, with the SaO_2 obtained using the settings selected by the attending physician, then we compared a low oxygenation level (SaO_2 between 88 and 90%; mild hypoxemia), and a high oxygenation level (SaO_2 of 98 to 99%). High and low oxygenation levels were obtained entirely by titrating FiO_2. Since brief exposure to hypoxemia (1–2 h) were demonstrated to be sufficient to detect significant renal function changes in healthy subject, each period was

maintained for 2 h [8–11]. There was no intermediate washout period.

Monitoring and instrumentation

The electrocardiogram, heart rate, systemic arterial blood pressure, and pulse oximetry (SpO_2), were monitored continuously. All patients had radial artery catheterization with a 20-G plastic catheter for arterial pressure measurement before the study and subsequently for collecting arterial blood for determinations of pH, $PaCO_2$, PaO_2, HCO^{3-}, lactates and hemoglobin saturation. Arterial oxygen content was calculated in volume percent as being equal to [1.39 × (oxygen saturation of arterial blood) × (hemoglobin in g/dL)] + (0.0031 × PaO2 in mmHg). Plasma sample were collected at the end of each oxygenation level.

The 120-min urines were collected at the end of each oxygenation level using a Foley catheter. Intra-abdominal pressure was measured before study inclusion via the bladder catheter after instillation of 25 ml of saline [28].

Renal perfusion indices were measured using Doppler ultrasonography at the end of each oxygenation level. All measurements were performed by the same investigator (M. D.) using a 5-MHz transducer (Envisor, Philips Medical Systems, Bothell, WA). In each patient, the right or left kidney was selected depending on the ease of access. After visualizing the kidney in gray scale and color Doppler mode, the absence of signs of chronic renal damage was checked. An interlobar or arcuate artery was then selected and measurements were obtained using pulse-wave Doppler. At least three readings were obtained from the selected artery, and the mean of the corresponding three determinations of the renal RI was used for the study. RI was computed as the difference between peak systolic velocity and end-diastolic velocity over peak systolic velocity. RI is an index of resistance to flow distal to the point of sampling. Lower RI is associated with less resistance to flow. RI values were compared under each oxygenation condition, and also after correction for heart rate, as previously proposed: corrected RI = RI − [0.0026 × (80 – heart rate)] [29].

Hemodynamic indices

At baseline and at the end of each oxygenation level, the following parameters were recorded: heart rate, arterial pressure, urine output, and urinary electrolytes, creatinine, urea, and urinary cystatin *C*. At the same time points, tidal volume (*V*t) and breathing rate (*f*) were read from the ventilator. Plateau pressure (*P*plat) and intrinsic PEEP were measured after an occlusion maneuver performed at end inspiration and expiration, respectively, and were used to compute respiratory system compliance defined as [tidal volume/(plateau pressure − total end-expiratory pressure)].

Definitions

The fractional excretion of sodium (FENa) was calculated as [(urinary sodium/plasma sodium)/(urinary creatinine/plasma creatinine)] × 100. Creatinine clearance over 2 h was calculated as [urinary creatinine × urine output (ml)]/[plasma creatinine × time (min)]. Urinary osmolality was computed as [(urinary sodium + urinary potassium) × 2 + urinary urea)]. Free water excretion was calculated as [diuresis (ml/min) − osmolar clearance]. Osmolar clearance was calculated as [(urinary osmolality/plasma osmolality) × diuresis (ml/min)].

Statistical analysis

As described in healthy subject [8–11, 17], the smallest variation in renal parameters function in response to hypoxemia, was expected to be the change in renal resistive index. Sample size was therefore calculated upon the supposed changes of renal resistive index. Twelve patients were needed, in a two-sided test performed with a 0.05 type I error and a 0.1 type II error to detect an absolute variation in resistive index between high and low oxygenation of 10%, assuming a basal resistive index of 0.7 and a standard deviation of 0.10 [17].

Results are reported as medians and interquartile range (IQR) or numbers and percentages (%), or mean ± SD to express the percentage of changes. Categorical variables were compared using Fisher's exact test, and continuous variables using nonparametric Wilcoxon test or Mann–Whitney test for two-by-two comparisons.

All tests were two-sided, and *P* values lower than 0.05 were considered statistically significant. Statistical tests were done using the SAS 6.12 software package (SAS Institute, Cary, NC).

Results

The main characteristics of the 12 patients included in the study are reported in Table 1. All patients had ALI and all but one met the ARDS criteria. Baseline FiO_2 was 0.50 and ranged from 0.40 to 0.80. At study inclusion, intra-abdominal pressure measured via the bladder was 10 mmHg [8.5–12]. The Doppler analysis did not find any sign of chronic renal failure in any patient. Five patients have suffered from acute renal failure earlier during their ICU stay and were included after recovery.

Table 1 Patient characteristics

	n (%) or median [IQR]
Age (years)	63 [42–72]
Male gender	10 (83%)
BMI (kg/m^2)	23.9 [21.3–27.9]
SAPS II (at admission)	42 [34–52]
LOD (at study inclusion)	6.5 [6–7]
Admission to inclusion (days)	7 [3–14]
PaO_2/FiO_2 ratio	167 [131–177]
Vt (ml/kg PBW)	6.2 [5.6–6.9]
PEEP level (cm H_2O)	9 [5–11]
Respiratory sytem compliance (ml/cm H_2O)	33 [26–41]
Vasopressors	6 (50%)
Hemoglobin (g/dl)	10.4 [7.5–12.3]
Creatinine (μmol/L)	72 [57–92]
FENa (%)	0.4 [0.19–2]

BMI body mass index (weight/height^2), *SAPSII* simplified acute physiology score [24], *LOD* logistic organ dysfunction score, which can range from 0 to 22 [25], FiO_2 fraction of inspired oxygen, *Vt* tidal volume, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure, *FENa* fractional excretion of sodium, Admission to inclusion: time (in days) between admission to the ICU and inclusion in the study

Table 2 reports the main study results, with comparisons of low and high oxygenation conditions, also showing the baseline condition. Below, we focus on comparisons of low and high oxygenation levels. FiO_2 and SaO_2 at low oxygenation conditions were of 89% [89–90] and 0.25 [0.23–0.32], respectively, compared with 99% [98–99] and 0.70 [0.63–0.81] during high oxygenation period. On average, arterial oxygen content was 15 ± 9% higher during high compared to low oxygenation period.

Hemodynamic and respiratory variables

Echocardiography was performed in 9 of the 12 patients. Hemodynamic parameters were not significantly influenced by oxygenation level and no change was noted in cardiac output or in systolic pulmonary arterial pressure (Table 2).

Under sedation, no significant variation in respiratory characteristics occurred between the two oxygenation periods. Respiratory rate, $PaCO_2$ and pH did not differ between the two periods (Table 2).

Renal function

Low oxygenation was associated with an increase in diuresis when compared with high oxygenation period (67 [55–105] vs. 55 [45–60] ml/h; $P = 0.003$) which occurred in every patient (Fig. 1; Table 2). The calculated 2-h creatinine clearance ($P = 0.005$) and urinary pH ($P = 0.05$) also increased during high oxygenation period but urinary creatinine level was not modified by low oxygenation. Fractional sodium excretion and natriuresis were not modified by changes in oxygenation.

Urinary osmolality was not modified during low oxygenation period, therefore, accordingly to the increased diuresis, low oxygenation period was associated with increases in osmolar clearance when compared with high oxygenation period (1.71 ml/min [1.01–2.51] vs. 1.01 ml/min [0.85–2.03]; $P = 0.01$), in C_{H_2O}/C_{osmo} ratio (−0.32 [−0.18 to −0.45] versus −0.83 [−0.59 to −0.92]; $P = 0.01$), and with no variations of free water excretion. Urinary cystatin *C* excretion was not modified by the oxygenation period.

Renal resistive index

Doppler-based RI was obtained under all three conditions in all 12 patients. Precision of RI are reported in the electronic supplementary material (Fig. E1 and 2). In the baseline oxygenation condition, RI was 0.73 [0.59–0.80] and correlated with age ($\rho = 0.88$; $P = 0.0001$) and mean arterial pressure ($\rho = -0.63$; $P = 0.03$) (Figs. E3 and 4).

Low oxygenation was associated with an increase in RI (0.78 [0.66–0.85] vs. 0.72 [0.60–0.78] during low and high oxygenation periods, respectively; $P = 0.003$) (Fig. 2). Similar results were obtained when RI was corrected for heart rate ([0.78 [0.74–0.84] vs. 0.73 [0.70–0.79] during low and high oxygenation period; $P = 0.003$).

The impact of oxygenation period on RI values was similar in patients with ($n = 6$) and without ($n = 6$) vasopressor therapy (Fig. E5). No correlations were found between the renal response to oxygenation and hemodynamic, respiratory or oxygenation variables.

Discussion

We report the first study specifically designed to compare the renal effect of a low or high oxygenation level with two levels of arterial oxygen content, in critically ill patients requiring mechanical ventilation. When compared with a high FiO_2 level, short-term exposure to low FiO_2 and oxygenation translated into a consistent increase in diuresis and was accompanied in all patients by an increase in the Doppler-based renal RI.

Although hypoxemia has well-known renal effects, no data were available on the renal effects of mild hypoxemia during mechanical ventilation of ICU patients. Studies of healthy volunteers evaluated the effects of more profound hypoxemia (FiO_2 10–12%, i.e., PaO_2 in

Table 2 Hemodynamic, respiratory, and renal parameters under the three oxygenation conditions

	Baseline	SaO_2 88–90% Low oxygenation	SaO_2 98–99% High oxygenation	*P* value Low versus high
Hemodynamic parameters				
Heart rate (breaths/min)	80 [67–92]	83 [71–96]	78 [67–97]	0.12
Systolic arterial pressure (mmHg)	122 [110–138]	124 [118–140]	117 [115–143]	0.75
Mean arterial pressure (mmHg)	78 [74–87]	80 [75–86]	78 [73–92]	0.35
Blood lactates (mmol/l)	1.1 [0.8–1.3]	1.0 [0.7–1.2]	0.8 [0.7–1.1]	0.09
Echocardiography ($n = 9$)				
Peak tricuspid regurgitant jet velocity (m/s)	2.9 [2.3–3.3]	2.7 [2.5–3.5]	2.9 [2.6–3.4]	0.75
Systolic arterial pulmonary pressure (mmHg)	34 [21–44]	35 [27–47]	35 [28–40]	0.71
Cardiac output (L/min)	5.2 [4.3–5.8]	6.2 [4.8–6.5]	5.7 [4.7–6.6]	0.67
Respiratory parameters				
Respiratory rate (breaths/min)	20 [18–25]	21 [19–27]	21 [19–25]	0.56
pH	7.39 [7.37–7.42]	7.42 [7.39–7.49]	7.42 [7.40–7.43]	0.41
$PaCO_2$ (mmHg)	42 [35–58]§	37 [34–51]	38 [37–54]	0.24
SaO_2 (%)	96 [94–98]§	89 [89–90]	99 [98–99]	**0.003**
PaO_2 (mmHg)	88 [69–102]§	55 [53–60]	128 [109–138]	**0.003**
$HCO3^-$ (mmol/l)	27.9 [24.5–33.2]	28.3 [24.9–33.6]	27.6 [24.1–34.6]	0.92
CaO_2 (ml oxygen per dl of blood)	14.0 [10.7–14.9]§	13.7 [10.1–14.1]	15.4 [11.6–16.1]	**0.002**
FiO_2	0.50 [0.40–0.70]	0.25 [0.23–0.32]	0.70 [0.63–0.81]	**<0.001**
Renal characteristics				
Diuresis (ml/h)	47 [32–64]§	67 [55–105]	55 [45–60]	**0.003**
Natriuresis (mmol/l)	44 [13–125]	53 [26–125]	50 [24–116]	0.17
FENa (%)	0.4 [0.2–2.0]§	0.6 [0.5–2.3]	0.7 [0.36–1.88]	0.06
Kaliuresis (mmol/l)	36 [20–68]§	28 [17–57]	43 [18–60]	0.06
2-h creatinine clearance (ml/min)	44 [32–95]§	63 [46–103]	35 [30–82]	**0.005**
Urinary creatinine (mmol/l)	4.9 [1.48–8.35]	5.6 [1.30–7.36]	4.54 [2.05–7.18]	0.13
Urinary pH	6 [5–6]§	6 [6–7]	6 [5–6]	**0.05**
Urinary osmolality (mmol/l)	458 [348–558]	449 [372–566]	459 [368–563]	0.37
Free water excretion (ml/min)	−0.27 [−0.46– −0.16]§	−0.34 [−0.78– −0.26]	−0.90 [−2 – −0.55]	0.14
Urinary cystatin C (mg/L)	0.16 [0.09–0.3]	0.14 [0.08–0.3]	0.16 [0.1–0.4]	0.26
Renal Doppler				
Resistive index	0.73 [0.59–0.80]§	0.78 [0.66–0.85]	0.72 [0.60–0.78]	**0.003**

Results are expressed as median [IQR]. The represented *P* value is the results of comparison of high oxygenation with low oxygenation period using Wilcoxon's nonparametric test

§ $P < 0.05$ when comparing the three periods using Friedman's nonparametric test

FeNa: fractional excretion of sodium [(urine sodium/blood sodium)/(urine creatinine/plasma creatinine)] × 100

Creatinine clearance: [urine creatinine × urine volume (ml)]/[plasma creatinine × time (min)]

Resistive index (*RI*) was calculated as [(peak systolic velocity – minimum diastolic velocity)/peak systolic velocity]

Urinary osmolality was calculated as [(urine sodium + urine potassium) × 2 + urine urea)]

Free water excretion was calculated as [diuresis (ml/min) − Osmolar clearance]

the 30–40 mmHg range) than usually tolerated in ICU patients [10, 30–32]. Whereas alterations in renal hemodynamic and function can be generated by multiple factors in critically ill patients, the renal impact of mild hypoxemia in our study was consistent with data obtained outside of the ICU setting. Interactions between kidney function and hypoxemia have been studied in animals, healthy volunteers, and in patients with chronic obstructive pulmonary disease. Increased diuresis and natriuresis occur in response to acute hypoxemia [8, 10, 11, 30, 32]. Hemoconcentration and decrease in sodium reabsorption might be adaptative mechanisms of oxygen transport and consumption.

In our study population, hypoxemia was associated with an increase in doppler-based renal RI. Previous studies produced conflicting results, with renal resistance being increased, decreased, or unchanged during short-term hypoxemia [16, 19, 32–36]. However, pentobarbital anesthesia was used consistently in animal studies and may have modified the vasomotor response to hypoxemia [17]. In our patients, the sedative infusion rate was kept constant throughout the study. In addition, renal perfusion assessment in early studies was based on the effective renal plasma flow as estimated from the clearance of *p*-aminohippurate or ^{131}I-hypuran [8, 32–34, 36], a method that requires the proximal tubule cells to transfert *p*-aminohippurate from the peritubular capillaries to the tubules [37]. Hypoxemia may alter proximal tubule function, making estimates of effective renal plasma flow poorly reliable [17, 32, 37]. Our data are in agreement with several studies in which both hypoxemia and hypercapnia were associated with increases in doppler-based renal resistance in patients with chronic obstructive pulmonary disease, in healthy volunteers, or in renal

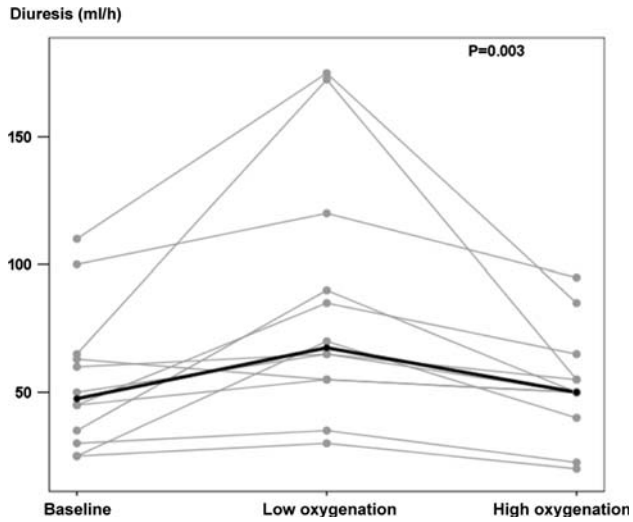

Fig. 1 Effect of mild hypoxemia on diuresis (ml/h). Individual values (*gray lines*) and median (*black line*) under the three oxygenation conditions. Wilcoxon's nonparametric test was used for comparisons of low oxygenation with high oxygenation period

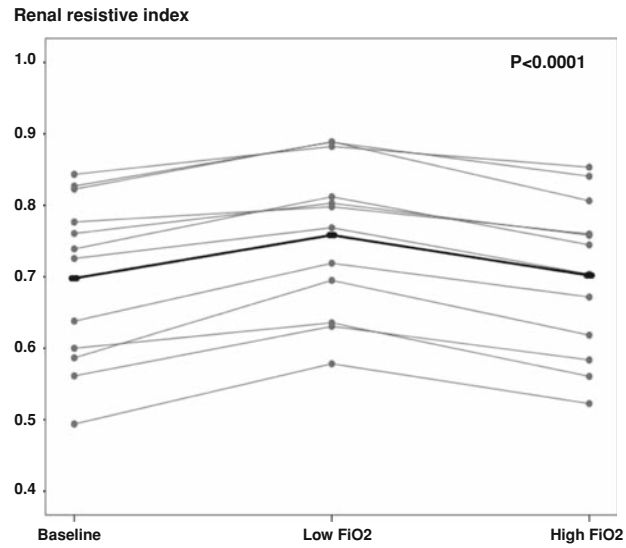

Fig. 2 Effect of mild hypoxemia on resistive index values. Individual values (*gray lines*) and median (*black line*) under the three oxygenation conditions. Wilcoxon's nonparametric test was used for comparisons of low oxygenation with high oxygenation period

transplant recipients [16–19, 33]. The RI increase found in our study may reflect an increase in pre- and/or postglomerular and/or peritubular capillary resistances. An increase in glomerular filtration pressure seems, however, unlikely because increased RI values are generally thought to indicate decreased renal perfusion and the development of renal injury [38, 39]. In addition, increase of resistive index as response to hypoxemia has been shown to occur in renal transplant recipients suggesting that this effect is not because of pre/postglomerular resistances regulation by the renal sympathetic nerves [17, 40].

The pathophysiological mechanisms underlying the renal response to mild hypoxemia documented in our study remain unclear. An hypoxic ventilatory response may have contributed to the diuretic response to hypoxemia in some studies [30, 41]. Hypoxic ventilatory response was, however, not present or minimal in our patients under continuous sedation. Another suggested mechanism is activation of the sympathetic system, which may increase cardiac output [42]. However, hemodynamic parameters showed no significant variations in our study. Interestingly, we found no increase in urinary cystatin C, which is used as marker for tubular dysfunction [43]. This suggests that the short-term effect of hypoxemia documented in our study could reflect a functional alteration of peritubular capillaries, or tubular cells without tubular lesions. In addition, we found an increase in creatinine clearance during the low oxygenation period. However, the limitations of urinary creatinine clearance over 2 h preclude any firm conclusion. An increased glomerular filtration rate with unchanged tubular function is uncertain because the observed variation of creatinine clearance was a pure consequence of diuresis increase alone without variations of urinary creatinine and will thus need confirmation before ensuring this reflects a change in glomerular filtration. Alteration in tubular function without change in glomerular filtration rate may also explain this result; however, we did not find significant variations of cystatin C, natriuresis and kaliuresis related to hypoxemia.

The order of the low and high sequences was not randomized, which can be a limitation for the interpretation of the results. The primary reason was that we considered that the baseline value would be much closer to the high oxygenation than the low oxygenation period, making a sort of control. This would ensure that a rapid physiological response, such as vascular changes, could be comparable during these two periods. This was indeed the case, since RI was found similar during the baseline and the high FiO_2 periods ($P = 0.58$). Ideally, a washout period would have been required between the different FiO_2 levels, but this would have extended the study duration from 6 to 10 h with a much greater risk of not keeping a relative steady state over a longer period in these critically ill patients. Therefore, although questionable, this seemed to be the simplest study design for such a preliminary study. The consistency of our results with physiological observations in healthy subjects suggests that the order of the sequences had probably little influence.The small number of patients in our study may have diminished our ability to detect the effects of mild hypoxemia on hemodynamic or respiratory variables. Nevertheless, we found important and highly consistent variations in renal function or perfusion in response to

mild hypoxemia. The potential beneficial or detrimental effects of the changes in renal function observed in our study remain difficult to predict. The clinical significance of these changes needs to be further evaluated since this study does not provide information on their long-term clinical significance. Renal response to hypoxia may also differ in case of decreased perfusion pressure [44]. This study, however, provides for the first time the evidence of a substantial renal effect of hypoxemia, justifying the need for further research to evaluate long-term renal effects and safety of hypoxemia levels usually tolerated in the ICU.

In conclusion, when compared with high oxygenation levels, low levels of oxygenation are associated with substantial and consistent modifications in renal function including increases in diuresis and renal RI. Whether these effects persist over time or adversely influence renal function, as well as their pathophysiological mechanisms, remains to be elucidated.

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References

1. (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 342:1301–1308
2. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondejar E, Clementi E, Mancebo J, Factor P, Matamis D, Ranieri M, Blanch L, Rodi G, Mentec H, Dreyfuss D, Ferrer M, Brun-Buisson C, Tobin M, Lemaire F (1998) Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. Am J Respir Crit Care Med 158:1831–1838
3. Richard JC, Girault C, Leteurtre S, Leclerc F (2005) Prise en charge ventilatoire du syndrome de détresse respiratoire aiguë de l'adulte et de l'enfant (nouveau-né exclu)—Recommandations d'Experts de la Société de Réanimation de Langue Française. Réanimation 14:313–322
4. Aboab J, Jonson B, Kouatchet A, Taille S, Niklason L, Brochard L (2006) Effect of inspired oxygen fraction on alveolar derecruitment in acute respiratory distress syndrome. Intensive Care Med 32:1979–1986
5. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT (2004) Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 351:327–336
6. Brezis M, Rosen S (1995) Hypoxia of the renal medulla–its implications for disease. N Engl J Med 332:647–655
7. Epstein FH, Agmon Y, Brezis M (1994) Physiology of renal hypoxia. Ann N Y Acad Sci 718:72–81 discussion 81–72
8. Berger E, Galdston M, Horwitz S, Jackenthal R, Pruss M (1949) The effect of anoxic anoxia on the human kidney. J Clin Invest 28:648–652
9. Olsen NV (1995) Effect of hypoxaemia on water and sodium homeostatic hormones and renal function. Acta Anaesthesiol Scand Suppl 107:165–170
10. Hohne C, Krebs MO, Boemke W, Arntz E, Kaczmarczyk G (2001) Evidence that the renin decrease during hypoxia is adenosine mediated in conscious dogs. J Appl Physiol 90:1842–1848
11. Hildebrandt W, Ottenbacher A, Schuster M, Swenson ER, Bartsch P (2000) Diuretic effect of hypoxia, hypocapnia, and hyperpnea in humans: relation to hormones and O(2) chemosensitivity. J Appl Physiol 88:599–610
12. Mannix ET, Dowdeswell I, Carlone S, Palange P, Aronoff GR, Farber MO (1990) The effect of oxygen on sodium excretion in hypoxemic patients with chronic obstructive lung disease. Chest 97:840–844
13. MacNee W (1994) Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. Part two. Am J Respir Crit Care Med 150:1158–1168
14. MacNee W (1994) Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. Part one. Am J Respir Crit Care Med 150:833–852
15. Farber MO, Roberts LR, Weinberger MH, Robertson GL, Fineberg NS, Manfredi F (1982) Abnormalities of sodium and H_2O handling in chronic obstructive lung disease. Arch Intern Med 142:1326–1330
16. Baudouin SV, Bott J, Ward A, Deane C, Moxham J (1992) Short term effect of oxygen on renal haemodynamics in patients with hypoxaemic chronic obstructive airways disease. Thorax 47:550–554
17. Sharkey RA, Mulloy EM, O'Neill SJ (1998) Acute effects of hypoxaemia, hyperoxaemia and hypercapnia on renal blood flow in normal and renal transplant subjects. Eur Respir J 12:653–657
18. Sharkey RA, Mulloy EM, O'Neill SJ (1999) The acute effects of oxygen and carbon dioxide on renal vascular resistance in patients with an acute exacerbation of COPD. Chest 115:1588–1592
19. Howes TQ, Deane CR, Levin GE, Baudouin SV, Moxham J (1995) The effects of oxygen and dopamine on renal and aortic blood flow in chronic obstructive pulmonary disease with hypoxemia and hypercapnia. Am J Respir Crit Care Med 151:378–383
20. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. J Am Med Assoc 294:813–818
21. Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten H, Ronco C, Kellum JA (2007) Continuous renal replacement therapy: a worldwide practice survey: the beginning and ending supportive therapy for the kidney (B.E.S.T. Kidney) investigators. Intensive Care Med 33:1563–1570
22. Darmon M, Schortgen F, Leon R, Brun-Buisson C, Brochard L (2007) Renal effects of different targets for arterial oxygenation during ARDS. Intensive Care Med 33:S99
23. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R (1994) The American-European consensus conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149:818–824

24. Le Gall JR, Lemeshow S, Saulnier F (1993) A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. J Am Med Assoc 270:2957–2963
25. Le Gall JR, Klar J, Lemeshow S, Saulnier F, Alberti C, Artigas A, Teres D (1996) The logistic organ dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU scoring group. J Am Med Assoc 276:802–810
26. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P (2004) Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the acute dialysis quality initiative (ADQI) group. Crit Care 8:R204–R212
27. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41
28. Malbrain ML, Cheatham ML, Kirkpatrick A, Sugrue M, Parr M, De Waele J, Balogh Z, Leppaniemi A, Olvera C, Ivatury R, D'Amours S, Wendon J, Hillman K, Johansson K, Kolkman K, Wilmer A (2006) Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome. I. Definitions. Intensive Care Med 32:1722–1732
29. Mostbeck GH, Gossinger HD, Mallek R, Siostrzonek P, Schneider B, Tscholakoff D (1990) Effect of heart rate on Doppler measurements of resistive index in renal arteries. Radiology 175:511–513
30. Hohne C, Boemke W, Schleyer N, Francis RC, Krebs MO, Kaczmarczyk G (2002) Low sodium intake does not impair renal compensation of hypoxia-induced respiratory alkalosis. J Appl Physiol 92:2097–2104
31. Swenson ER, Duncan TB, Goldberg SV, Ramirez G, Ahmad S, Schoene RB (1995) Diuretic effect of acute hypoxia in humans: relationship to hypoxic ventilatory responsiveness and renal hormones. J Appl Physiol 78:377–383
32. Vidiendal Olsen N, Christensen H, Klausen T, Fogh-Andersen N, Plum I, Kanstrup IL, Hansen JM (1998) Effects of hyperventilation and hypocapnic/normocapnic hypoxemia on renal function and lithium clearance in humans. Anesthesiology 89:1389–1400
33. Rose CE Jr, Kimmel DP, Godine RL Jr, Kaiser DL, Carey RM (1983) Synergistic effects of acute hypoxemia and hypercapnic acidosis in conscious dogs. Renal dysfunction and activation of the renin-angiotensin system. Circ Res 53:202–213
34. Bruns FJ (1978) Decrease in renal perfusion, glomerular filtration and sodium excretion by hypoxia in the dog. Proc Soc Exp Biol Med 159:468–472
35. Korner PI (1959) Circulatory adaptations in hypoxia. Physiol Rev 39:687–730
36. Zillig B, Schuler G, Truniger B (1978) Renal function and intrarenal hemodynamics in acutely hypoxic and hypercapnic rats. Kidney Int 14:58–67
37. Corrigan G, Ramaswamy D, Kwon O, Sommer FG, Alfrey EJ, Dafoe DC, Olshen RA, Scandling JD, Myers BD (1999) PAH extraction and estimation of plasma flow in human postischemic acute renal failure. Am J Physiol 277:F312–F318
38. Lauschke A, Teichgraber UK, Frei U, Eckardt KU (2006) 'Low-dose' dopamine worsens renal perfusion in patients with acute renal failure. Kidney Int 69:1669–1674
39. Lerolle N, Guerot E, Faisy C, Bornstain C, Diehl JL, Fagon JY (2006) Renal failure in septic shock: predictive value of Doppler-based renal arterial resistive index. Intensive Care Med 32:1553–1559
40. Denton KM, Shweta A, Anderson WP (2002) Preglomerular and postglomerular resistance responses to different levels of sympathetic activation by hypoxia. J Am Soc Nephrol 13:27–34
41. Murdaugh HV Jr, Sieker HO, Manfredi F (1959) Effect of altered intrathoracic pressure on renal hemodynamics, electrolyte excretion and water clearance. J Clin Invest 38:834–842
42. Honig A (1989) Peripheral arterial chemoreceptors and reflex control of sodium and water homeostasis. Am J Physiol 257:R1282–R1302
43. Conti M, Moutereau S, Zater M, Lallali K, Durrbach A, Manivet P, Eschwege P, Loric S (2006) Urinary cystatin C as a specific marker of tubular dysfunction. Clin Chem Lab Med 44:288–291
44. Whitehouse T, Stotz M, Taylor V, Stidwill R, Singer M (2006) Tissue oxygen and hemodynamics in renal medulla, cortex, and corticomedullary junction during hemorrhage-reperfusion. Am J Physiol Renal Physiol 291:F647–F653