

Feasibility and Clinical Experience of Arterial-urinary Oxygen ($\text{PaO}_2\text{-PuO}_2$) Gradient Monitoring for Early Detection of Acute Renal Failure in COVID-19 Patient: A Clinical Case Series

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ABSTRACT

Mechanisms of coronavirus disease 2019 (COVID-19) induced acute kidney injury (AKI) include local tissue inflammation due to immunological responses and activation of coagulation pathways following endothelial damage. It has been shown that reduced oxygen supply and renal hypoxia are significant risk factors for the development of AKI in postcardiac surgery patients. The urinary oxygen partial pressure (PuO_2) of the first discharged urine is comparable to that of the renal medulla. Therefore, the real-time monitoring of PuO_2 can be used to predict renal hypoxia and the risk of AKI in COVID-19 patients who are hospitalized [intensive care unit (ICU)]. In this observational study, we did a single time point measurement of blood–urine gas analysis in addition to routine arterial blood gas analysis in 20 critically ill COVID-19 patients. In this case series, we couldn't find an association between stagnant urine PuO_2 and renal hypoxia. However, serial monitoring of PuO_2 by urinary oximeter can be used for early detection of medullary hypoxia.

Keywords: Acute kidney injury, Coronavirus disease 2019, Hypoxemia.

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INTRODUCTION

The worldwide incidence of COVID-19-induced AKI is 29% in critically ill patients admitted to the ICU; however, it may increase up to 78% in patients requiring positive pressure ventilation.¹ Mechanisms of COVID-19-induced AKI include local tissue inflammation due to immunological responses and activation of coagulation pathways following endothelial damage.² Direct mechanism of renal damage caused by viral infection has also been proposed by some studies, but it is still controversial. Among the patients admitted to ICU, nonspecific factors associated with renal damage include positive pressure ventilation, oxygen desaturation, reduced cardiac output and blood pressure, and nephrotoxic drugs. In patients who have undergone cardiac surgery, the decreased tissue oxygen at the level of the kidney is thought to be an important factor in the development of AKI.³ Due to the high metabolic rate and low tissue perfusion of the thick ascending limbs of the renal medulla in comparison to the renal cortex, the renal medulla is the most susceptible to hypoxic injury. PuO_2 of the first excreted urine may represent tissue oxygen at the level of the renal medulla.⁴ So, in critically ill COVID-19 patients, the PuO_2 measurement might be used for real-time monitoring of renal medullary hypoxia and AKI risk. However, it has been demonstrated that the PuO_2 of stored urine in the

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bladder decreases due to sepsis, reduced renal blood flow, and reduced cardiac output.⁵ It is feasible to monitor (PuO_2) either in the bladder or by using a polarographic electrode after its placement into the urinary catheter.⁶ Silverton *et al.*⁷ monitored continuous PuO_2 data using a noninvasive

experimental urinary oximeter, which was inserted between the collecting bag and the urinary catheter.

MATERIALS AND METHODS

In this observational study, we did a single time point measurement of blood–urine gas analysis in addition to routine arterial blood gas analysis in 20 critically ill COVID-19 patients (Table 1). The purpose of this case series was to determine any possible association between urinary oxygen monitoring for early detection of acute renal failure in COVID-19 patients. Written and informed consent for publication was taken from the patients. Urine samples for PuO_2 measurement was collected in a 27 G arterial blood gas analyzing syringe to avoid air entrainment. The sample was taken after puncturing the silicone catheter present inside the urinary bladder. The PuO_2 measurement was performed with a blood gas analyzer. Serial monitoring of urea and creatinine was performed as a follow-up of the renal functions. We found decreased PuO_2 and increased arterial-urinary gradient in patients having AKI. In four patients, the PuO_2 was greater than the partial pressure of oxygen in the arterial blood (PaO_2), which might be due to the inadvertent entrainment of oxygen into the silicon catheter from the surrounding tissue or atmosphere. In this case series, the AKI severity grading was done on the basis of creatinine elevation only. In our cases, the urine sample for PuO_2 measurement was taken only when urine flow was >0.5 mL/kg/hour. This is the most

acceptable threshold for defining oliguria, and patients having urine flows below this threshold had the risk of AKI development.

DISCUSSION

Numerous investigations have shown a high correlation between medullary oxygen concentrations and PuO_2 , prompting the term “clinical window on the health of the renal medulla.”⁴ Animal study has proven that PuO_2 is a sensitive indication of reduced renal blood flow.⁸ In an ovine model of sepsis, the norepinephrine supplementation to restore mean arterial pressure results in increased urine output; however, there occurs a decrease in oxygenation of the renal medulla and PuO_2 . Silverton et al.⁷ examined PuO_2 during cardiac surgery by using a noninvasive urinary oximeter. The oximeter was positioned between the silicon urinary catheter and a collecting bag. According to them, the reduced PuO_2 was independently linked with AKI in post-cardiopulmonary bypass patients. The mean PuO_2 cutoff value found by Kainuma et al., Silverton et al., and Zhu et al. were between 65 and 73 mm Hg, 37 and 43 mm Hg, and 19 and 27 mm Hg, respectively.^{6,7} It is not beneficial to measure PuO_2 distal to the urinary bladder as it yields greater PuO_2 values. This is because of the ingress of oxygen inadvertently into the urine catheter from the surrounding tissue or atmosphere and was more pronounced when the urinary flow was very low.⁷

The Kidney Disease: Improving Global Outcomes (KDIGO) recommendations suggest diagnosing AKI with

Table 1: Arterial-urinary oxygen gradient and renal profile of patients

Sl no.	F_iO_2	PaO_2	PuO_2	$PaO_2 - PuO_2$ gradient	Urea	Creatinine
1	40	203	91	112	68	0.81
2	100	331	50	281	126.3	1.18
3	60	168	128.7	39.3	191.8	5.41
4	40	216	169.2	46.8	71.6	1.17
5	50	64.5	131	-66.5	50.1	1.00
6	40	193.2	147	45.8	128.5	4.67
7	28	82.4	55	17.4	44.7	0.84
8	100	278	173	105	71.7	0.51
9	28	197	168.5	29.5	125.8	7.50
10	36	197.4	118	79.4	162.8	5.86
11	80	237	134.7	102.3	106.1	2.15
12	21	69.3	89.5	-20.2	158.0	2.41
13	48	175.9	94.2	81.7	33.1	0.78
14	44	59.8	139.9	-80.1	16.6	0.27
15	21	189.2	53.9	135.3	177.2	4.31
16	100	145	62	83	106.0	1.67
17	30	120.1	105.6	14.5	75.3	1.19
18	100	61.2	144.7	-83.5	24.6	0.43
19	45	148.9	125.1	23.8	52.0	0.62
20	21	187.3	45.3	142	42.8	0.67

F_iO_2 , fraction of inspired oxygen; PaO_2 , partial pressure of oxygen in the arterial blood; PuO_2 , partial pressure of oxygen in the urine

elevated serum creatinine and oliguria. Glomerular filtration rate, a well-known indicator of renal function, is reflected in both measurements. However, the KDIGO recommendation for diagnosing a patient of AKI on the basis of urine output becomes inaccurate in a patient taking osmotic diuretics like mannitol or in patients undergoing surgery with massive fluctuation in fluid balance. According to one study, people with severe AKI had hospital costs that may reach 94%, a mortality rate that was 10 times higher than for people without the condition, and five times higher than for people with mild AKI.⁹ In a study by Silverton et al.,⁷ the mean PuO_2 was strongly associated with the AKI severity (KDIGO stage 2/3) if the cutoff threshold was kept to 25 mm Hg. In COVID-19 acute respiratory distress syndrome (ARDS) patients, resistant hypoxia was really a challenge. To explore renal medullary hypoxia as a cause of AKI, we did PuO_2 measurement in this observational study. In this observational study, we did not find PuO_2 of <40 mm Hg in any COVID-19 patient having AKI. This might be possible due to the ingress of oxygen inadvertently into the silicon urinary catheter from the tissue surrounding or from the atmosphere. From this observation, we suggest serial or continuous monitoring of PuO_2 by urinary oximeter for early detection of hypoxia as a cause of AKI or to take further preventive measures.

Previous research has revealed that PuO_2 values may be affected by excessive urinary flow, which may occur during diuretics therapy, soon after urinary catheter placement, and during patient posture changes. Sgouralis et al. in an animal study, have proven that the value of PuO_2 measured distal to the renal pelvis was affected by the urinary flow.¹⁰

Limitations

The main limitation of this clinical case series was the technique of collecting the urinary sample. There may occur ingress of oxygen from the surrounding tissue and air entrainment from the environment during low urinary flow. This may result in inaccurate PuO_2 in stagnant urine. Other limitations are—no established threshold exists for PuO_2 and we did single time point monitoring of PuO_2 in all COVID-19 patients. A well-structured study is required with continuous measurement of PuO_2 , to make a conclusion of threshold PuO_2 below which there is an increased chance of AKI in COVID-19 patients.

CONCLUSION

Serial monitoring of PuO_2 by urinary oximeter is a feasible noninvasive or partially invasive method for early detection of medullary hypoxia as a cause of AKI in COVID-19 ARDS patients. Stagnant urine PuO_2 cannot be used for monitoring renal hypoxia.

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