〈Regular Article〉

Assessment of urine partial oxygen pressure to predict postoperative acute kidney injury in major surgical patients

Naoto IKEMOTO[1)], Hiroshi KATAYAMA[1)], Naomasa ISHIDA[2)]
Masaaki MICHIDA[1)], Yukiko YOSHIDA[1)], Yoko OCHIAI[1)]
Masao HAYASHI[1)], Munenori TAKAOKA[2)], Tomoki YAMATSUJI[2)]
Ichiro OHASHI[1)], Hideki NAKATSUKA[3)]

1) Department of Anesthesiology & Intensive Care Medicine 3,
2) Department of General Surgery,
3) Department of Anesthesiology & Intensive Care Medicine 1, Kawasaki Medical School

ABSTRACT Urine partial oxygen pressure (PuO_2) was monitored in postoperative intensive care unit (ICU) patients to verify if an earlier diagnosis of acute kidney injury (AKI) is possible. Fifty-nine patients who were admitted to the ICU after surgery for at least 48 hours at Kawasaki Medical Center between January 2019 and June 2020 were assessed for AKI using the Kidney Disease: Improving Global Outcome (KDIGO) criteria. The AKI group had 15 patients while the non-AKI group had 44 cases. The PuO_2 of each group showed no significant difference. Arterial partial oxygen pressure (PaO_2) was measured concurrently with PuO_2. When the ratio of PuO_2 to PaO_2 (PuO_2 / PaO_2) from each group was compared, the AKI group had a significantly higher ratio just 2 hours after admission to the ICU. Reduced oxygen consumption in the renal medulla may be a possible cause of AKI in those patients. Thus, measuring the PuO_2 / PaO_2 ratio in postoperative patients 2 hours after ICU admission could be useful to predict AKI earlier than is currently done.

doi：10.11482/KMJ-E202147077 *(Accepted on March 31, 2021)*

Key words：Acute kidney injury, Urine partial oxygen pressure, Perioperative management, Intensive care, Oxygen consumption

INTRODUCTION

Acute kidney injury (AKI) is often encountered in the intensive care field. The reported mortality rate of patients with AKI is high, ranging from 15 to 60%[1)]. AKI is commonly diagnosed by using the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 criteria in which one definition is a change in serum creatinine[2, 3)]. However, one downside to any criteria's use of a rise in serum creatinine is the time lag of a few hours to as long as a few days from the actual decrease in the glomerular filtration rate (GFR)[4)]. To compensate

Corresponding author
Hideki Nakatsuka
Department of Anesthesiology & Intensive Care Medicine 1, Kawasaki Medical School, 577 Matsushima, Kurashiki, 701-0192, Japan
Phone : 81 86 462 1111
Fax : 81 86 462 1199
E-mail: hideki@med.kawasaki-m.ac.jp

for the time lag, biomarkers that can help detect AKI at an early stage such as liver-type fatty acid binding protein (L-FABP; A predictive marker of renal damage in chronic glomerular disease or diabetic nephropathy), neutrophil gelatinase-associated lipocalin (NGAL; A promising predictive biomarker of AKI), kidney injury molecule-1 (KIM-1; A molecule strongly expressed in proximal tubular cells after renal damage) and interleukin-11 (IL-11; A protective molecule against renal ischemic damage) have been drawing attention[5-11], but these are the same biomarkers that rise when disorders of the renal tubule occur. Also, questions remain regarding these biomarkers' characteristics on the kidney.

Lankadeva YR *et al*. conducted an animal experiment and reported that the renal medulla is easily affected by hypoxemia, that renal medulla tissue hypoxia is related to the mechanism of acute renal disorder and that medullary ischemia can be detected by measuring the partial oxygen pressure in the urine (PuO_2)[12]. Currently, PuO_2 is reported to be a possible new biomarker for diagnosing AKI in animal tests[13]. There are some reports regarding PuO_2 measurement in humans[14], however, it has yet to be adopted in actual clinical practice.

The reasons why we focus on the evaluation of PuO_2 rather than the substances in blood are its advantages in anatomical characteristics, non-invasive assays and continuous measurement. We conducted this study to examine whether hypoxic changes in the renal medulla are reflected in PuO_2. In addition, PuO_2 can be measured continuously and non-invasively using collected patient's urine. Assessment of PuO_2 is clinically convenient compared to blood samples and may be a novel biomarker which predicts AKI in real time. For these reasons, our study was examined whether measuring PuO_2 enables an early prediction of AKI in patients admitted to the intensive care unit (ICU) after major surgeries.

METHODS

Patients and surgical procedures

The subjects were adult surgical patients who were scheduled to be admitted to the ICU at Kawasaki Medical Center for more than 48 hours between January 2019 to June 2020. The surgeries were open-heart surgery, a thoracotomy or laparotomy for esophageal cancer and surgeries for pancreas cancer. Written consent was acquired before ICU admission or at the time of admission, signed by the patients themselves or their legally authorized representatives. Patients who had already started dialysis were excluded from eligibility.

Patient management

The hemodynamic management of patients during surgery and in the ICU was done in accordance with early goal-directed therapy[15]. The targets of this therapy were a CVP of 8-12 mmHg, a mean blood pressure of 65 mmHg or higher and a urine output of at least 0.5 mL/kg/hr along with properly adjusted fluid administration, blood transfusion, inotropes and vasopressors. The intensive care physician in charge decided the treatment details to attain those targets. For patients on mechanical ventilation, PaO_2 was adjusted to be in the range of 80-200 mmHg with FIO2 0.4-0.6, and a tidal volume of 8 mL/kg as a goal for pressure controlled ventilation. Oxygen administration was also adjusted to achieve a PaO_2 range of 80-200 mmHg in extubated patients.

Sampling

Urine and arterial blood samples were collected at the time of admission to the ICU, then 2, 6, 12, 24, 36 and 48 hours after admission. The urine was collected from the sample port of a Foley catheter (BARD Silver TSC tray 16 Fr, Medicon Inc.) (Fig. 1). A blood gas analyzer (ABL9 blood gas analyzer, Radiometer) was used to measure the PuO_2, and specialized syringes were used to collect urine and blood (SafePICO 1 × 1.5 mL, Radiometer) which

were analyzed immediately after collection. The amount of urine an hour before collection was also recorded. Serum creatinine was measured daily. Serum creatine data was tracked from before ICU admission until one week after ICU discharge and AKI was defined as at least stage 1 in the KDIGO criteria in the first 48 hours of ICU admission.

Data collection and statistical analysis

Basic patient data including age, gender, height, weight, reason for ICU admission, concurrent diseases and blood test data prior to ICU admission were acquired from each patient's medical records. Patients who developed AKI (fifteen cases) during the course of their original disease were categorized into the AKI group, while those who didn't were categorized into the non-AKI group (forty four cases). The background factors of both groups and the correlation between PuO_2 and the development of AKI were examined. Moreover, the relationship between the onset of AKI and the PuO_2 / PaO_2 ratio was also examined for the purpose of standardization, since PuO_2 can be easily influenced by the value of PaO_2. Statistics software EZR was utilized for t-test, univariate and multivariate analyses.

This study was approved by the Kawasaki Medical University Ethics Committee (approval number: 3294-2).

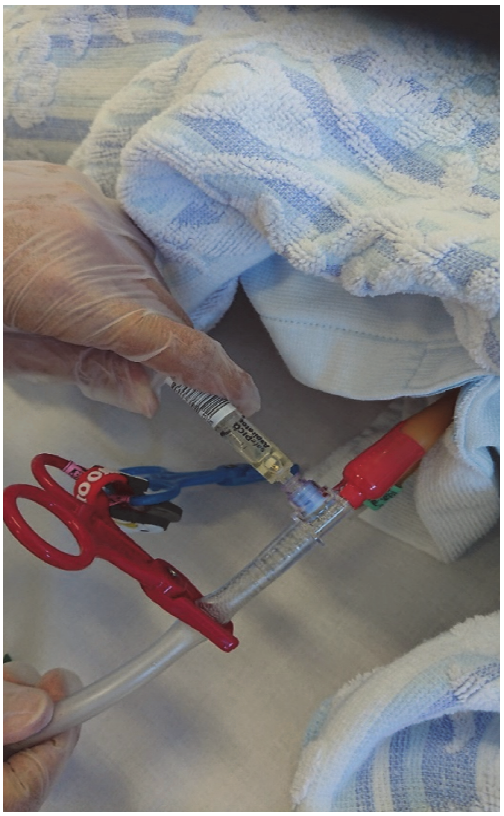

Fig. 1. Urine collection port; Urine samples of patients were collected from the sample port of a Foley catheter during ICU stay.

RESULTS

From 105 eligible cases during the study period, consent was obtained from 98 patients. Of those 98, 39 were excluded, leaving 59 cases for the study. The reasons for exclusion included 25 cases with a measurement failure (samples were not collected at the scheduled time or the samples were left for too long before measurement), and 14 cases that had an ICU stay under 36-hours (Fig. 2).

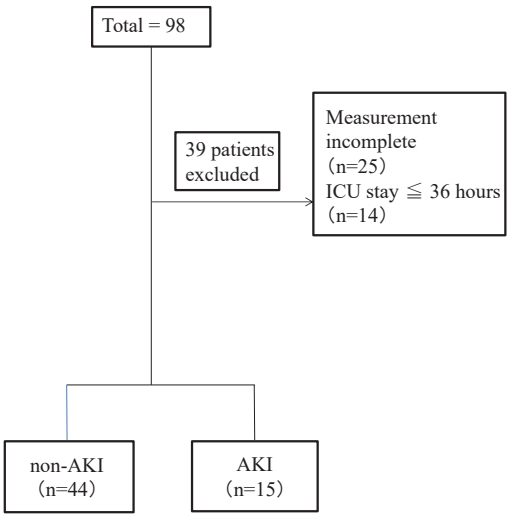

Fig. 2. Case selection flow chart; From 105 eligible cases, consent was obtained from 98 patients, 39 were excluded, finally 15 were met the AKI criteria.

Table 1. Patient Characteristics

Characteristic	non-AKI average〔SD〕(n = 44)	AKI average〔SD〕(n = 15)	P
Age	71.9	72.4	0.45
Male：female	23：21	12：3	0.03
Height (cm)	159.3〔9.54〕	165.9〔8.55〕	0.012
Body weight (kg)	55.3〔11.59〕	68.8〔17.2〕	0.0007
BMI (kg/m2)	22.2〔3.70〕	24.3〔4.14〕	0.037
Cardiac surgery	28 (63.6)	12 (80.0)	0.124
Digestive surgery	15 (34.1)	3 (20.0)	0.157
Other surgery	1 (2.27)	0 (0)	0.282
WBC (/μL)	6710〔3373〕	6779〔3235〕	0.47
Hb (g/dL)	11.9〔2.58〕	11.7〔2.69〕	0.44
PLT (10^3/μL)	204.3〔87.3〕	175.3〔54.8〕	0.12
PT-% (%)	91.4〔17.5〕	87.2〔20.6〕	0.22
APTT (sec)	37.1〔15.0〕	41.8〔16.7〕	0.16
T-Bil (mg/dL)	0.77〔0.36〕	0.83〔0.36〕	0.27
ALP (U/L)	289.4〔411.2〕	272.1〔118.4〕	0.44
γ-GT (U/L)	43.4〔116.3〕	59.1〔62.4〕	0.31
ALT (U/L)	25.1〔46.1〕	16.9〔8.64〕	0.25
AST (U/L)	30.1〔36.9〕	24.3〔13.4〕	0.28
CRE (mg/dL)	0.92〔0.57〕	1.31〔0.68〕	0.018
BUN (mg/dL)	20.4〔16.9〕	19.8〔8.80〕	0.45
ALB (g/dL)	3.59〔0.74〕	3.33〔0.65〕	0.12
CRP (mg/dL)	2.16〔6.15〕	3.97〔5.64〕	0.16
Diabetes mellitus	13 (29.5%)	7 (46.6%)	0.12
Hypertension	22 (50.0%)	10 (66.7%)	0.14
Hyperlipidemia	8 (18.2%)	2 (13.3%)	0.34
Ischemic heart disease	6 (13.6%)	3 (20.0%)	0.28
Cerebral infarction	4 (9.1%)	4 (26.7%)	0.44
Chronic kidney disease	3 (6.8%)	4 (26.7%)	0.02
ICU stay (days)	5.16〔2.59〕	6.36〔3.18〕	0.09

BMI; Body Mass Index, WBC; White Blood Cell, Hb; Hemoglobin, PLT; Platelet, PT; Prothrombin Time, APTT; Activated Partial Thromboplastin Time, T-Bil; Total Bilirubin, ALP; Alkaline Phosphatase, γ-GT; γ-glutamyl Transpeptidase, ALT; Alanine Transaminase, AST; Aspartate Aminotransferase, CRE; Creatinine, BUN; Blood Urea Nitrogen, ALB; Albumin, CRP; C-reactive Protein, ICU; Intensive Care Unit

There were 15 AKI cases that met the KDIGO criteria during the course of their original disease. The background factors and pre-ICU data of the 15 cases in the AKI group and 44 cases in the non-AKI group are shown in Table 1. There was no significant difference between the groups in average age, while the AKI group had higher averages in both height and weight. The reasons for ICU admission were as follows: 40 cases were admitted after open heart surgery, 18 cases had surgery on the digestive system, and 1 case had surgery for the respiratory system. The average elapsed time until AKI diagnosis was 23.5 ± 16.9 hours (average ± S.D.) after ICU admission, and surgery type was not significantly related to AKI. Hypertension, brain infarction and chronic kidney disease as pre-existing diseases before ICU admission were significantly higher in the AKI group. Two AKI cases required blood purification therapy after admission and chronic dialysis even after being discharged from the ICU, but all of the other AKI cases recovered naturally.

The PuO_2 of both groups gradually rose just after admission and began to decline after 24 hours in the ICU(Fig.3). There was no significant difference in the PuO_2 between the groups at any time course

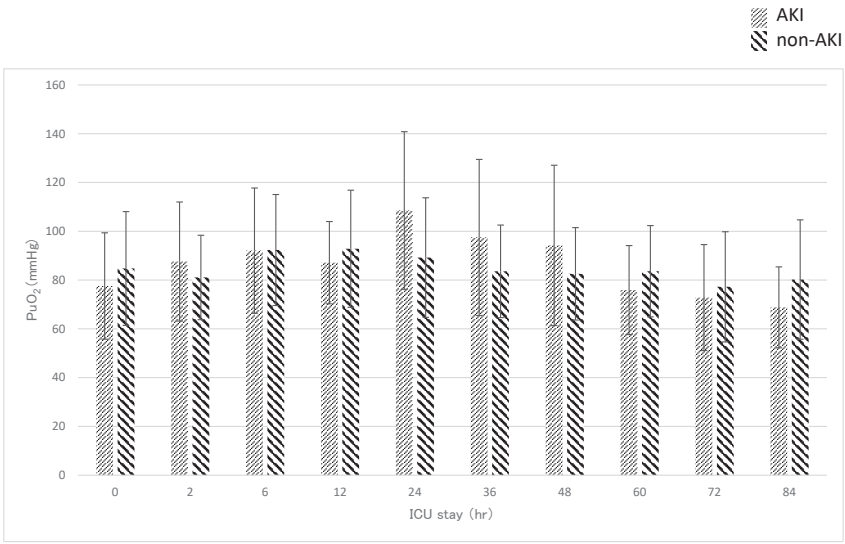

Fig. 3. PuO_2 levels of both AKI and non-AKI groups during ICU stay.

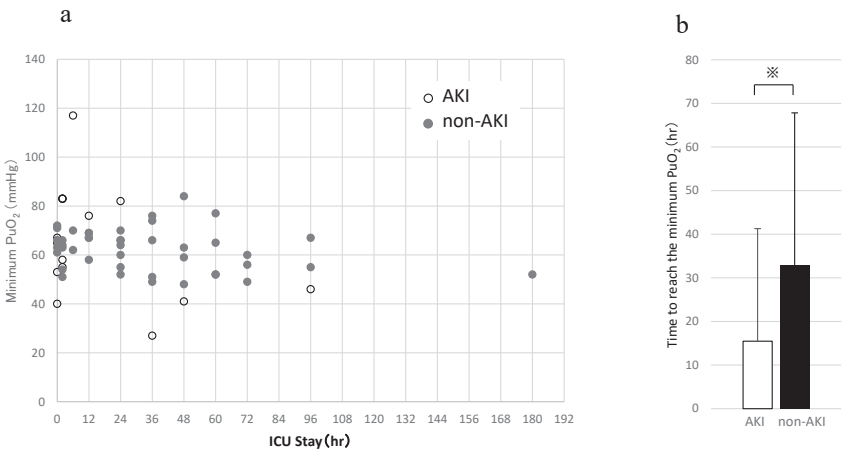

Fig. 4a. Time to reach the lowest / minimum PuO_2 after ICU admission for each case.
b; Comparison of average time to reach the lowest PuO_2 between AKI and non-AKI group.
※ P = 0.04

in ICU. We analyzed the time to reach lowest / minimum PuO_2 value for each case during ICU stay (Fig.4a). Most cases show lowest PuO_2 in a few days after ICU admission. The AKI cases reached their lowest PuO_2 value earlier than the non-Aki group (AKI group: 15.4 ± 25.8 hours, non-AKI group: 32.9 ± 34.8 hours) (Fig.4b).

The PuO_2 / PaO_2 ratio of both groups rose over the first 24 hours in the ICU and tended to decline after that. To test the possibility of early AKI diagnosis, a logistic regression analysis was performed on both groups using blood pressure, body weight and the amount of urine at the time of admission and six hours later. An analysis was also conducted on the blood gas including PaO_2 and other biochemical markers. The PuO_2 / PaO_2 ratio 2 hours after ICU

admission showed a significant difference in regard to AKI development (OR = 77.5 (95% CI: 2.79-2160)).

DISCUSSION

We found that the PuO_2 / PaO_2 ratio in patients with AKI increased in the early postoperative period (2 hours), although the temporal changes in PuO_2 in patients with AKI in the ICU were not significantly different from those in non-AKI patients. The PuO_2 in the AKI group did not decrease significantly compared to the non-AKI group, however, the PuO_2 in the AKI group reached its lowest value significantly earlier than non-AKI group. These findings would be pretty important to understand the clinical significance of the evaluation of PuO_2 during ICU stay.

Lankadeva *et al*. reported that a decrease of partial oxygen pressure in the renal medulla was detected in sheep with septicemia derived AKI, with a strong correlation to a decrease of PuO_2[12, 13]. In the same report, they also stated that medullary ischemia reflected on PuO_2 almost immediately. Their results differ from ours possibly because our measurements were not continuous over time as theirs were, and thus there is a possibility that the decrease of PuO_2 in our study was not detected precisely[12, 13]. Our AKI subjects were diagnosed using the clinical criteria of serum creatine rising by 0.3 mg/dL or more over 48 hours. Another difference is that Lankadeva *et al*. utilized animal models that developed complete septicemia, while our subjects had only comparatively mild kidney problems. In fact, in other study that measured PuO_2 in postoperative cardiac patients, the changes in PuO_2 were very similar to our results[16]. There is currently no device that can continuously measure PuO_2 in humans, although such a device seems technologically feasible and could be clinically beneficial if ever introduced.

Though hemodynamic monitoring was used throughout and after surgery, it is natural to recognize that various surgical and post-surgical factors can affect renal function. During postoperative ICU management, the primary doctor treats any decrease in urine output or blood pressure by adjusting the intravascular volume and / or pressor treatment. Since our patients were

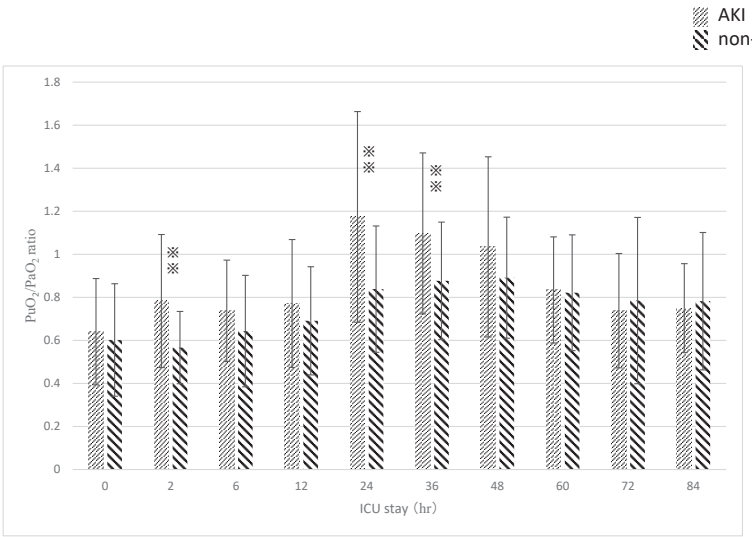

Fig. 5. Average of the PuO_2 / PaO_2 ratio during ICU stay.
※※ $P < 0.05$ (comparison between AKI and non-AKI group.)

managed according to basic principles of our unit, it is unlikely that differences in hemodynamic management would have affected the outcome.

On the other hand, some reports have stated that since renal medulla tissue hypoxia is an indication of developing AKI[9, 17], increasing the fraction of inspired oxygen concentration (FiO_2) might decrease the hypoxia. Thus, both PuO_2 and PaO_2 were measured at the same time in our study and the ratio was examined for any correlation. The results showed that the PuO_2 / PaO_2 ratio in the AKI group rose significantly two hours after admission and tended to show higher values over the first 36 hours compared to the non-AKI group. There is no published literature showing that PuO_2 / PaO_2 ratios are higher in AKI patients, and all but 2 AKI patients in our study recovered without blood purification treatment.

Our results indicate that oxygen consumption in the kidney is likely suppressed in mild AKI. Reduced oxygen consumption may cause a rise of partial oxygen pressure in the renal medulla and thus a rise in the PuO_2 / PaO_2 ratio. When PuO_2 and PaO_2 were individually compared at each measurement time, there was no significant difference between the groups. However, when the PuO_2 / PaO_2 ratio was compared, the result was noteworthy. It was found that the amount of oxygen consumed was less than the amount of oxygen supplied and can be considered to be part of the mechanism of non-septic AKI. Also, the elevated ratio appeared two hours after ICU admission, which is quite earlier than the average AKI diagnosis time of 23.5 ± 16.9 hours recorded in this study. Therefore, tracking the PuO_2 / PaO_2 ratio in the ICU may have the clinical benefit of earlier AKI diagnosis time.

One limitation of this study is that PuO_2 measurements were limited to patients who underwent surgery. Roughly 20% of ICU patients are admitted with septicemia or severe respiratory failure, and the mechanism of AKI in those patients is different than in our study. Those inflammatory diseases can also develop AKI and studying them would require urine collection similar to what was done in the current study, but it is difficult to speculate whether the results would be comparable to post-operative patients or not[18–20].

In addition, PuO_2 may vary significantly depending on the method of measurement and the amount of decrease in urine volume before and after measurement. Although it is common to use a sensor on a catheter as in the study conducted by Lankadeva YR *et al.*, a different study used a technique similar to ours[16]. In some cases, it was difficult to collect sufficient urine for measurement. However, even if continuous monitoring becomes feasible, a similar inaccuracy could occur if urine production mostly ceases. This is a fundamental limit to the use of urine for assessment.

CONCLUSIONS

Measuring the PuO_2 / PaO_2 ratio two hours after ICU admission can be useful to predict AKI during the perioperative period. Further detailed studies are needed on noninvasive and accurate AKI prediction.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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