Very Transient Cases of Acute Kidney Injury in the Early Postoperative Period After Cardiac Surgery: The Relevance of More Frequent Serum Creatinine Assessment and Concomitant Urinary Biochemistry Evaluation

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Objective: **To evaluate if more frequent serum creatinine (sCr) measurements in the early postoperative period (first 48 hours) after cardiac surgery would help in early diagnosis of acute kidney injury (AKI), as well as reveal cases of AKI duration of fewer than 24 hours (vtAKI). The sequential blood and urinary biochemical profile of patients who developed vtAKI was compared with that of the patients who did not develop AKI or who developed AKI for more than 48 hours (pAKI).**

Design: **A retrospective analysis of prospectively collected data.**

Setting: **Two intensive care units of 2 private hospitals.**

Participants: **Twenty-nine patients who underwent cardiac surgery who had 6 values of serum creatinine (sCr) measured within the first 48 hours after surgery and concomitant spot urine samples for urine biochemistry assessment.**

Interventions: **None.**

Measurements and Main Results: **Eighteen patients (62%) developed Acute Kidney Injury Network (AKIN) sCr-based AKI, half of them for fewer than 24 hours. Most AKI patients had the sCr increase diagnosed 6 to 12 hours after surgery. When comparing the sequential alterations of blood and urinary parameters among patients with no AKI, vtAKI, and pAKI, the authors found that most of them were similar among groups, differing only in magnitude and duration.**

Conclusions: **More frequent sCr measurements in the early postoperative period, together with urine biochemistry assessment, have the potential to anticipate AKI diagnosis after cardiac surgery and reveal cases of very transient AKI usually not diagnosed in current practice. The clinical relevance of these findings must be evaluated in larger, prospective studies.**

KEY WORDS: cardiac surgery, acute kidney injury, urine biochemistry, very transient physicochemical approach

CARDIAC SURGERY is one of the major causes of acute kidney injury (AKI) in the critical care setting.[1,2] Nonetheless, AKI diagnosis currently still relies on decreases in urine output and increases in serum creatinine (sCr), which are late markers of impaired renal function. Late AKI diagnosis probably is one of the main reasons for its high morbidity and mortality. Therefore, new strategies or markers are needed urgently in order to allow early diagnosis of AKI and, perhaps, early interventions to prevent its progression.

Most intensive care units (ICUs) routinely measure sCr only once a day. This practice also may be a factor in the delay of AKI diagnosis, especially in situations of rapid decrease in glomerular filtration rate (GFR), as may occur with the use of cardiopulmonary bypass and extracorporeal circulation. Also it is possible that such impaired GFR occasionally may be very transient, resolving in fewer than 24 hours. Therefore, except for eventual decreases in urine output, the sCr-based diagnosis of very transient AKI (vtAKI) would be missed with a single sCr measurement per day, underestimating the real incidence of AKI after cardiac surgery.

The authors have described the blood physicochemical and urinary biochemical alterations that occur with AKI development, distinguishing transient AKI (duration of fewer than 48 hours) and persistent AKI ([pAKI] duration of more than 48 hours).[3,4] In these studies, the authors proposed that low urinary sodium (NaU)[3] and high fractional excretion of potassium (FEK)[4] were early markers of decreased GFR in a mixed population of critically ill patients. The authors also reported, in a few patients, the possible utility of sequential and frequent NaU monitoring in the early postoperative period of cardiac surgery.[5]

Alterations in NaU and FEK may occur before increases in sCr. Both parameters were hypothesized to be representative of the level of glomerular hemodynamic impairment, which has been proposed to be related strongly to systemic inflammation and AKI development in critically ill patients.[6–8]

The authors' hypothesis was that more frequent sCr assessment, as well as simultaneous and sequential evaluation of urinary biochemical profile within the first 48 hours after surgery, would help in early AKI diagnosis, as well as reveal some very transient cases of renal impairment (vtAKI) usually not diagnosed in current practice. Although vtAKI diagnosis may be of uncertain clinical significance and prognosis, the confirmation of its occurrence certainly would be helpful in the understanding of still-obscured AKI pathophysiology induced by cardiac surgical procedures. Therefore, the aims of this preliminary study were to (1) evaluate if more frequent sCr measurements would help in early AKI diagnosis and reveal cases of vtAKI in the first 48 hours after surgery, and (2) describe the sequential blood physicochemical and urinary biochemical profile in the early postoperative period after cardiac surgery corresponding to AKI development and duration.

MATERIALS AND METHODS

The study was approved by the local ethics committee. The authors retrospectively retrieved the data from all consecutive patients who were admitted in the immediate postoperative period after cardiac surgery between October 2012 and December 2013 in 2 ICUs in São Paulo, Brazil. Most of the data were obtained using electronic medical records. Results of the blood and urinary

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laboratory examinations were retrieved from the Internet (local laboratory site), with access protected by individual password. This period (October 2012 and December 2013) was chosen because, at that time, a spot urine sample was included in the list of exam routinely collected simultaneously with blood examinations from all critically ill patients who had an indwelling urinary catheter, as part of another research protocol.[9] It also was protocolized at that period that patients who underwent cardiac surgery in the 2 ICUs would have repeated simultaneous laboratory examinations in blood and urine within the first 48 hours after ICU admission, including sCr. These examinations were collected at 6 distinct periods: at ICU admission (T0), and then at 6, 12, 24, 36, and 48 hours later. This protocol originally was designed for another study, of which only the preliminary results were published.[5]

Exclusion criteria for the present study were renal replacement therapy before surgery or in the first 48 hours after. All surgeries were performed by the same surgical and anesthesia staff. Anesthetic induction usually was made with propofol or etomidate, and maintenance of anesthesia with propofol and sufentanil in combination with sevoflurane. Only crystalloids were available for fluid therapy, and the infusion was at the discretion of the attending physician with no predetermined protocol. As a general rule, all patients were taken to the ICU under mechanical ventilation.

The authors retrospectively analyzed the prospectively collected data of these patients. Blood laboratory values included arterial and/or central venous blood gases plus lactate, urea, sCr, Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, phosphate, and albumin. The sCr was measured using the Jaffe kinetic method with an expected coefficient of variation of less than 6%. Spot urine samples were used to measure Na^+ (NaU), K^+ (KU), Cl^- (ClU), urea (UrU), and creatinine (CrU) levels. The standard base excess (SBE), apparent strong ion difference (SIDa), effective strong ion difference (SIDe), urinary strong ion difference (SIDu), strong ion gap (SIG), fractional excretion of sodium (FENa), potassium (FEK), and urea (FEUr), urine-to-plasma creatinine ratio (u/p creat) and urine-to-plasma urea ratio (u/p urea) then were calculated, using the following formulae:

- SBE (Van Slyke equation) (mEq/L) = $0.9287 \times [HCO_3^-$ (mEq/L) $- 24.4 + 14.83 \times$ (pH $- 7.4)]$
- SIDa (mEq/L) = Na^+ (mEq/L) + K^+ (mEq/L) + Ca^{2+} (mEq/L) + Mg^{2+} (mEq/L) – [Cl^- (mEq/L) + lactate$^-$ (mEq/L)]
- SIDe (mEq/L) = $2.46 \times 10^{-8} \times PCO_2/10^{-pH}$ + [(10 x albumin [g/dL]) $\times$ (0.123 $\times$ pH $-$ 0.631)] + [(phosphate [mg/dL]/3) $\times$ (0.309 x pH $-$ 0.469)]
- SIDu (mEq/L) = NaU (mEq/L) + KU (mEq/L) − ClU (mEq/L)
- SIG (mEq/L) = SIDa − SIDe
- FENa (%) = [(NaU[mEq/L] / Na^+ [mEq/L]) / (CrU [mg/dL] / sCr [mg/dL])] x 100 (the formula is analogous for the other fractional excretions)
- u/p creat = CrU (mg/dL) / sCr (mg/dL)
- u/p urea = UrU (mg/dL) / serum urea (mg/dL)

Values of FENa lower than 1%[10] and FEUr lower than 35%[11] were considered for the diagnosis of avid sodium and urea retention. Normal FEK values were considered lower than 16%.[12]

In parallel, demographic data, comorbidities, type of surgery, extracorporeal circulation time, aortic clamping time, use of vasopressors, mechanical ventilation, blood transfusion, diuretics, and bicarbonate, as well as urine output, were evaluated during the first 48 hours after surgery. The patients were categorized according to the occurrence or absence of Acute Kidney Injury Network (AKIN) sCr-based AKI criteria[13] (increases in sCr $\geq$ 0.3 mg/dL) during a period of 48 hours after surgery. For the purpose of this study, AKI that reverted within fewer than 24 hours after diagnosis was called very transient AKI (vtAKI), AKI that reverted between 24 and 48 hours was called transient AKI (tAKI), and AKI that remained beyond 48 hours was called persistent AKI (pAKI). To determine AKI duration, sCr values measured after the first 48 postoperative hours were used, if necessary. AKI diagnosed after the first 48 postoperative hours was excluded. The moment of AKI diagnosis was called "T0"; the term, "T-1" was used to determine the previous laboratory collection and "T+1" the subsequent laboratory collection. The authors considered only the periods "T-2" to "T+3" (whenever available) and only the periods that were included within the first 48 hours after surgery. AKI reversal was defined as sCr that decreased to a value lower than reference sCr + 0.3. Reference sCr was defined as the sCr on which the AKI diagnosis was based, ie, the first previously measured value of sCr that was at least 0.3 mg/dL lower than a subsequent sCr measurement, which actually was the value that made the AKI diagnosis. Baseline creatinine was the lowest sCr within the 48 hours preceding the surgical procedure, and it was only used to make AKI diagnosis at ICU admission after surgery. For patients with no data during this period, the first sCr after hospital admission was considered the baseline creatinine. For no-AKI patients, "T0" was considered the postoperative admission.

STATISTICAL ANALYSIS

Normality of the data distribution was made using the Shapiro-Wilk test. Values were presented as median and 25th and 75th percentiles or mean ± standard deviation (SD) according to nonparametric or parametric distribution, respectively. Multiple pairwise comparison of the general characteristics among no-AKI, vtAKI, and pAKI patients were made using the Student t-test or Rank Sum Mann-Whitney test for continuous variables, or Chi-square/Fisher exact test for categoric variables as appropriate. Multiple pairwise comparisons of the parameters among the 3 groups at each time of measurement (T-2 to T+3) were made using the Rank Sum Mann-Whitney test; $p > 0.05$ was considered significant. Statistical analyses were made using the SigmaPlot software version 12.0 (Systat Software Inc, San Jose, CA).

RESULTS

A total of 29 cardiac surgery patients were admitted in the 2 ICUs during the study period, 24 in ICU1 and 5 in ICU2. None of these patients had an exclusion criterion, so all 29 cases were evaluated. Eighteen out of the 29 patients (62%) developed AKI within the first 48 hours after surgery. Of these, 9 patients (50%) developed vtAKI, 2 patients (11%) developed tAKI, and 7 patients (39%) developed pAKI. The 2 patients with tAKI

Table 1. General Characteristics of the 27 Cardiac Surgery Patients Included in the Analysis

	no-AKI (n = 11)	vtAKI (n = 9)	pAKI (n = 7)	p Value
Age (years)	56 ± 9	59 ± 8	68 ± 9	0.011[*] / 0.048[†]
Gender (male)	9 (82%)	6 (67%)	5 (71%)	1.000 / 1.000
SAPS 3	37 (34, 39)	38 (34, 44)	43 (40, 52)	0.002 / 0.079
APACHE IV	30 (23, 38)	27 (17, 41)	47 (31, 73)	0.023 / 0.017
Baseline creatinine (mg/dL)	1.05 ± 0.28	0.96 ± 0.22	1.38 ± 0.53	0.103 / 0.050
Preoperative Hb (g/dL)	13.6 ± 1.8	13.5 ± 2.4	12.6 ± 1.9	0.314 / 0.471
Type of surgery				
Myocardial revascularization	7	6	7	
Valve replacement	3	3	1[‡]	
Aortic aneurysm	1	1[‡]	0	
Extracorporeal circulation time (min)	90 (65, 105)	85 (73, 90)	72 (70, 100)	0.856 / 0.750
Aortic clamping time (min)	73 (44, 87)	66 (60, 71)	64 (52, 880)	0.786 / 0.458
Comorbidities				
Arterial hypertension	8 (73%)	4 (44%)	7 (100%)	0.245 / 0.034
Diabetes mellitus	3 (27%)	4 (44%)	3 (43%)	0.627 / 1.000
Chronic renal failure	0	1 (11%)	1 (14%)	0.389 / 1.000
Congestive heart failure	2 (18%)	1 (11%)	2 (29%)	1.000 / 0.550
COPD	0	0	0	
Cirrhosis	0	0	0	
ICU support[§]				
Diuretic	4 (36%)	4 (44%)	6 (86%)	0.066 / 0.145
Blood transfusion	4 (36%)	2 (22%)	2 (29%)	1.000 / 1.000
Bicarbonate	0	1 (11%)	2 (29%)	0.137 / 0.550
Vasopressor	7 (64%)	9 (100%)	5 (71%)	1.000 / 0.175
Mechanical ventilation[‖]	4 (36%)	3 (33%)	4 (57%)	0.630 / 0.615
RRT	0	0	0	
Time between admission and AKI[#]	—	0 hours (1)	0 hours (2)	
		6 hours (3)	6 hours (2)	
		12 hours (4)	12 hours (2)	
		24 hours (1)	48 hours (1)	
AKI duration[**]	—	6 hours (3)	158 [110,456]	
		12 hours (3)		
		18 hours (1)		
		24 hours (2)		
Mortality				
ICU	1 (9%)	1 (11%)	2 (29%)	0.528 / 0.550
Hospital	1 (9%)	1 (11%)	2 (29%)	0.528 / 0.550

Abbreviations: vtAKI: very transient acute kidney injury; pAKI: persistent acute kidney injury SAPS: Simplified Acute Physiology Score; APACHE: Acute Physiology and Chronic Health Evaluation; Hb: serum hemoglobin (last before surgery); COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; RRT: renal replacement therapy.

*Between no-AKI and pAKI.

†Between vtAKI and pAKI.

‡Mixed surgeries.

§During the period of 48 hours after surgery.

‖Need of mechanical ventilation beyond the first 6 hours after surgery.

#In parentheses is the number of patients in each categorized interval.

**AKI duration in pAKI was expressed in continuous values because it persisted beyond the first 48 postoperative hours. The number of hours was obtained from the difference between the real clock time of AKI diagnosis and the clock time of the first serum creatinine assessment showing AKI resolution.

were excluded from the analyses for 2 reasons: (1) As a separate group, they would be a very small group; and (2) the AKI duration in these 2 patients was lower, but close to 48 hours, and the authors' intention was to have groups with clearly distinct AKI duration. Hence, the option was to compare patients with no-AKI with only the vtAKI and pAKI patients in order to have a well-marked gap in AKI duration among groups.

General characteristics of these 27 patients are shown in Table 1. Patients who developed AKI were older and had a higher prognostic score at ICU admission. A marginal difference was found between baseline creatinine between the 2 AKI groups. All surgeries were considered elective procedures except 2 (urgent procedures), both in the no-AKI group. Post-surgical AKI was diagnosed at ICU admission in 3 patients, at 6 hours after admission in 5 patients, and at 12 hours; after admission in 6 patients (Table 1). Only 1 case of AKI within the first 48 hours after surgery was diagnosed after the first 24 hours. Two-thirds of the patients diagnosed with

Table 2. Acid-base and Serum Urea and Creatinine Evolution in the Measurements Obtained in the First 48 Hours after Cardiac Surgery

	T-2	T-1	T0	T+1	T+2	T+3
pH						
no AKI	—	—	7.31 (7.29, 7.34)	7.33 (7.31, 7.33)	7.36 (7.31, 7.38)	7.36 (7.35, 7.40)
vtAKI	7.37 (7.30, 7.38)	7.33 (7.30, 7.37)	7.31 (7.26,7.37)	7.33 (7.32, 7.35)	7.36 (7.34, 7.37)	7.36 (7.33, 7.37)
pAKI	7.34 (7.32, 7.36)	7.32 (7.28, 7.36)	7.31 (7.24, 7.41)	7.32 (7.27, 7.37)	7.34 (7.32, 7.40)	7.36 (7.34, 7.40)
SBE (mEq/L)						
no AKI	—	—	−0.2 (−1.1, 0.5)	−1.9 (−2.6, −0.6)	−1.4 (−2.6, 0.2)	0.5 (−1.3, 1.8)
vtAKI	−2.5 (−3.4, −1.4)	−2.1 (−3.0, 0.1)	−1.6 (−3.7, 0.3)	−0.6 (-1.5,1.4)	0.4 (−0.6, 2.3)‡	0.5 (−1.0, 1.3)
pAKI	−3.6 (−4.5, −2.7)	−3.2 (−4.3, −2.4)	−5.4 (−7.0, −0.8)*	−4.6 (−6.3, −1.3)	−2.6 (−3.5, −0.1)	−0.7 (−3.4, 1.2)
Lactate (mEq/L)						
no AKI	—	—	3.9 (2.3, 6.5)	2.9 (2.3, 6.1)	3.3 (2.9, 4.7)	3.1 (2.3, 3.6)
vtAKI	4.1 (3.4, 5.1)	4.6 (3.1, 5.5)	4.0 (2.6, 4.8)	3.0 (1.9, 3.6)	2.4 (1.6, 3.1)*	1.8 (1.5, 2.6)*
pAKI	3.3 (2.7, 3.8)	4.2 (3.3, 5.5)	3.2 (2.8, 7.7)	4.0 (3.1, 5.0)	2.5 (1.7, 3.3)	3.1 (1.9, 3.9)
sCr (mg/dL)						
no AKI	—	—	0.98 (0.80, 1.09)	1.00 (0.91, 1.16)	1.00 (0.90, 1.10)	1.00 (0.80, 1.07)
vtAKI	0.93 (0.79, 1.16)	1.08 (0.90, 1.23)	1.40 (1.27, 1.54)†	1.20 (0.97, 1.25)§	0.95 (0.82, 1.20)§	1.06 (0.80, 1.15)§
pAKI	1.34 (1.16, 1.76)	1.00 (0.82, 1.62)	1.52 (1.28, 2.29)†	2.10 (1.60, 2.61)†	2.19 (1.80, 2.83)†	2.11 (1.60, 2.95)†
Serum urea (mg/dL)						
no AKI	—	—	32 (26, 40)	33 (30, 44)	33 (30, 43)	40 (34, 46)
vtAKI	37 (34, 43)	35 (32, 36)	38 (34, 42)	47 (36, 49)	44 (34, 53)§	47 (33, 56)‡
pAKI	41 (26, 50)	29 (21, 45)	53 (36, 62)	68 (44, 77)†	73 (53, 88)†	74 (67, 110)†

NOTE. Values are described as medians and 25th and 75th percentiles.

Abbreviations: AKI, acute kidney injury; pAKI, persistent acute kidney injury; SBE, standard base excess; sCr, serum creatinine; T0, time of postoperative admission for no-AKI patients or time of acute kidney injury diagnosis; vtAKI, very transient acute kidney injury.

*$p < 0.05$ in comparison to no-AKI.

†$p < 0.01$ in comparison to no-AKI.

‡$p < 0.05$ in comparison to pAKI.

§$p \leq 0.01$ in comparison to pAKI.

vtAKI had their AKI resolved within a maximum of 12 hours. pAKI had a median duration of almost 1 week. Of the 9 patients who developed sCr-based vtAKI, only 3 fulfilled urine output criteria for AKI.

Table 2 represents the evolution of traditional blood parameters used in AKI monitoring. Although sCr normalized in the subsequent measurements after AKI diagnosis (T0) in vtAKI patients, urea levels remained high until the end of the observation period, having intermediate values between those of the no-AKI and pAKI groups.

Acid-base behavior was similar between the 2 AKI groups: pH decreased, having a nadir at T0, increasing again in the

Table 3. Physicochemical Parameters in the Measurements Obtained in the First 48 Hours after Cardiac Surgery

	T-2	T-1	T0	T+1	T+2	T+3
SIDa (mEq/L)						
no AKI	—	—	36 (35, 39)	36 (35, 39)	38 (36, 39)	36 (35, 38)
vtAKI	36 (34, 37)	36 (35, 37)	37 (36, 41)	40 (37, 40)	39 (37, 41)	39 (38, 41)
pAKI	36 (35, 37)	35 (33, 36)	36 (33, 40)	38 (37, 40)	40 (37, 42)	40 (39, 40)
SIG (mEq/L)						
no AKI	—	—	1.1 (−1.5, 3.1)	1.7 (−0.1, 4.4)	3.1 (1.0, 6.1)	2.5 (−1.5, 4.4)
vtAKI	1.9 (0.8, 2.8)	1.2 (−0.8, 1.7)†	2.7 (1.1, 7.8)	2.3 (1.5, 4.8)	2.7 (1.6, 4.4)†	3.2 (1.2, 8.8)
pAKI	5.7 (5.1, 6.3)	2.3 (1.9, 5.1)	4.4 (2.6, 7.9)*	7.1 (4.5, 10.1)	7.8 (4.6, 9.9)	5.2 (4.7, 8.3)
Albumin (g/dL)						
no AKI	—	—	3.0 (2.9, 3.2)	3.1 (2.9, 3.2)	3.0 (2.9, 3.3)	2.9 (2.7, 3.1)
vtAKI	2.9 (2.8, 3.6)	3.2 (2.9, 3.3)‡	3.1 (2.9, 3.2)	3.0 (2.9, 3.0)	2.9 (2.7, 2.9)	2.7 (2.4, 2.8)
pAKI	2.6 (2.3, 2.9)	2.5 (1.9, 2.8)	2.7 (2.2, 3.1)	2.5 (2.2, 3.3)	2.5 (2.2, 2.7)	2.4 (2.0, 2.9)
Phosphorus (mg/dL)						
no AKI	—	—	3.3 (2.7, 4.5)	4.0 (3.2, 4.6)	3.4 (3.2, 4.2)	2.9 (2.6, 3.3)
vtAKI	3.6 (3.1, 3.7)	3.9 (3.2, 4.5)	3.1 (2.8, 4.5)	3.4 (2.7, 3.9)	2.9 (2.5, 3.8)	2.9 (2.2, 3.9)
pAKI	3.0 (2.0, 4.0)	4.0 (3.1, 4.1)	4.5 (3.8, 5.0)	4.8 (3.4, 5.5)	4.1 (3.3, 4.9)	3.6 (3.0, 4.4)

NOTE. Values are described as medians and 25th and 75th percentiles.

Abbreviations: AKI, acute kidney injury; pAKI, persistent acute kidney injury; SIDa, apparent strong ion difference; SIG, strong ion gap; T0, time of postoperative admission for no-AKI patients or time of acute kidney injury diagnosis; vtAKI, very transient acute kidney injury.

*$p < 0.05$ in comparison to no-AKI.

†$p < 0.05$ in comparison to pAKI.

‡$p \leq 0.01$ in comparison to pAKI.

Table 4. Urinary Parameters in the Measurements Obtained in the First 48 Hours after Cardiac Surgery

	T-2	T-1	T0	T+1	T+2	T+3
NaU (mEq/L)						
no AKI	—	—	62 (22, 83)	79 (39, 154)	92 (50, 117)	58 (46, 94)
vtAKI	100 (81, 115)	80 (42, 111)	76 (32, 111)	51 (25, 106)	56 (38, 86)	91 (51, 100)
pAKI	109 (82, 136)	101 (51, 115)	65 (47, 75)	30 (22, 39)*	21 (12, 66)	12 (11, 55)
KU (mEq/L)						
no AKI	—	—	31 (25, 56)	85 (59, 101)	111 (75, 160)	123 (90, 147)
vtAKI	50 (33, 59)	24 (23, 59)	54 (43, 95)	76 (68, 120)	127 (46, 145)	83 (79, 93)
pAKI	23 (17, 28)	42 (20, 77)	33 (33, 49)	47 (43, 64)	65 (50, 71)†	79 (74, 105)
ClU (mEq/L)						
no AKI	—	—	71 (34, 95)	95 (52, 157)	77 (37, 162)	77 (57, 108)
vtAKI	122 (96, 133)	111 (47, 119)	68 (42, 109)	87 (52, 122)	102 (71, 105)	123 (60, 138)
pAKI	122 (94, 150)	115 (83, 128)	85 (66, 98)	44 (37, 51)	48 (11, 72)	32 (16, 36)*
UrU (mg/dL)						
no AKI	—	—	706 (370, 1036)	1380 (1124, 1513)	1921 (1375, 1959)	2728 (2124, 3135)
vtAKI	847 (372, 1246)	601 (386, 1391)	1110 (648, 1554)‡	1684 (1175, 2081)	1982 (1314, 2237)‡	2260 (1141, 2652)
pAKI	456 (90, 821)	429 (307, 785)	419 (373, 431)	819 (705, 976)	577 (427, 951)	1340 (1173, 1498)
CrU (mg/dL)						
no AKI	—	—	48.6 (27.7, 62.1)	105.9 (70.4, 120.6)	185.1 (92.3, 238.3)	219.8 (160.3, 257.4)
vtAKI	37.1 (18.6, 71.1)	38.5 (20.5, 55.6)	71.6 (53.6, 141.3)	130.4 (84.6, 224.1)	133.7 (107.8, 183.3)	130.9 (103.6, 187.1)
pAKI	42.3 (10.0, 74.5)	55.5 (19.6, 94.3)	50.9 (15.8, 98.9)	88.2 (61.2, 111.1)	120.6 (98.1, 137.2)	157.0 (132.8, 217.8)
SIDu (mEq/L)						
no AKI	—	—	29 (19, 39)	68 (55, 100)	113 (96, 127)	101 (76, 123)
vtAKI	32 (8, 51)	18 (5, 63)	71 (19, 105)	54 (46, 81)	68 (33,101)	58 (49,83)
pAKI	10 (3, 16)	10 (–2, 71)	16 (3, 42)	37 (25, 63)	66 (8, 79)	104 (59, 114)

NOTE. Values are described as medians and 25th and 75th percentiles.

Abbreviations: AKI, acute kidney injury; ClU, urinary chloride; CrU, urinary creatinine; KU, urinary potassium; NaU, urinary sodium; pAKI, persistent acute kidney injury; SIDu, urinary strong ion difference; T0, time of postoperative admission for no-AKI patients or time of acute kidney injury diagnosis; UrU, urinary urea; vtAKI, very transient acute kidney injury.

*$p < 0.05$ in comparison to no-AKI.

†$p < 0.01$ in comparison to no-AKI.

‡$p < 0.05$ in comparison to pAKI.

subsequent measurements (Table 2). The SBE behavior was also similar in both groups, increasing in the subsequent measurements after AKI diagnosis. No significant metabolic acidosis was present in no-AKI patients.

In parallel with increases in pH and SBE, there was an increase in SIDa after AKI diagnosis in both groups, remaining stable in no-AKI patients. Unmeasured anions (SIG) consistently increased after T0 in pAKI patients, having median concentrations higher than in no-AKI and vtAKI patients at all measurements (Table 3). Lactate consistently decreased after AKI diagnosis, but only in vtAKI patients. It also decreased after postoperative admission in no-AKI patients. Although discrete, serum albumin was lower, and phosphorus was higher from T0 to T+3 in pAKI patients.

Common features of AKI development in both AKI groups were the decreases in NaU and ClU, apparently preceding AKI diagnosis; this was more intense and persistent in pAKI (Table 4). No-AKI patients had a progressive increase in median NaU in the 2 measurements after T0. Increasing avidity for sodium retention (low FENa) was a common feature of all 3 groups (Fig 1A). In parallel, the degree of avidity for urea retention (low FEUr) seemed to distinguish the 3 groups (Fig 1B), being greater in pAKI and having intermediate

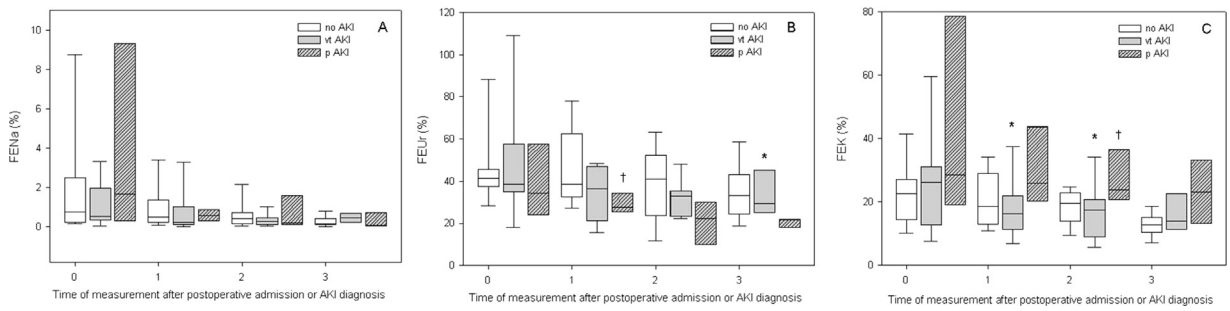

Fig 1. Temporal evolution of the fractional excretions of sodium (A), urea (B), and potassium (C) after acute kidney injury (AKI) diagnosis (T0). For no-AKI patients, T0 was the moment of postoperative admission. vtAKI, very transient AKI; pAKI, persistent AKI. *$p < 0.05$ in comparison to pAKI. †$p < 0.05$ in comparison to no-AKI.

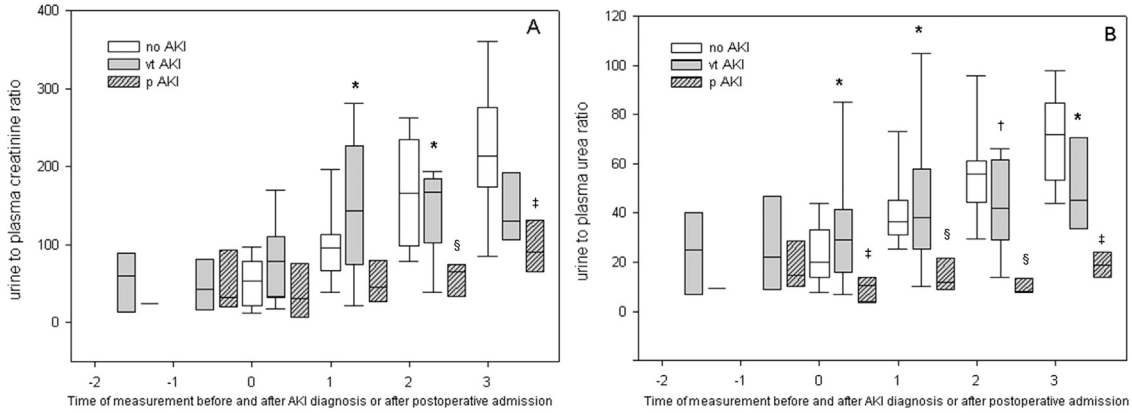

Fig 2. Temporal evolution of the urine-to-plasma creatinine (A) and urine-to-plasma urea ratio (B) before and after acute kidney injury (AKI) diagnosis (T0). For no-AKI patients, T0 was the moment of postoperative admission. vtAKI, very transient AKI; pAKI, persistent AKI. *p < 0.05 in comparison to pAKI. †p < 0.01 in comparison to pAKI. ‡p < 0.05 in comparison to no-AKI. §p < 0.01 in comparison to no-AKI.

values in vtAKI, as occurred with serum urea levels (Table 2). FEK values initially were increased in all groups (Fig 1C), with persistent higher values in pAKI, but decreasing toward normal values in both no-AKI and vtAKI patients after diagnosis. Increases in KU and SIDu occurred in no-AKI patients as well as in both AKI groups, coinciding with AKI diagnosis (T0). Median values of both UrU and CrU also increased progressively in the 3 groups (Table 4), a pattern similar to that of the u/p creat and u/p urea (Figs 2A and 2B). However, these ratios were lower consistently in pAKI.

DISCUSSION

In the present study, the authors observed that vtAKI was very frequent in the early postoperative period after cardiac surgery and that most diagnoses of postoperative AKI were made very soon after ICU admission, independently of their subsequent duration. Although vtAKI duration was a priori defined as being less than 24 hours, most cases resolved within the first 12 hours after diagnosis. Urinary biochemical profile had similarities among the 3 groups, such as significant evolutional decreases in FENa, increases in UrU and CrU, and initial increased levels of FEK. However, some characteristics distinguished the 3 groups: (1) FEK values decreased progressively in no-AKI and vtAKI groups, remaining high in pAKI; and (2) NaU decreased in parallel to the increase in sCr, recovering to higher values in vtAKI but remaining low and decreasing in pAKI in subsequent measurements.

Some important insights were based on the authors' findings. First, the major focus on AKI monitoring seemed to fall within the first 6 to 12 hours after ICU admission because most of the AKI diagnoses were made during this period, including in the pAKI group. It is noteworthy that an interval in sCr measurement greater than this probably would delay diagnosis in many cases (ie, some would be diagnosed by decreases in urine output only). Second, the short time in which AKI occurred *and* resolved after ICU admission in vtAKI (as short as 12 hours) might have been an additional reason for using a lower interval between sCr measurements in the early postoperative period.

As previously stated, increases in sCr are late markers of decreased GFR. The fact that sCr increased within 6 to 12 hours after ICU admission in most cases in the present study suggested that decreases in GFR were fast and intense in the very early postoperative period. Hence, even an early diagnosis of increased sCr was not early enough. In 2 previous studies,[3,5] the authors have suggested that decreases in NaU may precede increases in sCr, and, consequently, may serve as a potentially useful monitoring tool, at least within the first 6 to 12 hours after surgery.

It might be argued that the very transient increases in sCr in vtAKI were merely fluctuations of the laboratory sCr measurement or oscillations in fluid balance.[14] If the authors had used the risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) sCr-based criteria for AKI[15] (50% increase in sCr until 7 days), 6 out of the 9 patients classified as having vtAKI would be classified as no-AKI (data not shown). Notably, the authors used AKIN instead of RIFLE criteria in their study because, as suggested by their results, decreases in GFR after cardiac surgery seemed to be early and abrupt, making the AKIN criteria probably more sensitive. The authors did not believe that the vtAKI cases were false, unreal AKI cases because the behaviors of the simultaneous urinary parameters in vtAKI in the present study were very similar to those of the patients with transient AKI in a previous study by their group,[3] including transient decreases in NaU (Table 4) and persistently increased levels of serum urea after sCr normalization (Table 2), both classic characteristics of decreased GFR.

The relation between subtle increases in sCr and (not subtle) decreases in NaU in vtAKI (Table 4) seems to be of relevance in clinical practice because urine biochemistry is cheap and easily available in most hospitals and may alert for even minor impairments of renal function. Nonetheless, it is not possible to determine if such alterations were merely transient hemodynamic imbalances (truly prerenal states with renal hypoperfusion) based solely on increases in sCr and the changes in urine biochemistry. Some experimental studies already have demonstrated this similar "prerenal" pattern of urine biochemistry in the presence of increased renal blood flow, and this might be a result of impaired glomerular perfusion pressure triggered by inflammation.[7,8,16] The authors believe that, in both cases, a low or rapidly decreasing NaU value must be considered a warning sign of increased risk of AKI ("renal angina").

Some alterations in blood and urine characterized the early postoperative period independently of AKI development. Decreases in FENa and increases in KU, SIDu, u/p creat, and u/p urea occurred in all groups and probably were triggered by the surgical procedure itself. Interestingly, the magnitude of the alterations in some parameters was distinct among groups: the degree of the decreases in FEUr and FEK, the degree of the increases in u/p creat and u/p urea, and the sequential NaU and ClU behavior.

The values of the blood and urinary parameters in the vtAKI group frequently were intermediate between those of the no-AKI and pAKI patients, suggesting that changes in these parameters after cardiac surgery usually occur, but with different magnitudes according to the presence of AKI and its severity. In this hypothesis, vtAKI could be viewed as a similar but less severe pathophysiologic process than pAKI. This pathophysiologic process may be characterized, at least in part, by an exacerbation of sympathetic and renin-angiotensin systems activation,[6,7] as suggested by avid sodium retention, so that pAKI may be viewed as a prolonged functional impairment of the kidneys.[3,5,17,18] Furthermore, the authors speculated that increases in NaU and decreases in FEK in conjunction with decreases in sCr might be signs of GFR recovery in vtAKI. The fact that NaU recovered in this group (Table 4), even in the presence of very low FENa (Fig 1A), argued that increased tubular avidity for sodium remained despite increased glomerular sodium filtration. The extremely low NaU values in pAKI at T+3 (Table 4) probably were a combination of persistent low glomerular sodium filtration and remaining avid tubular sodium reabsorption. Such avidity for sodium and urea reabsorption did not cease even after sCr normalization (median FENa 0.5% and FEUr 29% at T+3 in vtAKI). This might explain elevated values of serum urea remaining in these patients.

Although diuretic use may mitigate urinary biochemistry interpretation, "artificially" increasing, for instance, NaU, FENa and FEK,[18] the authors did not believe that its use interfered much in their results because NaU continued decreasing in pAKI patients, the group that used more diuretic (statistically nonsignificant). Impaired natriuretic response to diuretics[9,19], as well as increasing SIDu in the presence of metabolic acidosis[20,21], previously were suggested to be markers of AKI. Higher values of phosphate and SIG, as well as lower albumin values (Table 3), also might be markers of AKI or merely epiphenomena of disease severity (higher SAPS 3 and APACHE IV in pAKI patients). Increases in UrU and CrU were common phenomena in all groups, from T0 to T+3, and, notably, in the same proportion (around fourfold in no-AKI, twofold times in vtAKI, and threefold times in pAKI for both parameters). The relevance of this finding is unknown and requires additional studies. Again, similar behaviors in all groups suggested a common trigger—the surgical procedure. A marginal difference in baseline sCr among AKI groups might reflect differences in glomerular function reserve before surgery.

Extracorporeal circulation and aortic clamping time were not different among groups, but this could have been a type-2 error due to a small sample of patients. In fact, it was quite possible that other real differences among groups could not be found in this study merely due to sample limitation. Nonetheless, the similarity of the median time values for these 2 variables between groups led the authors to speculate that they were not relevant to determine AKI occurrence and duration; other factors, such as baseline sCr and age (Table 1), might be more relevant in this matter, at least in the authors' sample. The fact that the surgical and anesthetic staff was the same for all surgeries led the authors to assume that there was homogeneous intraoperative management among the patients included in the study.

A major limitation of this study was certainly its small sample size. This was due to the retrospective nature of the analysis, low rate of cardiac surgeries in both services, and the fact that multiple sCr measurements in a single day were available only during a short period of time. Hence, major relevant questions, such as prognostic differences between the 2 AKI groups, could not be addressed properly in the present study. The authors' study suggested that more frequent sCr measurements, as well as simultaneous urine biochemistry assessments, at least within the first 12 hours after surgery, might be helpful in early diagnosis of AKI, especially in high-risk patients (those who are older, who have high SAPS 3 and APACHE IV scores, high baseline creatinine, etc). The real benefit, including the economic impact, of this approach must be tested in future and prospective studies to define the relevance of vtAKI diagnosis in clinical practice.

CONCLUSIONS

AKI is a serious consequence of cardiac surgery, and its occurrence still is underestimated or late in diagnosis. AKI seems to be triggered in the very early postoperative period. The combination of more frequent sCr assessment as well as simultaneous urine biochemistry evaluation, at least in the first 12 hours after surgery, may help reveal these cases. Some blood physicochemical and urinary biochemical changes occur after cardiac surgery independently of AKI development, but their magnitude and duration are related closely to AKI severity and may remain even after sCr normalization. Further larger and prospective studies are necessary to confirm the authors' findings and demonstrate their relevance in terms of outcome.

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