The Impact of Fluid Balance on the Detection, Classification and Outcome of Acute Kidney Injury After Cardiac Surgery

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Objective: To assess whether or not a positive fluid balance masks acute kidney injury (AKI) and is associated with adverse outcomes after cardiac surgery.

Design: Retrospective analysis.

Setting: Tertiary university-affiliated metropolitan hospital: single center.

Participants: Three thousand two hundred seven consecutive cardiac surgical patients admitted to the ICU from July 1, 2004 to June 30, 2012.

Interventions: None.

Measurements and Main Results: The authors used AKI Network criteria to classify AKI. They then adjusted creatinine levels for weight-corrected fluid balance and categorized patients into 3 groups: group A (No AKI); group B (AKI only after adjustment); group C (AKI before and after adjustment). No patients had "AKI" before but "No AKI" after adjustment. Among 2,171 patients with weight and baseline creatinine available, after adjusting for fluid balance, the proportion of patients classified with AKI increased from 25.3% to 37.2% ($p < 0.001$). In patients with AKI only after adjustment (group B), ICU mortality approximated that of group C (1.9% *v* 3.1%, $p = 0.35$) but was almost 3 times greater than group A (1.9% *v* 0.7%, $p = 0.04$). For group B, use of renal replacement therapy also was greater than group A (4.3% *v* 1.5%, $p = 0.004$) but less than group C (4.3% *v* 14.4%, $p < 0.001$). The same trend was found for ICU length of stay ($p \leq 0.001$) and other adverse outcomes.

Conclusions: Patients with AKI diagnosed after correction for the effect of a positive fluid balance on serum creatinine concentration have more adverse outcomes than patients *without* AKI by conventional criteria, but fewer than patients *with* AKI by conventional criteria.

KEY WORDS: acute kidney injury, fluid accumulation, fluid balance, cardiac surgery, cardiothoracic surgery, classification

IN CRITICAL ILLNESS, restoration of a stable hemodynamic state is considered a key therapeutic goal.[1,2] Fluid resuscitation is typically the first-line treatment to achieve this goal.[3,4] However, more recently, a positive fluid balance (FB) has been associated with worse outcomes for acute kidney injury (AKI) in several critically ill patient groups[5–7] Moreover, a positive FB has been shown to affect the identification, classification, and outcome of AKI in patients with acute respiratory distress syndrome (ARDS)[8] and in neonates undergoing a corrective procedure for a congenital cardiac defect.[9]

Despite the common administration of intravenous fluids, to the best of the authors' knowledge, the effect of a positive FB on the incidence and outcome of AKI has not been evaluated in adult cardiac surgery patients. In such patients, a positive FB could dilute serum creatinine concentration. Such dilution would, in turn, decrease the ability to identify the development of AKI, an effect similar to that reported by Liu and colleagues in patients with ARDS.[8] In a post hoc analysis of a trial of liberal versus conservative fluid protocols in patients with ARDS, these investigators found that before adjusting serum creatinine for FB, the incidence of AKI was greater in patients managed with a conservative fluid protocol, whereas after adjustment for FB, the incidence of AKI was greater in those managed with a liberal fluid protocol. In addition, after adjusting for the effect of FB, a substantial proportion of patients (13%) whose renal function had been considered normal before adjustment had, in fact, developed AKI, and these patients had a higher mortality rate than the others.[8] Similarly, in neonates after corrective surgery for congenital cardiac defects, prior to correction for FB, Basu and colleagues found no statistically significant association between AKI and postoperative morbidity.[9] However, after correcting serum creatinine for fluid balance, AKI was associated with increased ICU and hospital lengths of stay and greater duration of mechanical ventilation. There was no mortality in this population.

Accordingly, the authors tested the hypothesis that adjustment for the effect of FB in adult patients following cardiac surgery also would identify and classify more patients as having AKI. Moreover, they hypothesized that such patients would have outcomes (ICU and hospital death, need for renal replacement therapy, prolonged ICU and hospital lengths of stay, non-home discharge, and prolonged time on mechanical ventilation) that were intermediate between those of patients with AKI by standard criteria and those of patients without AKI by standard criteria.

METHODS

The authors conducted a retrospective analysis on all patients admitted after cardiac surgery to a tertiary hospital affiliated with the University of Melbourne (St Vincent's Hospital ICU, Melbourne, Australia) from July 1, 2004 to June 30, 2012 ($n = 3{,}207$). Approval to conduct the study was obtained from the hospital ethics committee. The AKI Network (AKIN) creatinine criteria were used to classify AKI.[10,11]

Stage 1 is increase of $\geq 50\%$ (1.5 fold) and <2 fold from baseline creatinine or increase of ≥ 0.3 mg/dL. Stage 2 is increase of >2 fold and ≤ 3 fold from baseline creatinine. Stage 3 is increase of >3 fold from baseline creatinine or baseline creatinine ≥ 4.0 mg/dL with an acute increase of ≥ 0.5 mg/dL. These criteria were applied in a standard manner before and after adjustment of serum creatinine concentration for the effect of FB.

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ICU FB ([total IV input] - [total urine output + chest drain losses]) was calculated for the first 18 hours postsurgery. The fluid balance was available from the ICU database sourced from hourly electronic charting of patient fluid input and output in the ICU through the clinical information system. An 18-hour period was chosen to allow sufficient time in which to detect a difference in cumulative FB between patients and because most patients (89%) were discharged from ICU after 18 hours. An adjustment for FB was performed as in previous studies[8,12] by multiplying the serum creatinine concentration (unadjusted) by the following adjustment factor, assuming a total body water content of 60% of the patient's body weight at baseline: (1+ [FB at 18 h/0.6*weight in kg]) Therefore, when the authors refer to adjustment for fluid balance throughout this article, they are referring to adjustment for a *weight-adjusted* fluid balance.

Patients were categorized into the 3 following groups based on the *presence* or *absence* of AKIN AKI *before* and *after* adjustment for FB. Group A is no AKI before or after adjustment for FB. Group B is no AKI before but AKI after adjustment for FB (the group of interest). Group C is AKI before and after adjustment for FB. There were no patients with AKI before but not after adjustment for FB.

Statistical Analysis

The proportion of patients with AKIN AKI stages 1 to 3 was measured and compared before and after adjustment for serum creatinine. Comparisons among groups (A, B, and C) were made using analysis of variance for continuously normally distributed variables, Kruskal-Wallis test for non-normally distributed variables, and chi-square test for categoric variables. Patients were separated into quartiles according to weight-adjusted FB and proportion of AKI was compared across quartiles using chi-square test for trend. Comparison of proportions within groups was made using McNemar's test. Continuous variables were summarized using means (standard deviations) or medians and interquartile ranges depending on the underlying distribution of the data. Multivariate linear regression analysis was performed to assess the independent effect of the 3 AKIN AKI combinations before and after creatinine adjustment for FB on ICU length of stay. As ICU length of stay had a positively skewed distribution, logarithmic transformation was applied prior to the linear regression analysis. The group with no AKI before or after adjustment for FB (group A) was the reference group used for comparison. These analyses also were conducted after removing patients with oliguria as a sensitivity analysis because such patients may have been more likely to have higher fluid balances (see Supplementary Material). Finally, a Kaplan-Meier analysis was performed for time to ICU discharge by AKI groupings, and log rank test was used to compare the difference among AKI groups. A multivariate Cox proportional hazards model of time to ICU discharge with AKI groupings also was done. Variables significant on univariate analysis or those judged to be clinically important were entered into the multivariate regression models to assess the independent association between AKI groups and ICU length of stay. Variables with a p value of ≤ 0.1 were retained in the models. A p value of ≤ 0.05 was considered statistically significant. Stata versions 11.1 and above (StataCorp, College Station, TX) were used for the analysis.

RESULTS

Among 3,207 patients admitted to ICU after cardiac surgery, baseline weight was missing for 911 patients (28.4%). A baseline creatinine value was not available for 125 (3.9%) patients, leaving a sample size of 2,171. Baseline serum creatinine was available for all patients and was taken within a median of 30 hours (mean 7.9 days) before admission to the ICU, and, for 96% of patients, their baseline creatinine was taken within 30 days prior to admission to the ICU. For 51 patients undergoing emergency surgery, baseline creatinine was taken within a median of 10 hours (mean 12.6) of ICU admission (range: 1-41 hours).

Patient characteristics across groups are compared in Table 1. The proportion of patients classified as having AKI (ie, with early AKI) increased from 550 to 808 (25.3% to 37.2%, $p < 0.001$) after adjusting for the effect of FB (Table 1). Moreover, the proportion of patients who were reclassified as having AKI after adjustment for FB (group B) increased in a stepwise fashion for each quartile of positive FB (Table 2) ($p < 0.001$), and, conversely, the proportion of patients with no AKI (group A) decreased with each quartile of positive fluid balance ($p < 0.001$). ICU fluid balance at 18 hours from admission was largely positive, ranging from 2.5 L negative to 23.6 L positive (mean +4 L, median +3.9 L).

Table 1. Patient Characteristics by Group

Variable	Group A n = 1,363 No AKI before or after FB Adjustment	Group B n = 258 AKI Only *after* FB Adjustment	Group C n = 550 AKI before and after FB Adjustment	*p Value
Age	65 ± 11	69 ± 10	69 ± 10	<0.001
Preop GFR	77 ± 20	70 ± 19	69 ± 22	<0.001
APACHE score	14 ± 4	16 ± 4	17 ± 5	<0.001
Complex surgery	293 (21.5%)	88 (34.1%)	187 (34.0%)	<0.001
Need for inotropes	776 (56.9%)	182 (70.5%)	418 (76.0%)	<0.001
Male	976 (71.6%)	205 (79.5%)	423 (76.9%)	0.005
Weight kg	81 ± 16	80 ± 16	84 ± 18	<0.001
Diabetes	375 (27.5%)	84 (32.6%)	200 (36.4%)	0.001
Previous AMI	290 (21.3%)	48 (18.6%)	106 (19.3%)	0.45
Cardiac failure	121 (8.9%)	31 (12.0%)	54 (9.8%)	0.28
Previous card. surgery	71 (5.2%)	17 (6.6%)	34 (6.2%)	0.54
Compromised LV	105 (7.7%)	24 (9.3%)	65 (11.8%)	0.02
Return to OR	45 (3.3%)	23 (8.9%)	35 (6.4%)	<0.001

NOTE. There were no patients classified with AKI before but not after adjustment for fluid balance. Values are expressed as mean ± standard deviation or n(%).

Abbreviations: AKI, acute kidney injury; AMI, acute myocardial infarction; APACHE, severity of injury score based on first 24 h in intensive care unit; Card. Surgery, cardiac surgery; Compromised LV, left ventricular function grade 3-4; FB, fluid balance; GFR, glomerular filtration rate; OR, operating rooms.

*p value is for the comparison among all 3 groups.