FLUID BALANCE AND ACUTE KIDNEY INJURY: A PROSPECTIVE OBSERVATIONAL STUDY

By

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To my wife, mentors, colleagues, co-investigators and friends who guided, supported and participated in this clinical trial and helped me successfully accomplish my goal on time

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FLUID BALANCE AND ACUTE KIDNEY INJURY: A PROSPECTIVE OBSERVATIONAL STUDY

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Positive fluid balance (FB) has been linked to adverse clinical outcomes in patients with acute kidney injury (AKI). However, it is unclear whether FB is the cause or result of AKI. We therefore performed a prospective, observational study to investigate the relationship of FB and AKI.

Adult patients undergoing non-transplant cardiovascular surgery with estimated glomerular filtration rate>30mL/min/1.73m^2 were included. Patients were divided into quartiles based on FB in the first 24 hours from initiation of surgery. Incidences of AKI, urine Neutrophil Gelatinase-Associated Lipocalin (NGAL) and IL-18 concentrations, serum cytokine concentrations and serum creatinine (SCr) levels were compared between the lowest (Low-FB) and highest (High-FB) quartile groups. AKI was defined per Acute Kidney Injury Network criteria. One hundred patients were included for analyses. Patients in the High-FB were significantly older, had higher baseline SCr, lower mean arterial pressures (MAP) and >92% of patients in each group were on angiotensin converting enzyme inhibitors or angiotensin receptor blockers preoperatively. The major finding was that the High-FB group had a significantly (six-fold) increased risk for AKI (adjusted OR 6.48, $CI_{95\%}$1.37-30.51, p=0.018) and was

associated with significantly higher urine NGAL (p=0.038), IL-8 (p=0.01), MCP-1 (p=0.03) and TNF-alpha (p=0.003) concentrations. An important observation was that positive FB occurred early in the intraoperative period and continued into the initial ICU period. Positive FB preceded the development of AKI. The High-FB group received significantly more blood product transfusions (p=<0.001), medications (p<0.001) and fluids (p<0.001) and had significantly longer duration of surgery (p=0.003) and time on cardiopulmonary bypass machine (p=0.018). Urine output was not significantly different (p=0.483) between groups in the intraoperative period. Both groups demonstrated a 35-40% reduction in intraoperative mean arterial pressure from baseline values, but significant differences between them were not observed (p=0.954). High-FB group had longer ICU (p=0.001) and hospital stay (p=0.048).

Positive FB in the first 24 hours from initiation of surgery may be an independent risk factor for postoperative AKI. Positive FB was associated with increased biomarkers of AKI and mediators of inflammation. Positive FB occurred early in the intraoperative period and preceded the development of AKI. The data is suggestive of the causal role of FB in AKI; however, more studies will be required to confirm this relationship.

CHAPTER 1
INTRODUCTION

Study Aim

The primary aim of this study was to investigate the relationship between fluid balance and acute kidney injury using clinical parameters, biochemical (serum creatinine) and biomarkers of acute kidney injury (urine NGAL and IL-18). Other endpoints for the study included 2-day and hospital peak serum creatinine, discharge serum creatinine, postoperative complication rates, length of intensive care unit and hospital stay, incidence of 30-day dialysis and/or all-cause mortality, and inflammatory response profile. Acute kidney injury was defined as an absolute increase in serum creatinine $\geq$ 0.3mg/dL from baseline within 48 hours after surgery in accordance with the Acute Kidney Injury Network's criteria.[9] Twenty-four hour fluid balance is defined as the difference between intake and output within 24 hours from the start of surgery (time 0hr-24hr).

Background

Positive fluid balance in critical care patients has been proposed to be a major determinant of adverse outcomes in patients with acute kidney injury (AKI). In post-hoc analysis, a 10% increase in body weight from baseline[1] or positive fluid balance during the patient's intensive care stay[2] was associated with increased 60-day mortality in patients with acute kidney injury. The median cumulative fluid balance after the onset of acute kidney injury has been shown to increase from 2.7 liters on day 2 to 6.5 liters on day 7 in critically ill patients, suggesting severity progression of AKI.[3] Positive fluid balance has also been shown to be an independent risk factor for adverse outcomes in patients with acute lung injury[4,5] where the proposed mechanisms involve tissue edema,

impaired oxygenation and metabolite diffusion, impaired capillary blood flow and lymphatic drainage, and disturbed cell-cell integrity that contribute to organ dysfunction. However, it is still unclear from reported studies whether positive fluid balance was the result of acute kidney injury or contributed to acute kidney injury that culminated in adverse outcomes. We therefore investigated the relationship of fluid balance and acute kidney injury in a prospective, observational study in patients undergoing cardiovascular surgery where rapid changes in fluid volume during surgery offer unique opportunities to study this relationship.

Study Design and Inclusion Criteria

This is a prospective, observational study designed to investigate the relationship between fluid balance and acute kidney injury. Acute kidney injury was ascertained by traditional (serum creatinine [SCr]) and non-traditional biomarkers urine neutrophil gelatinase-associated lipocalin, (urine NGAL) and IL-18 of kidney injury. Other outcomes studied were peak serum creatinine, postoperative complications, length of hospital stay and inflammatory response profiles in patients undergoing cardiovascular surgery.

We set the criteria for inclusion into the study based on previous reports[6] to maximize the likelihood of seeing an effect. Specifically, we limited recruitment of subjects to older than 18 years of age undergoing cardiovascular surgery (thoracic aortic aneurysm, cardiac valve or coronary artery bypass graft surgery) and with estimated glomerular filtration rate $\geq$ 30ml/min/1.73m^2. Patients with a prior history of organ transplant, on preoperative intra-aortic balloon pump or on natriuretic peptides were excluded from study participation. The study was performed by the Division of Nephrology, Transplantation and Hypertension and the Division of Thoracic and

Cardiovascular Surgery at the University of Florida (UF) in Gainesville, FL, was approved by the UF Institutional Review Board and conforms to regulations of the UF ethics committee on human research. Patients were recruited from the cardiovascular surgery clinics. The study was registered at www.ClinicalTrials.gov, unique identifier NCT01168583. Written informed consents were obtained from all patients.

Study Protocol

Baseline clinical data on demographics, comorbid conditions, medications, vital signs, and pertinent laboratory tests were obtained by patient interviews and review of electronic medical records. All patients received routine postoperative supportive care for their medical and surgical problems, including care for acute kidney injury, optimization of fluid and nutritional status and inotropic support as required. Cardiopulmonary bypass was utilized in all patients using standard cardiopulmonary bypass protocol. The standard cardiopulmonary bypass prime consisted of 1400mL of Plasmalyte, 5000units of heparin, 12.5gm of mannitol, 50meq of sodium bicarbonate, 25gm of albumin in 100mL of normal saline, and 250mg of methylprednisolone. The postoperative fluid protocol included the administration of up to 1 liter of normal saline for cardiac index <2, unstable systolic blood pressure <80mmHg with left atrial pressure or pulmonary artery diastolic pressure < 15mmHg. Diuretics could be administered for volume management per established protocol of the cardiovascular surgery intensive care unit that included central venous pressure parameters, physical, radiological or physiological index evidence for pulmonary congestion and inadequate oxygenation. The need for renal replacement therapy was determined independently by the patients' treating nephrologists per current standard of care criterion, which included blood urea nitrogen > 80mg/dL, electrolyte or acid-base disorders not responding to medical

management, and diuretic unresponsiveness with urine output < 0.5ml/kg/hour and refractory volume overload as defined by central venous pressures > 15 mmHg. Estimated glomerular filtration rate (GFR) was calculated using the National Kidney Foundation's MDRD Calculator (©2000-2001).

Intraoperative data on fluid volume and surgical procedure were obtained from the standardized anesthesia operative room records. Postoperative data were collected daily at patient bedside from standardized intensive care unit flow charts and medical records. Serum and urine samples were collected at 24 hours from start of surgery and stored at -80^{O}C. Urine NGAL measurements were performed in the laboratory of Dr. Prasad Devarajan at the Cincinnati Children's Hospital Medical Center Biomarker Laboratory, Cincinnati, Ohio using a previously published ELISA method.[7] Urine IL-18 measurements were performed in the laboratory of Dr. Charles Edelstein at the University of Colorado Health Sciences Center, Denver using a previously published ELISA method.[8] Inflammatory cytokines were quantified by enzyme-linked immunosorbent assay using multiplex human cytokine/chemokine kit. The following thirty-nine serum and urine biomarkers were measured: EGF, Eotaxin, FGF-2, Flt-e ligand, Fractalkine, G-CSF, GM-CSF, GRO, IL-10, IL-12(p40), IL-12(p70), IL-13, IL-15, IL-17, Il-1a, IL-1b, Il-1ra, IL-2, Il-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, INF-alpha2, INF-gamma, IP-10, MCP-1, MCP-3, MDC, MIP-1a, MIP-1b, sCD40L, sIL-2Ra, TGF-alpha, TNF-alpha, TNF-beta, VEGF.

Statistical Methods

Patients were divided into quartiles based on 24-hour fluid balance status. Outcome variables were calculated for each quartile and compared between quartiles. Comparisons between groups were assessed using parametric tests for normally

distributed variables (chi-squared t-test) and nonparametric tests (Mann-Whitney U-test) for variables which are not normally distributed as appropriate. Results are presented as mean $\pm$ standard error of mean with *P* value. Median values are provided for several variables. *P* value < 0.05 was considered statistically significant. All analyses were conducted using SPSS version 18, Chicago Ill.

CHAPTER 2
RESULTS

Baseline Patient Characteristics

One hundred patients were enrolled and all of them completed the study. Most of the patients were Caucasian males and most of them were chronically taking angiotension-converting enzyme inhibitor or angiotensin receptor blocker medications (Table 2-1). Renal and cardiac functions appeared to be well-preserved. Preoperative cardiac catheterizations were performed in 39% of patients within 72-hours of planned surgery. The three types of surgical procedures (thoracic aortic aneurysm, cardiac valve or coronary artery bypass graft surgery) were performed in relatively equal proportions.

The mean intake, output and fluid balance for the first 24 hours from the start of surgery (time 0hr -24hr) for the full cohort are as follows: intraoperative (OR) intake, blood products 1169.3±102.5mL, medications/fluids 1580.5±105.7mL, total OR intake 2749.8±159.3mL; OR output, blood loss7.50±6.6mL, urine output1079.8±62.9mL, total OR output 1087.3±63.2mL, OR fluid balance 1662.5±145.9mL; total postoperative (end of surgery until 24-hour) intake 2629.4±124.1mL, urine output 1101.2±54.5mL, drainage and other outputs 640.8±51.4mL, total postoperative output 1742.1±68.7mL, postoperative fluid balance 887.3±112.8mL; 24-hr fluid balance mean 2567.2±202.2mL, median 2268.5mL, mode 2706.0mL, 25^{th} percentile 936.2mL, 50^{th} percentile 2268.5mL and 75^{th} percentile 3898.2mL. To investigate the relationship between fluid balance and study outcomes, patients were divided into quartiles based on 24-hr fluid balance status. Outcomes in the highest quartile group were then compared with the lowest quartile group. Baseline characteristics of the groups are exhibited in Table 2-1**.** The highest quartile group was older, had lower mean arterial pressures and higher serum

creatinine levels, although estimated glomerular filtration rate was not significantly different compared to the lowest quartile group. There were no differences in the types of surgery performed or in preoperative exposure to contrast agents.

Patients in the highest quartile received significantly more blood products and fluids in the intraoperative, postoperative and intensive care unit stay period (Figure 2-1). Urine outputs were not different between the groups in the intraoperative period, but thereafter was significantly reduced in the highest quartile group in the postoperative and intensive care unit period (Figure 2-2). Differences in fluid balance emerged early in the intraoperative period between the groups and continued to increase in the intensive care unit period (Figure 2-3). More patients in this group required diuretic therapy in the immediate postoperative period than in the lowest quartile group (lowest quartile 32% vs. highest quartile 100%, $p<0.001$).

Intraoperative Parameters

The mean duration of surgery for the full cohort was 403.5±12.5min, mean cardiopulmonary bypass time was 167.0±7.3min and mean aortic cross-clamp time (N=91) was 105.2±5.5min. Investigation of events in the intraoperative period demonstrated that the highest quartile group had a longer duration of surgery (lowest quartile 363.0±17.2min vs. highest quartile 467.6±27.9, $p=0.003$) and prolonged time on heart-lung perfusion machine (cardiopulmonary bypass time, lowest quartile143.4±44.7min vs. highest quartile192.6±17.7min, $p=0.018$). Aortic cross-clamp time was not significantly different (lowest quartile 95.5±8.9min vs. highest quartile 115.8±13.0, $p=0.208$) between the groups. A large reduction in mean arterial pressure from baseline values was noted in the intraoperative period; however significant differences between the groups were not evident (Figure 2-4).

Table 2-1. Patient characteristics.

Variables	Full cohort N=100	24-hour fluid balance		
		Lowest quartile	Highest quartile	p-value*
Demographics				
Age (years)	61.4±1.4	56.8±2.4	66.4±1.9	0.003
Male gender (%)	60	56	64	0.773
Race (%): Caucasian	85	76	76	
African-American	8	16	12	0.842
Others	7	8	12	
Co morbid conditions (%)				
Hypertension	66	56	76	0.232
Diabetes mellitus	26	16	28	0.496
Coronary artery disease	37	28	44	0.377
Congestive heart failure	10	4	8	1.000
Previous cardiac surgery	13	4	16	0.349
Peripheral vascular disease	9	4	12	0.609
COPD	12	12	20	0.702
Medications (%)				
ACE-inhibitors/ARBs	93	92	96	1.000
Diuretics	35	40	36	1.000
Beta-blockers	47	44	60	0.259
Calcium channel blockers	19	20	28	0.742
Cardiac function NYHA class	1	1	1	-
Mean arterial pressure (mmHg)	79.6±1.0	84.3±2.1	76.1±2.1	0.009
LVEF (%)	52.7±1.6	50.9±4.1	52.7±2.7	0.709
Renal function				
BUN (mg/dL)	18.4±0.7	18.1±1.6	19.4±1.2	0.495
Serum creatinine (mg/dL)	0.9±0.0	0.8±0.0	1.0±0.1	0.046
Estimated glomerular filtration rate (mL/min/1.73m^2)	85.9±3.1	84.4±4.0	93.2±6.1	0.239
Surgical procedures (%)				
TAA	28	32	32	
Valves	40	32	36	0.943
CABG	32	36	32	
Preoperative cardiac catheterization (%)	39	40	52	0.571

*p-value calculated for lowest vs. highest quartiles; LVEF: Left ventricular ejection fraction; mean arterial pressure: mean arterial pressure; TAA: thoracic aortic aneurysm; valves: cardiac valves; CABG: coronary artery bypass graft; BUN: blood urea nitrogen; COPD: chronic obstructive pulmonary disease; ACE-inhibitors: angiotensin converting enzyme inhibitors, ARB: angiotensin receptor blocker; NYHA: New York Heart Association.

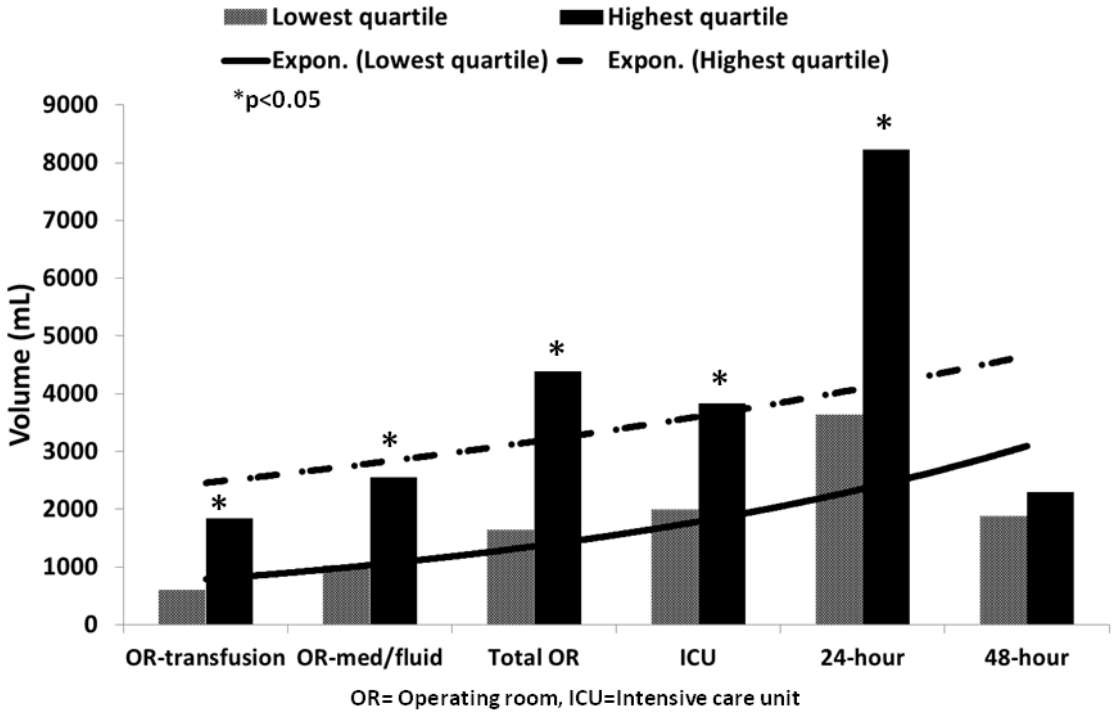

Figure 2-1. Intake volumes in lowest vs. highest quartiles.

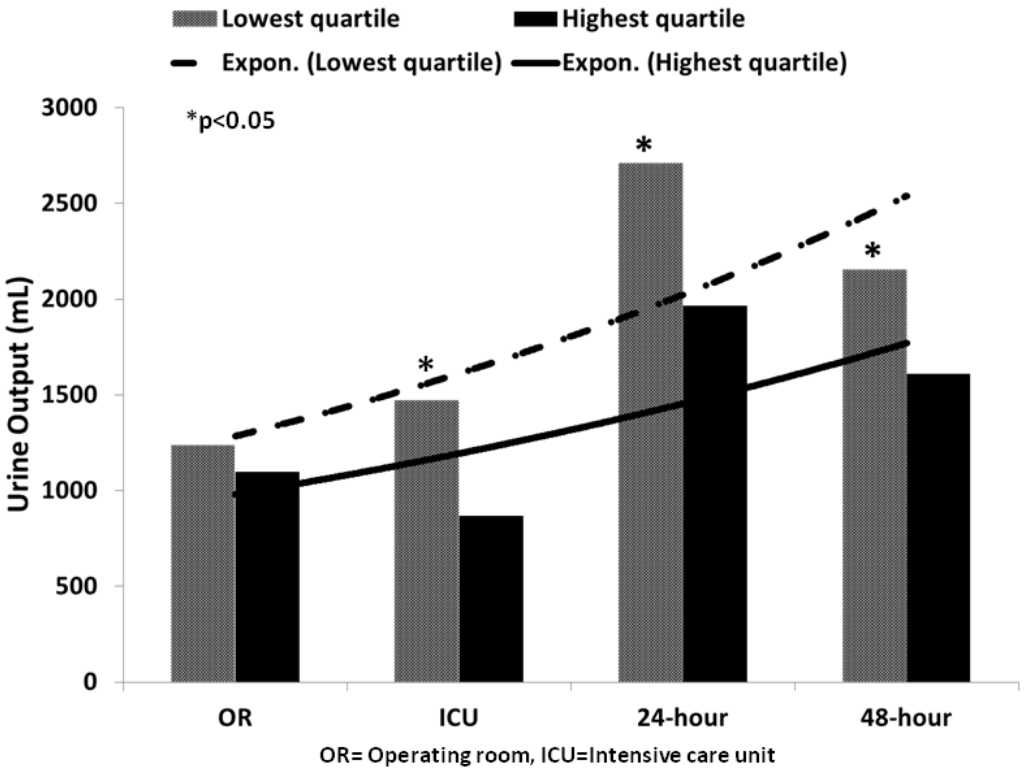

Figure 2-2. Urine output in lowest vs. highest quartiles.

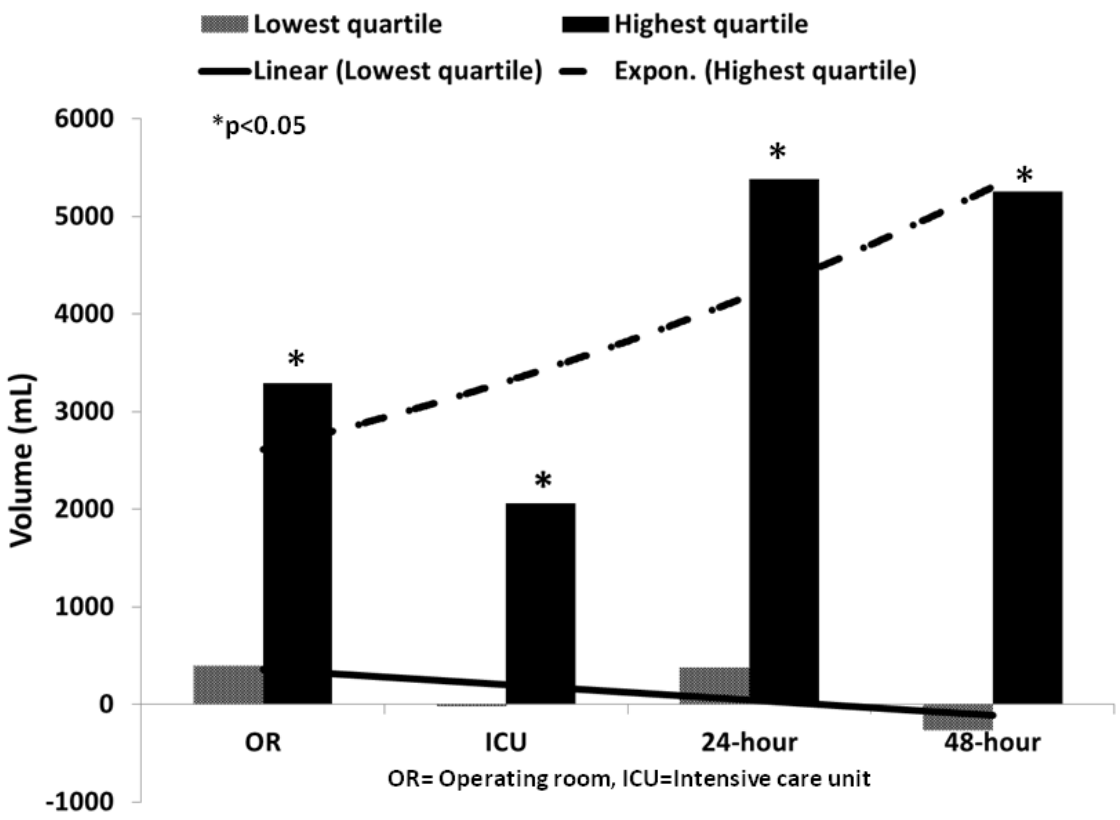

Figure 2-3. Fluid balance in lowest vs. highest quartiles.

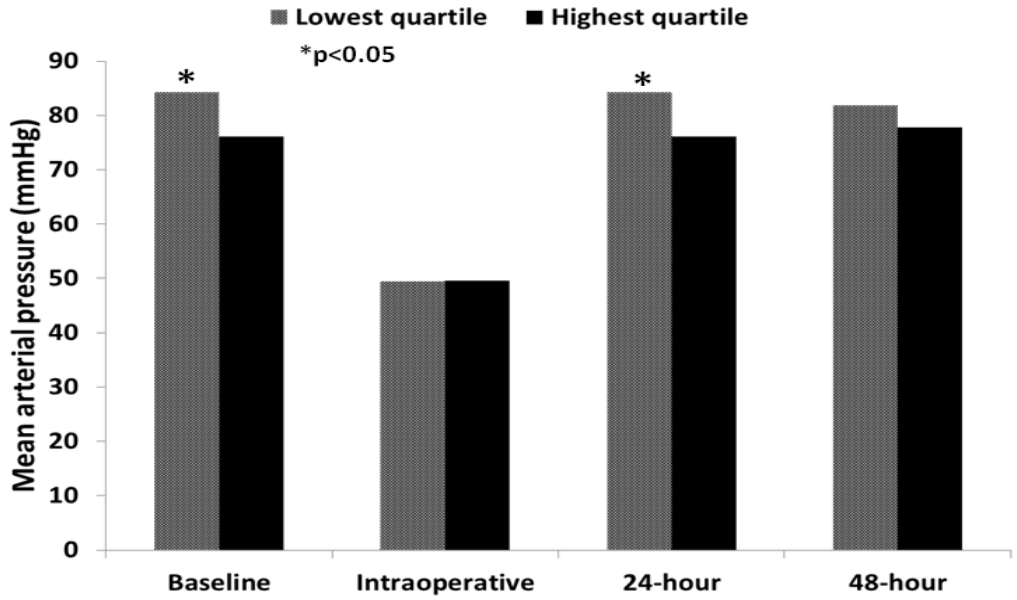

Figure 2-4. Perioperative mean arterial pressures.

CHAPTER 3
OUTCOMES

Fluid Balance and Biomarkers of Acute Kidney Injury

Early acute kidney injury was investigated by two different urinary biomarkers of kidney injury, IL-8 and NGAL. The mean and median values of urine IL-18 concentrations respectively were as follows: full study cohort, 249.6±50.3pg/mL and 90.7pg/mL; lowest quartile, 244.2±120.3pg/mL and 89.9pg/mL and highest quartile, 380.4±144.8pg/mL and 95.2pg/mL. There was no significant difference in IL-18 between the two groups (p=0.741). As expected, patients with acute kidney injury had higher urine IL-18 levels compared to those without acute kidney injury (546.5± 163.7pg/mL vs. 139.8±23.9pg/mL, p=0.021). There were no significant differences in urine IL-18 levels between patients with acute kidney injury (n=27) and patients in the highest quartile group (n=25): acute kidney injury 546.5± 163.7pg/mL vs. highest fluid balance 380.4±144.8pg/mL, p=0.454). However, the highest quartile group had higher urine IL-18 levels than the no acute kidney injury group (highest quartile380.4±144.8pg/mL vs. no acute kidney injury 139.8±23.9pg/mL, p=0.011).

Significantly higher urine NGAL concentrations were noted in the highest quartile group (lowest quartile mean 42.8±19.7ng/mL, median 9.5ng/mL vs. highest quartile mean 107.0±66.4ng/mL, median 22.1ng/mL; p=0.038) in comparison to the lowest quartile group. Patients with acute kidney injury had higher urine NGAL concentration than those with no acute kidney injury (107.8±61.4ng/mL vs. 34.0±7.5ng/mL, p=0.018).

Since the earliest evidence of positive fluid balance was observed in the intraoperative period, we investigated the correlation of blood product transfusion, medication/fluids, total intake and fluid balance in this period with urine NGAL as the

biomarker for kidney injury. In the full cohort, significant correlation was demonstrated between transfusion volume (r=0.281, p=0.005), total intake volume (r=0.274, p=0.006), and fluid balance (r=0.254, p=0.011) with urine NGAL concentrations. When the analysis was restricted to only the highest quartile group, transfusion volume was the only variable that significantly correlated with urine NGAL (r=0.397, p=0.050), however transfusion volume did not show any correlation with serum creatinine, the traditional marker of acute kidney injury.

The receiver operating characteristics (ROC) curves for fluid balance, urine NGAL and IL-18 to predict acute kidney injury vs. no acute kidney injury are shown in Figure 3-1. The overall ability to predict acute kidney injury vs. no acute kidney injury was not significantly different between fluid balance, urine NGAL and IL-18 (AUC for fluid balance: 0.669$\pm$0.064, $CI_{95\%}$ 0.545-0.794, p=0.010; IL-18: 0.654$\pm$0.065, $CI_{95\%}$ 0.526-0.782, p=0.018; NGAL: 0.624$\pm$0.065, $CI_{95\%}$ 0..497-0.751, p=0.058).

Fluid Balance and the Incidence of Acute Kidney Injury by Acute Kidney Injury Network Criteria

The overall incidence of acute kidney injury in the full cohort was 27%. Most (97%) of the patients had Stage 1 acute kidney injury, defined as serum creatinine increase ≥0.3 mg/dl or increase to 1.5–2.0-fold from baseline.[9] The highest quartile group was associated with a significantly higher incidence of acute kidney injury compared to the lowest quartile group (lowest quartile16% vs. highest quartile52%, p=0.016). In the univariate analysis performed to determine the odds ratio (OR) for acute kidney injury, age, diabetes status, cardiopulmonary bypass time >200min and 24-hour fluid balance were significant predictors of acute kidney injury (Table 3-1). The highest quartile group had a 6-fold increased risk for acute kidney injury (OR 6.0, $CI_{95\%}$

1.7-21.3, p=0.006). When all risk factors in Table 3-2 were included, without selection, in the multivariate model, the highest quartile group was again associated with a 6-fold increased risk for acute kidney injury (OR 6.48, $CI_{95\%}$1.37-30.51, p=0.018) compared to the lowest quartile group.

The incidence of acute kidney injury during the entire hospital stay was also higher in the highest quartile group compared to the lowest quartile group (lowest quartile 20% vs. highest quartile 60%, p=0.009), associated with a six-fold increased risk for in-hospital acute kidney injury (OR 6.0, $CI_{95\%}$ 1.7-21.3). Intraoperative urine output or fluid balance per se was not a significant predictor of acute kidney injury.

Fluid Balance and Cytokine Profiles

Only four of the 39 serum and urine biomarkers that were measured were significantly different between the groups: serum IL-8 (lowest quartile 27.1pg/mL vs. highest quartile 41.3pg/mL, p=0.010), IL-10 (lowest 21.7pg/mL vs. highest quartile 47.5pg/mL, p=0.009), MCP-1 (lowest quartile 333.0pg/mL vs. highest quartile 527.0pg/mL, p=0.030) and TNF-alpha (lowest quartile 6.9pg/mL vs. highest quartile 11.2pg/mL, p=0.003). IL-1a/IL-1ra ratios were not significantly different between the groups (p=0.797). In the urine, significant differences were observed in IL-1ra (lowest quartile 52.9pg/mL vs. highest quartile 143.0pg/mL, p=0.031), and IL-10 (lowest quartile 9.9pg/mL vs. highest quartile 13.7pg/mL, p=0.048).

Fluid Balance, Peak Serum Creatinine and Glomerular Filtration Rate

Significant differences in 48-hour peak, hospital peak and discharge serum creatinine were noted between the groups (Figure 3-2). However, the discharge estimated glomerular filtration rates were not significantlydifferent between the groups (lowest quartile78.6$\pm$7.2mL/min/1.73m^2 vs. highest quartile87.4$\pm$8.4mL/min/1.73m^2

(p=0.428). Serum creatinine values were noted to return to baseline values at discharge (p=0.434).

Fluid Balance, Hospital Complications, Ventilation Support and Length of Hospital Stay

The incidence of postoperative complications such as cardiac arrhythmias, pacemaker insertions, pleural effusions, pneumonias, pneumothorax, tracheostomy, intra-aortic balloon pump placement, poor wound healing, gastrointestinal bleeding, stokes and infections were significantly higher in the highest quartile group (lowest quartile 8% vs. highest quartile 56%, $p<0.001$). These patients also spent significantly more time in the intensive care unit and had a significantly longer duration of hospital stay (Figure 3-3). Time on mechanical ventilation support was not different between the groups (p=0.65).

Fluid Balance, Renal Replacement Therapy and Thirty-day Mortality

Two patients in the highest quartile group and none in the lowest quartile group required renal replacement therapy (p=0.490). Thirty-day mortality rates were not significantly different between the groups (lowest quartile 0% vs. highest quartile 4%, p=1.000).

Table 3-1. Predictors of acute kidney injury by univariate analysis.

Variables	Odds ratio	$CI_{95\%}$	p-value
Demographics			
Age (years)	0.97	0.94-0.99	0.038
Race	0.64	0.31-1.30	0.218
Gender	1.24	0.54-2.84	0.611
Type of surgery			
Thoracic aortic aneurysms	0.82	0.33-2.03	0.675
Cardiac valves	0.90	0.39-2.05	0.802
Coronary artery bypass grafts	1.34	0.57-3.14	0.505
Co morbidities			
Diabetes mellitus	3.55	1.4-9.0	0.008
Hypertension	2.31	0.94-5.7	0.068
Chronic obstructive pulmonary disease	1.64	0.49-5.5	0.424
Peripheral vascular disease	2.10	0.53-8.3	0.294
Coronary artery disease	1.89	0.83-4.35	0.132
Previous cardiac surgery	0.66	0.19-2.31	0.516
Cardiac function			
Ejection fraction <45%	1.26	0.44-3.64	0.670
Renal function			
Estimated glomerular filtration rate (ml/min/1.73m^2)	0.99	0.98-1.00	0.350
Intraoperative			
Duration of surgery	0.99	0.99-1.00	0.280
cardiopulmonary bypass time>200 minutes	2.85	1.13-7.16	0.026
Fluid balance			
24-hour fluid balance	1.00	0.99-1.00	0.004
Lowest vs. Highest quartile	5.69	1.51-21.41	0.010

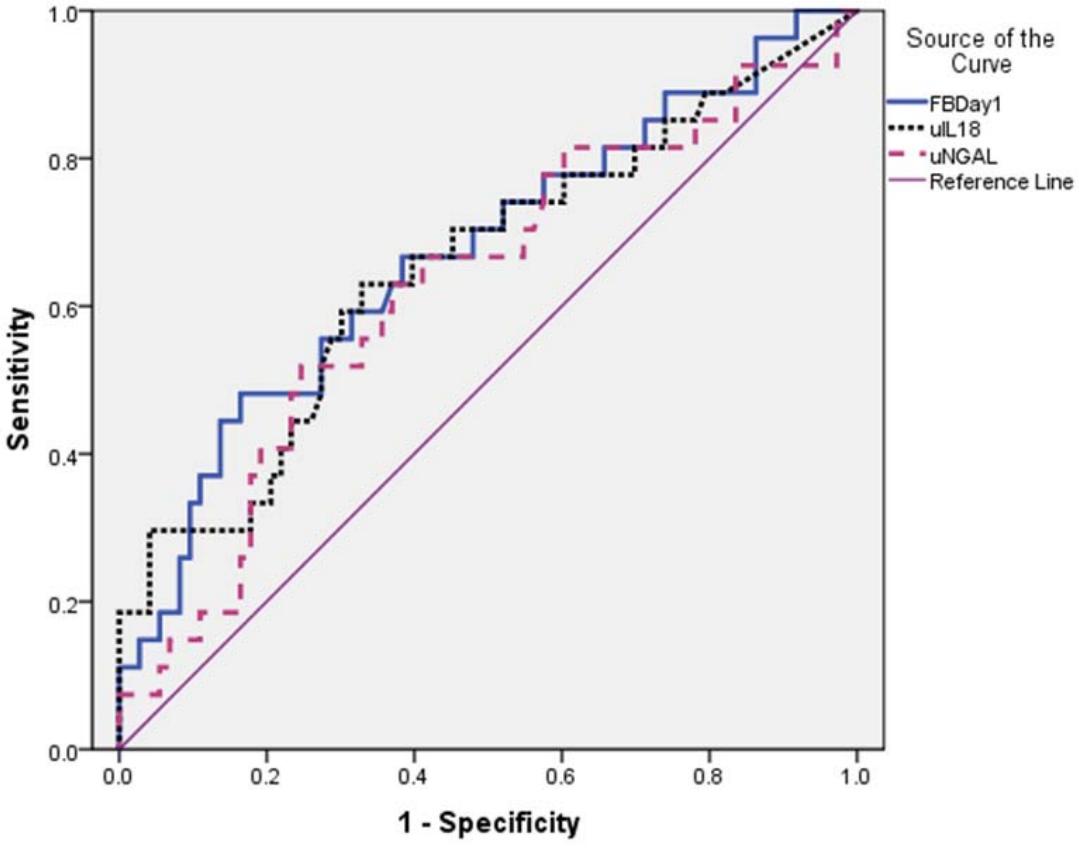

Figure 3-1. Receiver operating characteristics curves.

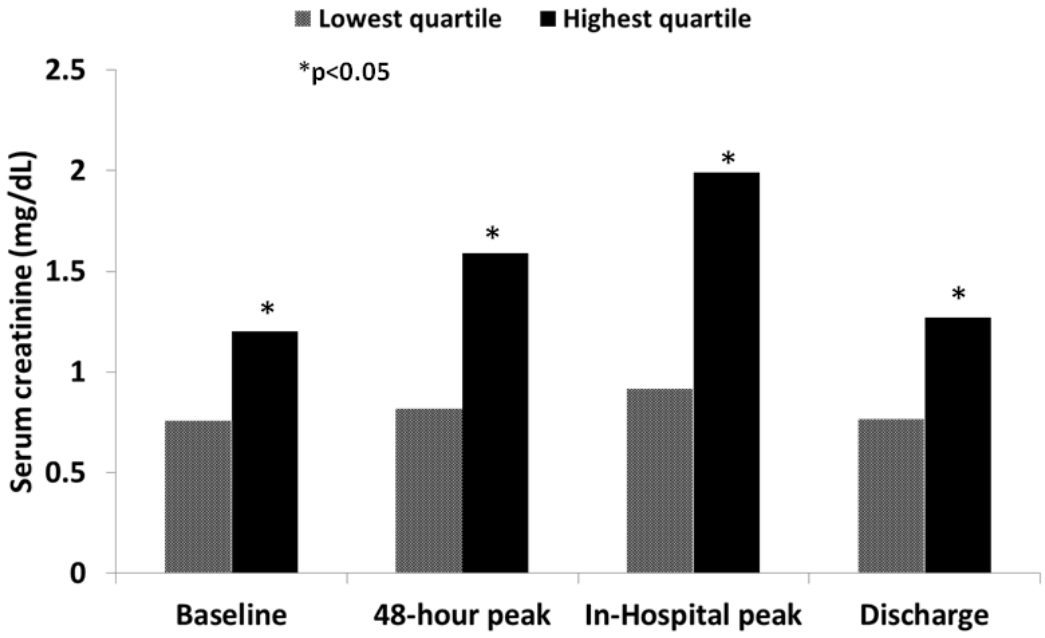

Figure 3-2. Serum creatinine levels in lowest vs. highest quartiles.

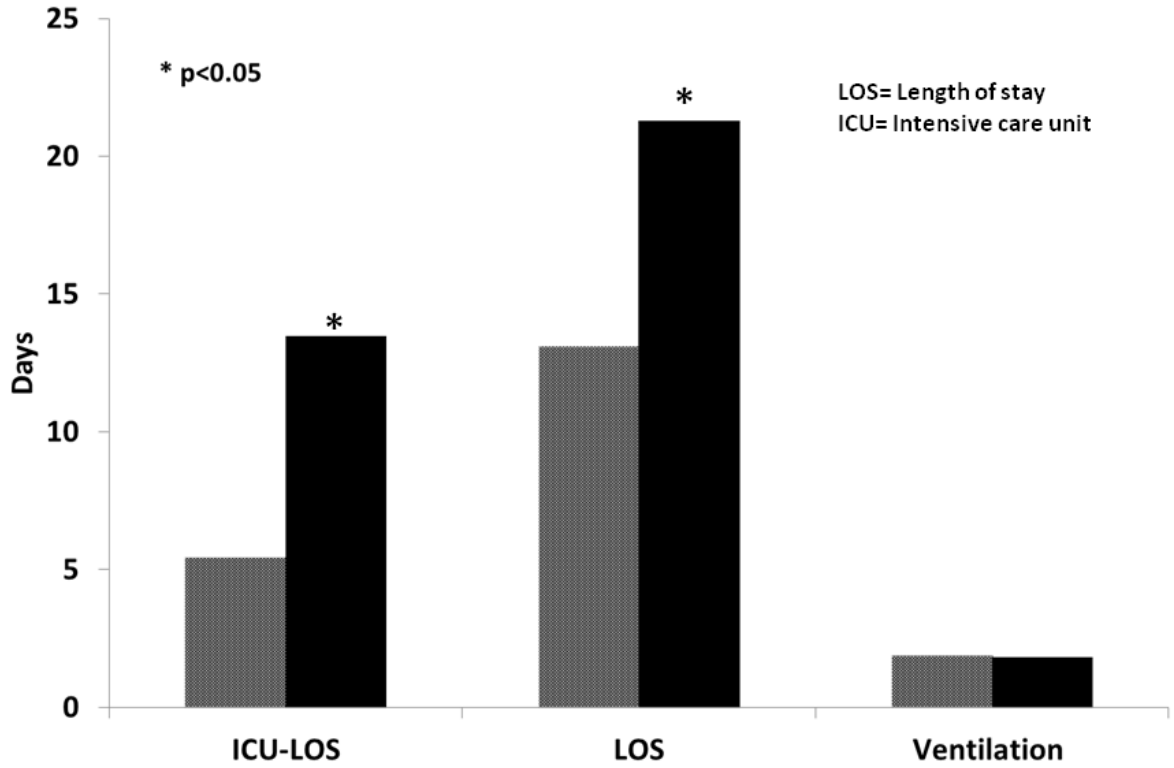

Figure 3-3. Fluid balance and resource utilization.

CHAPTER 4
DISCUSSION

Several retrospective studies have linked positive fluid balance with adverse clinical outcomes in patients who had developed acute kidney injury,[1-3] however the temporal relationship of fluid balance and acute kidney injury remains unclear. We investigated the relationship between fluid balance and acute kidney injury in a prospective manner in patients undergoing cardiac surgery using standard surgical protocols. This setting allowed for relative timelines to be established between events and outcomes. The major finding of the study was that positive fluid balance in the first 24 hours from initiation of surgery was an independent risk factor for postoperative acute kidney injury. The risk was six-fold higher in the highest quartile vs. lowest quartile group. Positive fluid balance was also associated with increased urine biomarkers of acute kidney injury and high serum creatinine levels during hospital stay.

An important observation was that positive fluid balance occurred early in the intraoperative period and preceded the rise in serum creatinine. We did not evaluate fluid balance status beyond postoperative day 2 due to reported inaccuracies in multi-day intakes and outputs tracking in the intensive care unit setting.[10] However others have reported increasing cumulative positive fluid balance with progression severity of acute kidney injury.[3] Patients in the highest quartile group received more blood product transfusions, medications and fluids in the intraoperative period than the lowest quartile group. Perioperative red blood cell transfusions have been independently linked to acute kidney injury.[11] Urine output was not different between the groups. We investigated other pre- and intraoperative events that could possibly have precipitated the increased intake and found that the highest quartile group included older patients

with higher baseline serum creatinine, lower baseline mean arterial pressure, longer duration of surgery and prolonged cardiopulmonary bypass time than the lowest quartile group. Both groups demonstrated a 35-40% reduction in intraoperative mean arterial pressure from baseline values, but significant differences between them were not observed. Blood loss was not different between the groups. It is noteworthy that volume and method of intraoperative fluid administration, whether due to preferences of the surgical team, complexity of surgery or other issues, may also be an important determinant of outcomes. Indeed, a recent study in children has reported an increase in 48-hour mortality in critically ill children treated with fluid boluses,[12] and also conservative strategy of fluid management in patients with acute lung injury has been shown to improve lung function and shorten the duration of mechanical ventilation and intensive care stay without increasing nonpulmonary-organ failures.[5]

Urine NGAL and mediators of inflammation were elevated in the highest quartile group, suggesting an association between fluid balance, inflammation and acute kidney injury. The possibility that intraoperative acute kidney injury due to longer cardiopulmonary bypass time and complexity of surgery was the initiating event in this study cannot be entirely excluded. However, intraoperative biomarkers of acute kidney injury and inflammatory mediators were not available to make that determination. Serum and urine samples were collected at 24 hours following initiation of surgery to separate the effects of positive fluid balance on inflammation and kidney injury from that of surgery-related injury. In light of the findings of the study that positive fluid balance occurs as early as in the intraoperative period, the focus of the time period of investigation may need to be modified in future studies.

Another significant observation was that at 24 hours from start of surgery, there were no differences between the overall ability of fluid balance, urine NGAL and IL-18 to predict acute kidney injury vs. no acute kidney injury. That is, simple clinical observation may give similar information as urine NGAL and IL-18 in this setting and time period. However, it needs to be emphasized that urine NGAL and IL-18 are reliable biomarkers that can detect acute kidney injury within 2-6 hours after renal injury.[7,13] Postoperative complication rates were higher in the highest quartile vs. lowest quartile group, and is in accordance with other published reports of the adverse effects of positive fluid balance in surgical patients.[14-16] Intensive care unit and hospital lengths of stay were longer but no differences were observed in the need for dialysis or duration of mechanical ventilation confirming previous findings. The strengths of the study was its setting, observations of events and outcomes during the course of routine surgical procedures, and association of operative and clinical variables with traditional and non-traditional biomarkers of acute kidney injury and inflammatory mediators. The limitations of the study were the lack of intraoperative biomarker and cytokine data and relatively small sample size. However, our data is hypothesis-generating and highlights the need for investigations regarding fluid balance and acute kidney injury to be performed much earlier than after the onset of acute kidney injury.

We conclude that positive fluid balance in the first 24 hours from initiation of surgery may be an independent risk factor for postoperative acute kidney injury. Positive fluid balance is an excellent and simple predictive marker that precedes the rise in serum creatinine.

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BIOGRAPHICAL SKETCH

Ganesh Kambhampati was born in Hyderabad, India, and is the younger of two children; he grew up primarily in Hyderabad, India. He graduated with a medical degree from Osmania Medical College in India and subsequently moved to Bronx, New York. He completed his residency in internal medicine at Albert Einstein College of Medicine and decided to pursue his career in nephrology. He then moved to Gainesville, FL, where he is currently a fellow in the College of Medicine, Department of Medicine, Division of Nephrology, at the University of Florida. He completed his Master of Science in medical sciences with a concentration in clinical and translational research in August 2011. Ganesh has been married to his wife, Supriya, for 5 years.