

## Endothelin levels predict post-operative AKI in patients with coronary artery bypass surgery

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### Abstract

**Background:** Acute kidney injury (AKI) occurs in up to 40% of patients undergoing cardiac surgery and is associated with substantial morbidity and mortality, prolonged hospitalizations, and increased costs. Thus, there is a critical need to identify patients at increased risk for developing AKI when undergoing cardiac surgery. Endothelin is a natriuretic peptide which serves an important role in the regulation of renal hemodynamics and hemofiltration.

**Objectives:** We evaluate the role of endothelin in predicting post-operative AKI in patients undergoing cardiac surgery.

**Methods:** 105 patients undergoing cardiac surgery were recruited (either coronary bypass surgery and/or valve surgery) were recruited and their plasma samples pre-operatively and at 2, 6, 12, 24, and 48 hours post-operatively were collected. A post-hoc analysis was then performed to determine the ability of pre-operative endothelin levels to predict post-operative AKI.

**Results:** Of 105 patients, 29 patients (28%) developed AKI post-operatively. Endothelin levels were elevated at baseline in patients who had a RIFLE score of at least 1, which is indicative of baseline renal injury. Preoperative endothelin was elevated in patients with post-operative AKI vs. no AKI (4.03 pg/mL [3.43-5.49] vs. 3.14 pg/mL [2.56-4.10],  $p=0.016$ ). Interestingly, it was also determined that endothelin was superior to baseline creatinine in predicting AKI. Preoperative endothelin was predictive of post-operative AKI  $p=0.016$ , while there was no significant association between preoperative creatinine and post-operative AKI;  $p=0.282$ .

**Conclusions:** In conclusion, elevation of pre-operative endothelin levels predicts post-operative AKI in patients undergoing cardiac surgery.

**Keywords:** Endothelin, Acute kidney injury, Cardiac surgery

### Introduction

Acute kidney injury (AKI) following cardiac surgery is a serious complication, occurring in up to 40% of patients [1]. It is associated with prolonged hospitalization and increased mortality [1]. In one study, patients who developed AKI after cardiac surgery had a 4.6

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increase in relative risk of death at 1 year [1]. Given the substantial morbidity and mortality associated with AKI in patients undergoing cardiac surgery, there is a clinical need to identify patients at increased risk for developing AKI. Known predictors of AKI prior to coronary artery bypass graft surgery (CABG) include pre-existing renal dysfunction, peripheral artery disease, diabetes, age, and technique and duration of cardiopulmonary bypass [2]. However, one of the challenges in preventing AKI is the lack of early, accurate predictors.

Following CABG, AKI is diagnosed by monitoring creatinine and urine output. However, creatinine has multiple weaknesses including a delayed rise, a low sensitivity with potentially up to a 50% loss of the glomerular filtration prior to a rise in creatinine. Additionally, several factors such as liver function, muscle mass, age, sex, and protein intake may influence the measurement [3-5]. Thus, there is a need for novel, noninvasive, and cost effective renal biomarkers which can identify patients that are at risk for AKI. Biomarkers can also provide insights into underlying mechanisms and lead to better understanding of the pathophysiology of complex disease states such as AKI. This enhanced understanding can then be integrated into disease management which can lead to better therapies and ultimately to improved patient outcomes.

Current biomarkers studied for prediction of AKI include neutrophils gelatinase-associated lipocalin, kidney injury molecule-1, and N-acetyl- $\beta$ -D-glucosaminidase. The expression of neutrophils gelatinase-associated lipocalin is unregulated in the renal proximal tubule cells following ischemic injury [6]. Meanwhile, kidney injury molecule-1 is a cell membrane glycoprotein which is shed in urine after acute kidney injury. Therefore, elevated urinary levels of kidney injury molecule-1 are also highly sensitive and specific for AKI [6]. Finally, increased levels of N-acetyl- $\beta$ -D-glucosaminidase are also indicative of proximal tubular damage. These tubular damage markers have therefore been extensively investigated in predicting the occurrence of acute kidney injury. However, none of these markers in isolation when assessed in the pre-operative setting have been shown to predict post-operative AKI in cardiac surgery patients.

Endothelin is a 21-amino acid peptide that is produced by the vascular endothelium as well as numerous tissues within the kidney. It is a crucial modulator of renal function. Endothelin serves as a potent vasoconstrictor of cortical and medullary vessels, regulating glomerular filtration and renal hemodynamics. It also functions as a natriuretic peptide by inhibiting sodium and water reabsorption along the collecting duct. Recent studies have revealed that endothelin exerts a pathophysiological role in renal disorders characterized by increased vascular resistance, including renal ischemia [7-8]. In fact, one study noted that a rise in endothelin from 100 to 900 pmol/l was associated with a reduction in glomerular filtration rate by 90%. Thus, events associated with acute renal failure will inevitably increase endothelin levels. Endothelin can therefore serve as

a biomarker of acute renal failure [1]. The role of endothelin and endothelin receptor antagonists have been studied in renal disease. However, this is the first study to evaluate the predictive value of endothelin for AKI in patients undergoing cardiac surgery (either coronary bypass surgery or valve surgery).

## Methods

We prospectively studied 105 patients undergoing CABG with or without valve surgery at the Veteran Affairs San Diego HealthCare System between 2011 and 2013. Choice of on-pump and off-pump CABG was at the discretion of the treating surgeon. The study participants signed written informed consent and the protocol was approved by the Institutional Review Board at Veteran Affairs San Diego HealthCare System.

All patients received standard medical care. Baseline demographics, vital signs, comorbidities and laboratory values were recorded and stored in an encrypted online database. For assessment of endothelin, blood samples were collected prior to surgery and at 2, 6, 12, 24, and 48 hours post-operatively. The plasma was separated by 2 centrifugation steps; the first at 300xg for 10 min to remove the red cells and buffy coat, the second at 5000xg for 10 min to remove the platelets. The cell-free plasma was stored at -80 C until assayed in a single batch for blinded determination of endothelin levels. Baseline creatinine was based on labs drawn within 2 weeks of surgery.

The endothelin assay used was the Singulex Endothelin assay which demonstrates greater than 5 logs of dynamic range and a sensitivity of 0.07 pg/mL. The Singulex Endothelin assay is a sandwich immunoassay for the detection of endothelin in human plasma. In this assay, paramagnetic particles coated with endothelin antibody recognizing the endothelin c-terminal regions and a fluorescently labeled anti-endothelin antibody are incubated with plasma samples in a one-step reaction. During incubation, endothelin antigens present in a sample are bound by the capture endothelin antibody as well as by the fluorescently labeled detection antibody, thus completing the sandwich. This is followed by a wash step to remove unbound reagents and an incubation with elution buffer which dissociates the bound immune complex from the paramagnetic particles, releasing the fluorescently labeled antibodies. The labeled molecules are then detected and counted by Singulex SMC™ technology. The assay sensitivity allows for 100% detection of endothelin in the plasma of normal, healthy individuals and thus provides high positive predictive value, effectively discriminating healthy and disease states, such as chronic heart failure.

The primary endpoint was AKI defined using the RIFLE criteria [9]. The RIFLE criteria were used given that it provides a uniform and accepted definition of AKI. RIFLE is an acronym of Risk, Injury, Failure, Loss, and End-Stage kidney disease. It consists of three graded levels of renal dysfunction (risk, injury, and failure) based on the rise in

serum creatinine as well as two outcome measures: loss and end-stage renal disease. We investigated to see if elevated endothelin levels are predictive of AKI.

Statistical analyses were performed in SPSS Version 13 (SPSS Inc, Chicago, IL, USA). Figures were created in SigmaPlot (Systat Software Inc, San Jose, CA, USA) and MS Excel (Microsoft Inc, Seattle, WA, USA). Continuous variables were compared with a 2-sample t-test where distributions were normal, or with Mann-Whitney U tests otherwise. Spearman’s coefficient was used to compare two discrete variables such as endothelin and creatinine. Means (SD) and medians (quartiles) are reported, respectively. Nominal variables were evaluated with chi-square tests. Receiver operating characteristic (ROC) curves were used to determine area under the curve for prediction of AKI. Statistical significance was defined as a p-value of <0.05.

### Results

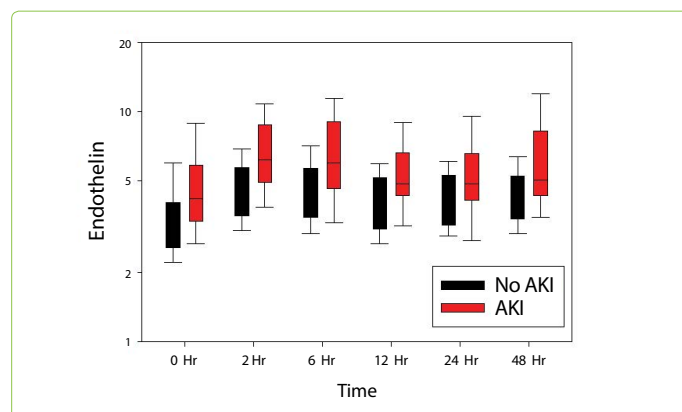
The Table 2 demonstrates characteristics of the 105 patients in the study cohort, separated by AKI. Twenty-nine (28%) patients developed AKI post-operatively. Patients who developed AKI had a trend towards a higher prevalence of chronic kidney disease, though this did not reach statistical significance (p=0.075). There was no difference between groups in preoperative creatinine (p=0.282), age (p=0.465), administration of nephrotoxic agents (IV contrast and/or medications) (p=0.274), or comorbidities of diabetes (p=0.663), hypertension (p=0.224), liver disease (p=0.544), or cancer (p=0.733).

Preoperative endothelin was found to be significantly elevated in patients who developed AKI versus those who did not develop AKI (p=0.016). The degree of elevation was predictive of development of AKI (AUC 0.653, 95% CI 0.541-0.766). An endothelin value of 2.79 had an 83% sensitivity and 65% specificity for predicting the development of AKI while an endothelin value of 4.625 had a 31% sensitivity and 80% specificity. Furthermore, endothelin was consistently and significantly elevated at most time points assessed in patients who developed AKI post-operatively (2-hour, 12-hour, 24-hour, and 48 hours, all p-values < 0.05) Figure 1. Endothelin peaked at 2 hours post-operatively in patients with AKI. The 2-hour post-operative endothelin level was also strongly predictive of developing AKI (AUC=0.660, CI=0.542-0.777) Figure 2.

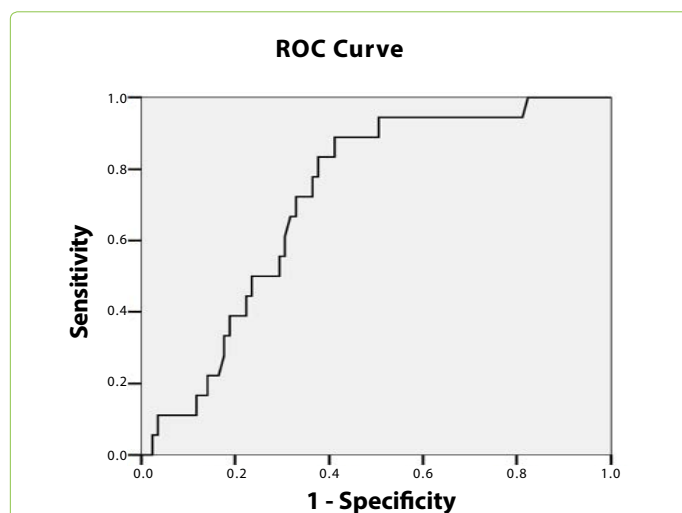
There was no correlation found between preoperative endothelin and creatinine (correlation coefficient 0.126, p=0.203), compared using Spearman’s correlation. ROC curve analysis was also performed using preoperative creatinine to predict AKI and had an AUC of 0.568 (95% CI = 0.428-0.708). There was no association between preoperative creatinine and AKI; p=0.282. Additionally, bivariate logistic regression was also performed comparing endothelin to history of chronic kidney disease. Endothelin was associated with chronic kidney disease (p= 0.026). However, as illustrated above, endothelin demonstrates a greater association with AKI than chronic kidney disease or creatinine.

### Discussion

Post-operative AKI is a common and serious complication after cardiac surgery, with an occurrence of up to 40% [1, 10-13]. Even small increases in serum creatinine following cardiac surgery are independently associated with increased mortality [14-16]. Creatinine, however, is an imperfect and often late indicator of renal function and dysfunction and may not change until there is a loss of up to 50% of glomerular filtration rate [17]. Before we can find ways to prevent and treat AKI, we must first find effective predictors of renal injury prior to surgery that rise early after the onset of surgery. Biomarkers are essential in identifying patients at risk for AKI so early preventative strategies can be instituted.



**Figure 1:** Endothelin in AKI vs. No AKI groups. Endothelin was significantly and consistently elevated in patients who developed AKI post-operatively (2-hour, 6-hour, 12-hour, 24-hour, and 48 hours, all p values < 0.05).



**Area Under the Curve**

Test Result Variable(s): ETO

Area	Std. Error <sup>a</sup>	Asymptotic sig. <sup>b</sup>	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.721	.056	.003	.611	.830

The test result variable(s): ETO has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.  
 a. Under the nonparametric assumption  
 b. Null hypothesis: true area = 0.5

**Figure 2:** ROC curve analysis showed post-operatively endothelin at 2 hours to have good predictive ability for developing AKI (AUC=0.738, CI=0.613-0.863, p=0.003).

**Table 1:** This table provides a summary of the clinical trials which investigated renal biomarkers and AKI after cardiac surgery.

Author, Publication Year	Population (n)	Biomarker(s) Being Evaluated	Observations
Haase-Fielitz A et al. [20]	adult cardiac surgical patients, n=100	Plasma & Serum CysC, plasma NGAL	Measurement of NGAL in patients post operation showed their likelihood of developing AKI after cardiac surgery. Together, NGAL and serum cystatin C were better than current biomarkers in predicting AKI.
Perry TE et al. [6]	patients after CABG, n=879	Plasma NGAL	Early increases of post-operative plasma NGAL is associated with AKI in adult patients undergoing CABG surgery. However, it has a low sensitivity. Thus, Plasma NGAL alone has a limited use in predicting AKI in this population.
Koyner JL et al. [27]	adults undergoing elective cardiac surgery for analysis, n=72	Urine NGAL	Combination of post-operative urinary CyC and NGAL are superior to existing biomarkers in the early diagnosis of AKI following cardiac surgery.
McIlroy DR et al. [28]	adult cardiac surgery patients, n=426	Urine NGAL	Post-operative urinary NGAL was elevated in all patients who developed AKI after cardiac surgery.
Tuladhar SM et al. [29]	subjects who underwent CPB, n=50	Urine NGAL	Post-operative urinary NGAL predicts subsequent renal injury.
Wagener G et al. [30]	adult cardiac surgical patients, n=426	Urine NGAL	Elevation of post-operative urinary NGAL has limited diagnostic accuracy in predicting AKI defined by change in serum creatinine after cardiac surgery.
Liang XL et al. [31]	subjects who underwent CPB, n=122	Urine KIM-1	Increased levels of post-operative urinary KIM-1 was associated with the AKI. When combined with IL-18, together they provided an early diagnosis and assessment of AKI after CPB.
Liangos O et al. [32]	patients undergoing cardiac surgery, n=103	Urine KIM-1	Post-operative urinary KIM-1 performed as an early biomarker for AKI after cardiac surgery.
Koyner JL et al. [33]	adults undergoing cardiac surgery, n=123	Urine KIM-1 & $\alpha$ -GST	The combination of preoperative KIM-1 and $\alpha$ -GST predicted the development of stage 1 and stage 3 post-operative AKI.

**Table 2:** Demographics in Subjects with AKI vs no AKI. No significant differences were found among the two groups in terms of the patients' age, gender, baseline creatinine, and/or co-morbidities.

	AKI (n=29)	No AKI (n=76)	p-value
Age	65.72±1.892	66.43±0.781	0.465
Male gender	28 (97%)	76 (100%)	0.276
Baseline creatinine (mg/dL)	1.04 (0.75-1.37)	1.02 (0.90-1.15)	0.282
History of hypertension	27 (93%)	62 (82%)	0.224
History of diabetes mellitus	11 (38%)	33 (43%)	0.663
History of liver disease	22 (76%)	65 (86%)	0.544
History of cancer	4 (14%)	8 (11%)	0.733
History of chronic kidney disease	7 (24%)	8 (11%)	0.075
Nephrotoxic medication administration	20 (69%)	43 (57%)	0.274

AKI: acute kidney injury

The role of endothelin as a mediator in the pathogenesis of acute renal failure has been extensively studied. Endothelin is an important modulator of renal function via its binding to abundant receptors in renal tissue and by the ability of renal endothelial and epithelial cells to synthesize and release endothelin. In the kidney, endothelin may function as a paracrine-autocrine factor in the regulation of renal blood flow, glomerular hemodynamics, and sodium and water homeostasis. More specifically, endothelin 1 and 3 are produced mainly in the vasa rectae and collecting ducts of the renal medulla. Endothelin receptors A and B are distributed throughout the kidney, with the A receptor dominant in the vascular compartment and B receptors prevalent in the renal tubules [18-19]. In the kidney, endothelin serves as a potent vasoconstrictor of cortical and medullary vessels, regulating glomerular filtration and renal hemodynamics. It also functions as a natriuretic peptide by inhibiting sodium and water reabsorption along the collecting duct.

Elevated levels of endothelin have been demonstrated in patients with renal injury. A recent study evaluated the role of endothelin in renal disease and noted that endothelin is linked to renal disorders characterized by increased renal vascular resistance such as acute ischemic renal failure [8, 20]. Another study noted that infusion of endothelin vasoconstricts the afferent and efferent glomerular arterioles, raises internal vascular resistance, reduces renal blood, and effectively decreases the glomerular filtration rate [19, 21]. These properties make endothelin a key modulator of AKI by contributing to renal ischemia. In fact, one study detailed that a rise in endothelin from 100 to 900 pmol/l was associated with a reduction in glomerular filtration rate by 90% [1]. As such, these studies have revealed that endothelin has the potential to serve as a biomarker for the early prediction of AKI. While previous studies have explored the role of endothelin as a marker of AKI, our study is unique in that we are the first to evaluate endothelin as an early predictor of

renal injury in patients undergoing cardiac surgery. Table 1 summarizes recent studies of biomarkers of renal injury in cardiac surgery patients. Our study is unique from prior studies in that a single preoperative sample predicts post-operative injury.

Other biomarkers including neutrophils gelatinase-associated lipocalin, kidney injury molecule-1, and N-acetyl- $\beta$ -D-glucosaminidase have been studied in patients undergoing cardiac surgery. A study evaluating the diagnostic utility these three biomarkers noted that a multi-marker panel of these biomarkers is needed to detect post-operative AKI after cardiac surgery [6]. However, our study reveals that endothelin as an individual biomarker can predict post-operative AKI after cardiac surgery and prior to the rise in serum creatinine.

To summarize, there were two major findings in this study. First, there were significant elevations of plasma endothelin levels in patients undergoing coronary artery bypass graft surgery who subsequently developed AKI. The data was far more significant than usual predictors of perioperative and postoperative AKI, including chronic kidney disease, diabetes and creatinine levels. Second and somewhat surprisingly, plasma endothelin increased early after surgery, as demonstrated by the 2-hour post-operative endothelin elevations, a finding seen in some of the renal tubule AKI markers such as kidney injury molecule-1 and N-acetyl- $\beta$ -D-glucosaminidase [17, 20].

Given that pre-operative endothelin levels are predictive of post-operative AKI and endothelin levels rise in response to what is probably tubular injury, endothelin can serve as an excellent biomarker monitoring, preventing, and potentially treating AKI itself. This may be especially true whether preoperative or postoperative use of endothelin antagonists could prove to be beneficial; however, these prospective studies have not yet been performed.

## Conclusions and Limitations

This is the first study to demonstrate elevations of endothelin levels in the preoperative cardiac surgery setting can predict AKI post-operatively. Further studies analyzing endothelin levels in patients may help us further understand the mechanisms of AKI and target strategies to prevent its occurrence. Endothelin maybe a useful biomarker in a variety of clinical settings in which patients are at risk for AKI.

This was a single center analysis of primarily male patients undergoing cardiac surgery at the VA San Diego Healthcare System. Therefore, generalizability is limited. Also, measurements of endothelin and creatinine were not all timed contemporaneously, limiting the ability to compare them directly. Of note, the number of subjects at each time point is inconsistent (i.e. each patient doesn't have data at each time point.) Thus, in our analysis of the association between AKI and endothelin, we only included those subjects that had complete data points across all time intervals. Lastly, the study would benefit from a larger sample size

and evaluation of long term renal outcomes: background research of the Article [22-26].

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