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# Early Blood Biomarkers Predict Organ Injury and Resource Utilization Following Complex Cardiac Surgery

**T Kim**[1], **G. J. Arnaoutakis**[1], **A. Bihorac**[2], **T. D. Martin**[1], **P. J. Hess Jr**[1], **C. T. Klodell**[1], **C. G. Tribble**[1], **A. A. Ejaz**[3], **L. L. Moldawer**[4], and **T. M. Beaver**[1]

[1]Department of Surgery, Division of Thoracic and Cardiovascular Surgery, University of Florida College of Medicine, Gainesville, FL

[2]Department of Anesthesiology, Division of Critical Care Medicine, University of Florida College of Medicine, Gainesville, FL

[3]Department of Medicine, Division of Nephrology, Hypertension, and Renal Transplantation, University of Florida College of Medicine, Gainesville, FL

[4]Department of Surgery, Laboratory of Inflammation Biology and Surgical Science, University of Florida College of Medicine, Gainesville, FL

## Abstract

**Background—**Patients undergoing complex cardiac surgery (thoracic aorta and valve) are at risk for organ failure and increased resource utilization. Neutrophil gelatinase-associated lipocalin (NGAL) has been found to be an early biomarker for renal injury. Multiplex cytokine immunoassays allow the evaluation of the early inflammatory response. We examined the relationship between early biomarker appearance (NGAL and multiplex cytokines) and organ injury and resource utilization.

**Materials and Methods—**NGAL and multiplex cytokine immunoassays were performed at baseline, 1, 6, and 24 hours following surgery on 38 patients undergoing thoracic aorta and valve operations. The mean age was 65 yrs with 26 males and 12 females. Acute kidney injury (AKIN definition), pulmonary failure (>24 hrs intubation), and intensive care unit and hospital stays were examined.

**Results—**One hour following complex cardiac surgery, the quartile of patients with the greatest IL-6 response had higher serum NGAL levels compared to the lowest quartile (347 vs. 145 ng/mL, p=0.002), and 70% of these patients progressed to clinical kidney injury. Six hours following surgery, the quartile of patients with the greatest IL-10 response had higher serum NGAL



Corresponding Author: Thomas M Beaver, MD, MPH, Associate Professor, Division of Thoracic and Cardiovascular Surgery, University of Florida College of Medicine, 1600 SW Archer Rd., PO Box 100286, Gainesville, FL 32610-0286, Office: 352-273-5503, Fax: 352-273-5513, beavetm@surgery.ufl.edu.

compared to the lowest quartile (271 vs. 160, p=0.04), more pulmonary failure (60% vs 10%, p=0.01), and longer ICU and hospital stays (p=0.001).

**Conclusions—**Patients with early elevated biomarkers of inflammation exhibited higher NGAL, more pulmonary failure, and greater resource utilization. Earlier identification of patients at risk for organ injury may allow for earlier intervention and reduce resource utilization.

### Keywords

cardiac surgery; thoracic aorta; aortic operation; valve operation; cardiopulmonary bypass; inflammatory mediator; biomarker; neutrophil gelatinase-associated lipocalin

## Introduction

Patients undergoing complex cardiac surgery are at risk for organ failure, including kidney injury. After cardiac surgery anywhere from 5% to 30% of patients can develop acute kidney injury (AKI), and 1–2% may require dialysis.[1,2] Of patients undergoing "high risk" aortic arch surgery, 8% percent of patients may need dialysis.[3] Operative mortality in patients with AKI requiring dialysis is as high as 64%.[1]

Multiple classification systems exist to stratify degrees of acute kidney injury. The acute kidney injury network (AKIN) criteria is now updated to include an acute (within 48 hours) increase in serum creatinine of more than or equal to 0.3mg/dl.[4] Outcomes have been shown to be worse with even the mildest degrees of acute kidney injury.[3]

Early detection of biomarkers may aid us in the timely diagnosis and management of organ injury. Neutrophil gelatinase-associated lipocalin (NGAL) has been reported to be a predictive early biomarker of AKI after cardiac surgery.[5] The inflammatory response to cardiopulmonary bypass (CPB) previously has been characterized with individual immunoassays demonstrating rises in the pro-inflammatory cytokines: tumor necrosis factor-α (TNF), interleukin (IL)-6, and IL-8.[6] A correlation between the magnitude of cytokine response and severity of myocardial injury has been demonstrated.[7] In lung transplant patients, it has been shown that the magnitude of the early inflammatory response is associated with the severity of lung injury following transplantation.[8] Multiplex cytokine assays now allow measurement of 22 biomarkers simultaneously.

This study is a descriptive analysis utilizing multiplex cytokine and serum NGAL assays to evaluate the relationship between early biomarker appearance and organ injury/resource utilization in patients undergoing high risk cardiovascular surgery.

## Materials and Methods

This was a descriptive, nonrandomized study of patients undergoing high risk (aorta and/or valve) cardiac surgery. Patients were recruited from a larger prospective, double blind, placebo-controlled, randomized clinical trial investigating the effect of brain natriuretic peptide on the incidence of dialysis or death at 21 days in adult patients undergoing high-risk cardiothoracic surgery (The Nesiritide Study).[9] The Nesiritide Study was approved by the Western Institutional Review Board and was registered at the National Institute of

Health's Clinical Trials.gov (NCT00110201) website. Included in this study were patients: 1. Older than 18 years of age; 2. Undergoing high-risk cardiovascular surgery, defined as thoracic aortic aneurysm and/or cardiac valve surgery; and 3. With an estimated glomerular filtration rate between 30–90ml/min/1.73m$^2$.[10,11] Patients with organ transplants, preoperative intra-aortic balloon pump, or acutely decompensated congestive heart failure were excluded from the study.

## Cardiopulmonary Bypass

Patients undergoing valve operations underwent aortic cannulation and either dual-stage venous cannulation via the right atrial appendage or bicaval cannulation of the superior and inferior vena cava. During cross-clamp, blood cardioplegia was administered (15ml/kg) antegrade and at 15–20 minutes via a retrograde catheter. The cardiopulmonary bypass circuit utilized centrifugal pumps (Medtronic Biomedicus, Minneapolis, MN), and the circuit tubing was not heparin-bonded. Cardiopulmonary bypass flows were targeted to maintain cardiac index >2.0 Liters/min/m$^2$. Patients undergoing arch aortic operations underwent circulatory arrest as previously described.[3]

## Laboratory and Clinical Data

Serum samples were taken at baseline and then after aortic cross-clamp release at 1, 6, and 24 hours. Samples were centrifuged, and the supernatants were stored at −80°C. NGAL and multiple inflammatory cytokines were quantified by enzyme-linked immunosorbent assay. Using multiplex technology, 22 biomarkers were measured: TNF-α, eotaxin, granulocyte macrophage colony stimulating factor (GM-CSF), interferon (IFN)-γ, IL-1a, IL-1b, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IP-10, IL-12p40, IL-12p70, IL-13, IL-15, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1a, and regulated on activation, normal T cell expressed and secreted (RANTES). Preoperative and operative variables recorded were age, sex, operation performed, cardiopulmonary bypass (CPB) time, duration of time spent with mean arterial pressure below 50 mmHg (MAP<50) while on bypass, aortic cross-clamp time, and circulatory arrest time. Baseline and postoperative daily levels of serum creatinine were also recorded. AKI was measured as defined by the acute kidney injury network (AKIN): either an acute rise (within 48 hours) in serum creatinine of greater than or equal to 0.3mg/dl or a 50% increase in serum creatinine over baseline within 7 days. Pulmonary failure (PF) was defined as ventilator dependence for greater than 24 hours postoperatively, according to the Society of Thoracic Surgeons Database. Intensive care unit length of stay (ICU LOS) and hospital length of stay were recorded. Post-crossclamp release biomarker levels were divided into quartiles, and outcomes of the highest quartile were compared to outcomes of the lowest quartile.

## Statistical Analyses

Data were analyzed using Statistica 8.0 (Statsoft Inc, Tulsa, OK). Categorical variables were reported as proportions. Continuous variables with normal distribution, such as operative times, were expressed as means with standard deviation. Nonparametric variables were reported as medians with interquartile ranges. Repeated measures of biomarkers across time were compared using Friedman analysis of variance. The Mann-Whitney U test was used to compare continuous variables between groups for non-paired data. Relationships between

variables were analyzed using logistic and linear regression, for categorical and continuous dependent variables, respectively. A double-sided p-value less than 0.05 was considered statistically significant for all tests.

## Results

The mean age was 65 years with 26 males and 12 females. Patient characteristics and intraoperative data are summarized in Table 1.

Among the biomarkers assayed, 14 of 22 had a statistically significant increase in the first 24 hours compared to baseline: eotaxin, IFN-γ, IL-1a, IL-1b, IL-6, IL-10, IL-12p40, IL-12p70, and IL-15 and the chemokines IL-8, IP-10, MCP-1, MIP-1a, and RANTES (Table 2). For 9 of these 14 elevated biomarkers (eotaxin, IFN-γ, IL-1a, IL-1b, IL-12p40, IL-12p70, IP-10, MCP-1, MIP-1a), serum levels were elevated through 6 hours but returned to baseline by 24 hours. Peak levels occurred at 1 hour in all but 2 biomarkers: IL-1a and IL-12p70, which peaked at 6 hours. Five elevated biomarkers (IL-6, IL-10, IL-15, and the chemokines IL-8 and RANTES) reached peak levels at 1 hour post-crossclamp release and remained elevated through 24 hours, compared to baseline. In particular, IL-6 and IL-10 levels were very significantly elevated ($p<0.001$) through 24 hours and, thus, were used for analysis of outcome variables, in accordance with previous reports.[8]

Patients in the highest IL-6 quartile one hour after crossclamp release had higher serum NGAL levels compared to patients in the lowest IL-6 quartile (347 vs 175 ng/mL, p=0.002); they had higher incidence of AKI by AKIN criteria (70% vs 50%, p=0.39), but this difference was not statistically significant. Patients in the highest IL-6 quartile also had significantly longer intensive care unit (ICU) length of stay (median 10 vs 4 days, p=0.03) and overall hospital length of stay (20 vs 7 days, p=0.03) (Table 3).

Patients in the highest IL-10 quartile six hours after crossclamp had higher serum NGAL compared to patients in the lowest IL-10 quartile (271 vs 160 ng/mL, p=0.04). These patients also had more pulmonary failure, defined as >24hrs time on ventilator (60% vs 10%, p=0.02), longer ICU stay (7 vs 4 days, p=0.04), and overall hospital stay (27 vs 7 days, p=0.001) (Table 4).

Univariate linear regression analyses were performed to identify statistically significant predictors of early biomarker (IL-6, IL-10, and NGAL) elevation, among operative factors such as cardiopulmonary bypass (CPB) time, aortic crossclamp time, deep hypothermic circulatory arrest (DHCA) time, and MAP<50mmHg time while on bypass. Shown in Table 5, predictors of elevated 1 hour IL-6 levels were crossclamp time (OR 1.41, 95% CI 1.01–1.96) and MAP<50mmHg time (OR 1.99, 95% CI 1.53–2.60). Predictors of elevated 1 hour NGAL levels were CPB time (OR 1.44, 95% CI 1.04–1.99) and MAP<50mmHg time (OR 1.52, 95% CI 1.09–2.12). When we controlled for all operative variables of interest, we found that MAP<50mmHg time was an independent predictor of both 1 hour IL-6 ($p<0.001$) and 1 hour NGAL ($p<0.01$) levels.

## Discussion

This descriptive study provides a comprehensive analysis of 22 multiplex cytokines and serum NGAL following high-risk cardiovascular surgery, whereas prior studies have examined cytokine profiles following more routine cardiac surgery. Recently, Castellheim et al. reported biomarker profiles using multiplex cytokine analysis comparing on-pump versus off-pump coronary artery bypass grafting, though they examined samples from induction of anesthesia to only 2 hours postoperatively.[12] In both their on and off pump groups 14 of 25 biomarkers analyzed had increased levels compared to baseline – eotaxin, TNF-α, IL-1Ra, IL-2R, IL-6, IL-8, IL-10, IP-10, IL-12, IL-15, monokine induced by IFN-γ (MIG), MCP-1, RANTES, and MIP-1β. In particular, serum levels of IL-6, IL-10, IL-15, MCP-1, and RANTES remained significantly elevated at the end of their 2 hour observation period – similar to findings in our study.

Our study also analyzed samples at later time points (6 and 24 hours postoperatively) and found the majority of cytokines had returned to baseline by 24 hours. However, 5 biomarkers showed early and sustained elevation: IL-6, IL-10, IL-15 and the chemokines IL-8 and RANTES.IL-6 is a generalized marker of inflammation with both proinflammatory and anti-inflammatory functions. IL-10 is a counterregulatory cytokine that inhibits the synthesis of proinflammatory cytokines. The cytokine IL-15 plays an important role in development and function of natural killer and $CD8^+$ T cells.[13] IL-8 is a chemokine responsible for neutrophil recruitment and activation.[8] RANTES is a chemoattractant for monocytes, T lymphocytes, and eosinophils.[14]

Prior data suggest an association between the magnitude of the early inflammatory response and organ dysfunction. Gessler et al. showed that plasma levels of IL-6 and IL-8 two hours after cardiopulmonary bypass correlated with cardiorespiratory dysfunction.[15] Wei et al. reported that plasma levels of IL-6, IL-8, and IL-10 at 5 minutes after crossclamp release correlated with myocardial injury, indicated by creatine kinase-MB levels at 6 hours.[7] We previously have found that elevated plasma levels of IL-6, IL-8, and IL-10 at 4 hours after reperfusion in lung transplantation correlated with progressive injury in the recipient allograft.[8] Thus, the early biomarker profile can identify patients more likely to progress to clinically apparent organ injury. In this study patients with a more severe inflammatory profile had prolonged ventilation and longer stay both in the ICU and also in the hospital.

AKI is currently diagnosed with serum creatinine levels which may be elevated 2 to 3 days after the injury has occurred. It would be ideal to identify patients at higher risk of developing AKI in real time to allow early intervention. We have shown that nesiritide may ameliorate AKI in the setting of cardiac surgery.[17] There are several potentially useful serum biomarkers for the early diagnosis of AKI including cystatin C, NGAL, and IL-18.[17] Larger prospective studies are still needed to confirm these findings.

Neutrophil gelatinase-associated lipocalin (NGAL) is a small secreted polypeptide, the product of a gene (LCN2) which was found to be markedly upregulated after kidney ischemia. Mishra et al. reported that both serum and urine NGAL at 2 hours after cardiopulmonary bypass correlated with AKI as defined by a 50% increase in serum

creatinine over baseline.[5] In our study, elevated serum NGAL was not predictive of AKI, by either RIFLE (50% increase in serum creatinine over baseline within 7 days)[3] or AKIN (creatinine rise greater than or equal to 0.3 mg/dL within 48 hours)[4] criteria, likely due to the small sample size and our inclusion criteria of "high-risk" cardiovascular surgery patients, the majority of whom had small elevations in serum creatinine.

Interestingly, in this study there was an association between serum NGAL and both IL-6 and IL-10 elevations (Tables 3 and 4). In the future, early assessment of elevations in the inflammatory profile may be an additional way to identify patients at risk for developing kidney injury, thereby allowing treatment in a timely manner.

The question arises as to what may be the inciting event for the elevated inflammatory profile that puts patients at risk for organ injury and increased resource utilization. Accordingly, in a post hoc analysis, perfusion records were reviewed to examine CPB, crossclamp, and DHCA times and relative hypoperfusion defined as total time spent with MAP<50 mmHg. We found MAP<50mmHg time to be a common predictor of both elevated NGAL and elevated IL-6 at one hour. This suggests that hypotension, despite presumed adequate cardiopulmonary bypass flows (maintaining cardiac index > 2.0), may be an inciting event for the early, elevated inflammatory profile. Gold et al. have shown a reduction in neurologic and cardiac morbidity when mean perfusion pressures were empirically maintained above 80mmhg.[18] This study appears to confirm that maintaining higher perfusion pressures during cardiopulmonary bypass is an adjunctive strategy to reduce organ injury and resource utilization.

## Limitations

This was a nonrandomized descriptive analysis. Due to its small sample size and retrospective nature, the study is limited by selection bias. The study does not represent the general or even cardiac surgical population, but rather a subset of patients undergoing "higher-risk" cardiovascular surgery. The small sample size also limits us from controlling for all potential variables which may influence early biomarker elevation and outcome. Furthermore, the increased kidney injury we saw in the highest IL-6 quartile was not statistically significant, likely due to the fact that the majority of these higher risk patients had small postoperative elevations in creatinine. However, despite its limitations, this study describes the baseline and postoperative biomarker profiles in "high-risk" cardiovascular surgery patients and provides further evidence that early inflammatory biomarker elevations are associated with risk for organ injury.

## Conclusion

Multiplex cytokine analysis and serum NGAL identified patients with early elevated biomarker profiles. Patients in the highest quartiles of IL-6 and IL-10 had higher NGAL, pulmonary failure, and greater resource utilization. Earlier identification of patients at risk for organ injury may allow for timely intervention and reduce resource utilization.

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## Abbreviations

| | |
|---|---|
| **AKI** | acute kidney injury |
| **AKIN** | acute kidney injury network |
| **CPB** | cardiopulmonary bypass |
| **CI** | confidence interval |
| **GM-CSF** | granulocyte macrophage colony stimulating factor |
| **ICU** | intensive care unit |
| **IFN** | interferon |
| **IL** | interleukin |
| **LOS** | length of stay |
| **MAP** | mean arterial pressure |
| **MCP** | monocyte chemoattractant protein |
| **MIP** | macrophage inflammatory protein |
| **OR** | odds ratio |
| **NGAL** | neutrophil gelatinase-associated lipocalin |
| **RANTES** | regulated on activation, normal T cell expressed and secreted |
| **RIFLE** | Risk, Injury, Failure, Loss, Endstage (classification for acute kidney injury) |
| **TNF** | tumor necrosis factor |

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## Table 1

Preoperative and Intraoperative Data

| Variable | |
|---|---|
| Age (years) | 65±12 |
| Male | 26 (68%) |
| CAD | 18 (47%) |
| COPD | 11 (29%) |
| Diabetes | 7 (18%) |
| HTN | 31 (82%) |
| Preoperative ejection fraction (%) | 58±22 |
| Redo sternotomy | 14 (37%) |
| Thoracic aorta operation | 17 (45%) |
| Valve operation | 7 (18%) |
| Combined aortic valve and thoracic aorta | 14 (37%) |
| CPB time (min) | 190±73 |
| MAP<50 time (min) | 109±59 |
| Aortic crossclamp time (min) | 110±59 |
| Intraoperative blood transfusions (Units) | 2.9±3.8 |

Continuous data are reported as means with standard deviation; categorical data as frequencies with percentages.

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; HTN = hypertension; CPB = cardiopulmonary bypass; MAP = mean arterial pressure

## Table 2

Elevated Biomarker Profiles Post-Crossclamp Release

| Biomarker | Baseline | 1 hour | 6 hours | 24 hours |
|---|---|---|---|---|
| Eotaxin | 29(21–34) | ***84(58–152) | **38(30–49) | 26(19–32) |
| IFN-γ | 61(25–114) | ***284(140–426) | ***216(149–420) | 70(57–118) |
| IL-1a | 378(228–880) | 542(381–782) | **589(453–937) | 502(349–728) |
| IL-1b | 24(14–46) | ***139(62–349) | ***77(49–189) | 37(22–95) |
| IL-6 | 21(10–33) | ***291(148–600) | ***276(197–423) | ***105(86–194) |
| IL-10 | 0.9(0.7–1.1) | ***317(203–546) | ***73(35–147) | ***2.4(1.5–4.3) |
| IL-12p40 | 282(209–392) | ***1110(869–2540) | ***923(695–1410) | 427(305–558) |
| IL-12p70 | 1.9(1.3–3.1) | ***4.1(1.7–72.9) | ***6.4(2.0–21.3) | 2.1(1.6–3.6) |
| IL-15 | 15(11–22) | ***30(19–41) | ***26(19–37) | **20(15–31) |
| IL-8 | 201(101–425) | ***1062(582–2310) | ***959(565–1670) | **470(230–1170) |
| IP-10 | 427(301–569) | ***3340(2430–11100) | ***1935(947–7270) | 350(227–540) |
| MCP-1 | 23(16–32) | ***109(61–193) | ***54(31–97) | 24(19–44) |
| MIP-1a | 115(72–197) | ***390(310–561) | ***267(195–377) | 132(101–196) |
| RANTES | 140(110–181) | ***16950(807–36000) | ***4300(680–3130) | *192(154–279) |

Values are reported as medians with interquartiles ranges, in pg/mL

* denotes p<0.05;

** denotes p<0.01;

*** denotes p<0.001

## Table 3

Kidney Injury & Resource Utilization for Hi vs Lo IL-6 Quartiles at 1 hour

| Variable | Total n=38 | $IL6^{Hi}$ n=10 | $IL6^{Lo}$ n=10 | p |
|---|---|---|---|---|
| 1hr NGAL (pg/mL) | 263±131 | 347±109 | 175±97 | <0.01 |
| AKIN | 20(52.6%) | 7(70%) | 5(50%) | 0.39 |
| Pulmonary failure | 16(42.1%) | 6(60%) | 3(30%) | 0.20 |
| Time on ventilator (hrs) | 20(16–120) | 83(18–360) | 20(17–26) | 0.36 |
| ICU LOS (days) | 5(4–13) | 10(5–30) | 4(3–5) | 0.03 |
| Hospital LOS (days) | 13(7–26) | 20(15–36) | 7(6–25) | 0.03 |

AKIN = acute kidney injury network criteria for AKI

ICU = intensive care unit

LOS = length of stay

## Table 4

Kidney Injury & Resource Utilization for Hi vs Lo IL-10 Quartiles at 6 hours

| Variable | Total n=38 | $IL10^{Hi}$ n=10 | $IL10^{Lo}$ n=10 | p |
|---|---|---|---|---|
| 6hr NGAL (pg/mL) | 233±142 | 271±120 | 160±101 | 0.04 |
| AKIN | 20(52.6%) | 5(50%) | 3(30%) | 0.39 |
| Pulmonary failure | 16(42.1%) | 6(60%) | 1(10%) | 0.02 |
| Time on ventilator (hrs) | 20(16–120) | 45(20–408) | 17(3–20) | <0.01 |
| ICU LOS (days) | 5(4–13) | 7(4–28) | 4(3–5) | 0.04 |
| Hospital LOS (days) | 13(7–26) | 27(10–70) | 7(6–9) | <0.01 |

AKIN = acute kidney injury network criteria for AKI

ICU = intensive care unit

LOS = length of stay

**Table 5**

Univariate Predictors of Elevated IL-6 and NGAL

| Dependent | Independent | OR | 95% CI | p |
|---|---|---|---|---|
| IL-6 at 1hr | MAP<50 | 1.99 | 1.53–2.60 | <0.01 |
| | CPB time | 1.34 | 0.96–1.87 | 0.08 |
| | Xclamp time | 1.41 | 1.01–1.96 | 0.04 |
| | DHCA time | 0.98 | 0.70–1.38 | 0.91 |
| NGAL at 1hr | MAP<50 | 1.52 | 1.09–2.12 | 0.02 |
| | CPB time | 1.44 | 1.04–1.99 | 0.03 |
| | Xclamp time | 1.23 | 0.87–1.74 | 0.23 |
| | DHCA time | 1.30 | 0.94–1.80 | 0.11 |