Intra-abdominal Hypertension and Postoperative Kidney Dysfunction in Cardiac Surgery Patients

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Objective: **To determine the incidence of intra-abdominal hypertension (IAH) in adult cardiac surgery patients and its association with postoperative kidney dysfunction.**

Design: **Prospective cohort study.**

Setting: **Single tertiary-care university hospital.**

Participants: **Forty-two adult patients having cardiac surgery with cardiopulmonary bypass.**

Interventions: **Intra-abdominal pressure (IAP) was measured preoperatively, immediately after surgery, and at the following time points after surgery: 3 hours, 6 hours, 12 hours, and 24 hours. Urine neutrophil gelatinase-associated lipocalin (NGAL) levels were measured as a marker of kidney dysfunction at the following time points: prior to surgery, immediately after surgery, 4 to 6 hours after surgery, and 16-to-18 hours after surgery.**

Measurements and Main Results: **Two hundred fifty-two IAPs were measured, and 90 (35.7%) showed IAH. Thirty-five of 42 patients (83.3%) had IAH at 1 time point or more. Peak urine NGAL levels were lower in patients with normal IAP (mean difference = –130.6 ng/mL [95% CI = –211.2 to –50.1], p = 0.002). There was no difference in postoperative kidney dysfunction by risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) criteria in patients with normal IAP (mean difference = –31.4% [95% CI = –48.0 to 6.3], p = 0.09). IAH was 100% sensitive for predicting postoperative kidney dysfunction by RIFLE criteria, but had poor specificity (54.8%).**

Conclusions: **IAH occurs frequently during the perioperative period in cardiac surgery patients and may be associated with postoperative kidney dysfunction.**

KEY WORDS: intra-abdominal hypertension, acute kidney injury, postoperative kidney dysfunction, complications, cardiac surgery, NGAL

INTRA-ABDOMINAL HYPERTENSION (IAH) increasingly has been recognized in critically ill patients and is associated with organ dysfunction, particularly acute kidney injury.[1,2] In 2004, the World Society of Abdominal Compartment Syndrome (WSACS) was formed and endorsed by both European and American critical care societies. WSACS standardized the definition for IAH as intra-abdominal pressure (IAP) $\geq$12 mmHg and described a standard method for measuring IAP via bladder pressure measurement.[3]

A number of observational studies have suggested that IAH is common in critically ill patients. In a study of 151 critically ill medical patients, IAH was present in 68%.[4] Risk factors for developing IAH included fluid resuscitation and capillary leak syndrome. Patients with IAH had a higher mortality rate than those without, 46% versus 32%. In a second study of 83 patients in a mixed medical-surgical intensive care unit (ICU), 66% of patients had IAH upon admission or during their ICU stay.[5] In this study, patients with IAH had higher mortality (53% *v* 27%), higher renal sequential organ failure assessment scores, and lower glomerular filtration gradients. In a third study, IAP >12 mmHg was shown to have a sensitivity of 91.3% and specificity of 67% for predicting acute renal failure.[6] One limitation of these studies was that they included patients with different diseases and potential causes of both IAH and acute kidney injury.

To date, there have been few investigations of IAH in cardiac surgery patients. Cardiac surgery patients are at increased risk for postoperative kidney dysfunction, with approximately 25% of patients having a glomerular filtration rate (GFR) that decreases by 25% or more after surgery.[7] IAH was found to occur in approximately 33% of adult cardiac surgery patients in Italy.[8] In this study, IAH was associated strongly with total fluid volume administered and acute kidney injury. A second study of 50 Australian patients showed that 46% of cardiac surgery patients developed IAH during their postoperative ICU stay.[9]

The goals of the current study were (1) to investigate the incidence of perioperative IAH in a relatively homogeneous patient population represented by a contemporary academic cardiac surgery practice, and (2) to investigate the association between IAH and postoperative kidney dysfunction, as quantified by peak urine neutrophil gelatinase-associated lipocalin (NGAL) levels after surgery and risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) criteria. The authors hypothesized that IAH would occur frequently in cardiac surgery patients and would be associated with higher levels of urinary NGAL after surgery, reflecting a higher degree of postoperative kidney dysfunction.

METHODS

Subjects

The institutional review board at the University of Maryland, Baltimore, approved the study. The target enrollment for the study was 50 subjects, based on the authors' sample size calculation. To

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detect a mean difference in peak urine NGAL of 100 ng/mL between patients with and without IAH (IAP <12 mmHg) and assuming a peak NGAL of 20 ng/mL in the control group, the authors calculated a necessary sample size of 50 subjects (25 in each group). This sample size calculation was made using 80% power, an alpha of 0.05, and an estimated population standard deviation for peak urine NGAL of 100 ng/mL. The NGAL values used in the sample size calculation were based on data from previous studies that showed urine NGAL levels of 20 ng/mL in healthy controls and levels in the mid-100s in patients with acute kidney injury.[10,11]

All patients were enrolled at a single tertiary-care center, and each subject gave written informed consent to participate in the study. Study inclusion criteria were age >18 years and having cardiac surgery with cardiopulmonary bypass (CPB). Study exclusion criteria were end-stage renal disease requiring dialysis, previous bladder or urinary tract surgery, and active urinary tract infection. All patients had surgery with non-pulsatile CPB with a goal to maintain mean arterial blood pressure >65 mmHg, and CPB flow set to maintain a cardiac index >2.2 L/min/m^2.

Patient Data

For all subjects, the authors collected the following demographic and clinical data: patient age, sex, body mass index, diabetes mellitus, hypertension, dyslipidemia, baseline plasma creatinine level, chronic lung disease, peripheral vascular disease, cerebrovascular disease, preoperative hemoglobin, left ventricular ejection fraction, surgery type, duration of CPB, and intravenous fluid and transfusion volumes administered during surgery and the first 24 hours after surgery.

Measurement of Intra-abdominal Pressure

IAP was measured using bladder pressures based on recommendations from the WSACS. Patients were in the supine position at the time of measurement and had a pressure transducer zeroed at the level of the bladder. High-pressure tubing attached to a port on the urinary catheter collection tubing. The tubing then was clamped 1-to-2 cm distal to this connection, and 25 mL of sterile saline were injected retrograde into the bladder slowly. Care was taken not to measure bladder pressure during a period of intra-abdominal straining, and measurements were taken at end-expiration. After 30 seconds, the bladder pressure was recorded. IAP was measured at the following time points: prior to surgery; immediately after surgery in the operating room; and 3, 6, 12, and 24 hours after surgery. Cardiac anesthesiologists and cardiac surgery ICU nurses were trained on proper technique in measuring bladder pressure to achieve consistent measurements. Individuals trained in proper technique performed all bladder pressure measurements during the study.

Patients were ventilated using volume-control intermittent mandatory ventilation in the operating room and using pressure-regulated volume control or synchronized intermittent mandatory ventilation postoperatively. Positive end-expiratory pressures (PEEP) ranged from 2 mmHg to 15 mmHg. The median PEEP value was 5 mmHg, and only 1 patient was ventilated with a PEEP >10 mmHg during the perioperative period.

Hemodynamic Data

In addition to measuring IAP, the following hemodynamic data were collected at the same time points: mean arterial blood pressure (MAP); central venous pressure; and pulmonary artery diastolic pressure. Renal perfusion pressure (RPP) was calculated as the difference between MAP and IAP.

Outcome Variables

The study's primary outcome variable was peak urine NGAL level during the first 24 hours after surgery. Secondary outcome variables were kidney dysfunction measures based on the RIFLE criteria using either urinary output or plasma creatinine level.[12] Patients were followed for 72 hours after surgery to determine whether they developed kidney dysfunction by RIFLE criteria.

Measurement of Urine NGAL Level

Urine specimens were collected from all subjects at the following time points: prior to surgery; immediately after surgery; 4-to-6 hours after surgery; and 16-to-18 hours after surgery. Urine specimens were centrifuged at 2,000g for 10 minutes to remove particulate matter. The supernatant then was frozen at –80°C in microtubes so that urinary NGAL levels could be measured simultaneously at a later date. Urine NGAL levels were measured using an NGAL enzyme-linked immunosorbent assay (ELISA) (Bioporto Diagnostics, Gentofte, Denmark). ELISA was performed according to the manufacturer's instructions. Microwells coated with monoclonal antibody against NGAL were mixed with urine samples and then washed. A second anti-NGAL antibody, labeled with biotin, then was added to the wells. The assay was developed with horseradish peroxidase-conjugated streptavidin followed by a color-forming substrate. An ELISA reader was used to read absorbances of the wells at 450 nm (reference wavelengths 650 or 620 nm). Urine NGAL concentrations were reported in ng/mL.

Statistical Analysis

All statistical analysis was performed using SAS 9.3 (SAS, Cary, NC) and p values < 0.05 were considered statistically significant. Patient characteristics were described for the cohort as a whole and after stratification by IAH. Continuous variables were examined using histograms, and normality was tested using the Shapiro-Wilk Test. Normally distributed variables were reported as mean $\pm$ standard deviation and non-normally distributed variables were reported as the median and interquartile range [Q1, Q3]. Categorical variables were described using the number and percentage of the total population with a particular characteristic. Normally distributed continuous variables were compared using Student's t-test, and non-normally distributed continuous variables were compared using the Wilcoxon rank sum test.