Is Calcium Score in the Abdominal Aorta or Renal Arteries Predictive of Acute Kidney Injury After Cardiopulmonary Bypass: An Exploratory Study

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Abstract

Introduction
Acute kidney injury (AKI) remains a serious complication after surgery with cardiopulmonary bypass (CPB). A relationship similar to the one between coronary artery calcification and increased incidence of cardiac complications is hypothesized to exist for aortic calcification and the development of AKI. Elevated pulse pressure (PP) hypertension has been shown to be a predictor of AKI-CPB (AKI after CPB surgery), and calcium deposition and stiffening of the body’s conduit arteries may be part of this process. We hypothesized that calcium scores obtained from non-contrast computed tomography (CT) scans of the infrarenal aorta and renal arteries would be independently and significantly associated with AKI-CPB.

Methods
We conducted a retrospective study of 65 subjects who underwent non-emergent open heart surgery with CPB in a tertiary healthcare center. AKI-CPB was diagnosed using the Acute Kidney Injury Network criteria. Aortic and renal artery calcium (Agatston) scores were obtained and entered into a multivariable logistic regression model alongside other significant predictors of AKI-CPB from a univariable analysis.

Results
Pulse pressure, body surface area, and pre-operative serum creatinine were significantly associated with the development of AKI-CPB, but the calcium scores were not. For PP, the odds ratio (OR) was 1.062, (95% Wald confidence interval {CI}=1.012 - 1.114). The OR for the calcium score in the aorta was 1.0000 (95% CI=1.0 - 1.0).

Conclusions
Agatston calcium scores in the renal arteries and infrarenal aorta were not independently associated with AKI-CPB, but arterial stiffening, as indicated by elevated pulse pressure, was predictive of AKI-CPB.

Categories: Anesthesiology, Cardiac/Thoracic/Vascular Surgery, Nephrology
Keywords: calcium score, cardiopulmonary bypass, hypertension, pulse pressure, acute kidney injury

Introduction
Acute kidney injury (AKI) remains a serious complication after surgery with cardiopulmonary bypass (AKI-CPB). By some estimates, it occurs in 20 to 70% of cases, with the exact incidence depending in part on the definition of AKI [1,2]. It is associated with increased morbidity, mortality, and healthcare costs [3,4]. Numerous predictors of AKI-CPB have been described, many of which are non-modifiable. One such predictor is elevated pulse pressure (PP) hypertension, which can be seen as a marker of arterial senescence and stiffening [5-8]. A positive correlation exists between calcification in the renal arteries, hypertension, and renal disease [9-11]. Oxygen delivery index (DO_2I) has also been shown to be independently associated with AKI in retrospective studies and in one prospective, randomized trial [12-16]. In this exploratory study, we hypothesized that calcium scores obtained from non-contrast-enhanced computed tomography scans of the aorta and renal arteries would be independently and significantly associated with AKI when analyzed alongside other predictors of AKI-CPB in a logistic regression model.

Materials And Methods
Between 2015 and 2019, our group developed a retrospective, observational dataset of patients undergoing coronary artery bypass grafting (CABG), valve, or CABG + valve open heart surgery with CPB in a tertiary...
healthcare center in the United States. Post-operative AKI-CPB was scored using the Acute Kidney Injury Network (AKIN) criteria [17]. CPB was performed using centrifugal arterial pumps, low-circuit priming volumes, and ultra-low prime oxygenators. DO$_2$I was calculated retrospectively based on arterial blood gas sample results, including arterial hemoglobin values and oxygen saturation, performed no less than every 30 minutes during CPB. DO$_2$I was derived for each 30-minute epoch between blood gases by using the formula for oxygen delivery: $(1.34 \times \text{Hgb} \times \text{SaO}_2) + 0.003 \times \text{PaO}_2$, where Hgb, SaO$_2$, and PaO$_2$ are in grams/dL, %, and mmHg, respectively, and pump flow is in L/min. We used the Mosteller formula to calculate BSA [18].

After obtaining approval from our Institutional Review Board (approval number 19-307), the medical records of the subjects in this dataset were examined for the presence of non-contrast abdominal computed tomography (CT) scans performed for any reason within the 12-month period preceding or following the subjects’ index cardiac surgery. Using CT scans performed post-surgery was considered acceptable, as calcium deposition and arterial aging is a slow process that, if significant, likely had begun well ahead of the surgery. This enabled the development of a larger sample. All retrieved scans were performed on a Toshiba Aquillion 64 Slice CT scanner (Canon Medical Systems USA Inc., Tustin, CA). The presence and extent of calcifications in the infrarenal abdominal aorta and the renal arteries were assessed utilizing an independent Aquarius workstation (TeraRecon, Durham, NC) and an Agatston score was calculated [19]. Calcifications were defined as regions of high density >130 Hounsfield Units (HU) and as areas of 3 or more contiguous pixels. The length of each renal artery was evaluated from the ostium to the renal hilum for the presence of calcification. The infrarenal abdominal aorta was evaluated from the renal ostium to the bifurcation.

**Statistical analysis**

Factors known to be predictive for AKI-CPB (dichotomous) were evaluated separately for their relationship with AKI-CPB using logistic regression. Pre-operative variables included age, history of congestive heart failure (CHF), history of myocardial infarction (MI), diabetes mellitus, beta-blocker (BB) use, serum creatinine, angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) use, BSA, and PP. Intra-operative independent variables in the univariable analysis were duration of CPB, inotrope use (epinephrine, dobutamine, or milrinone), and mean DO$_2$I. Calcium scores in the right and left renal arteries (CS-RRA and CS-LRA) and infrarenal aorta (CS-Aorta) were obtained as described above.

Odds ratios (OR), 95% confidence intervals (CI), and p-values were calculated to estimate the quantitative risk for the development of AKI-CPB. Only those parameters found to be significantly associated with AKI-CPB in the univariate analysis (p<0.05) were entered into a multivariable logistic regression model. A p-value of 0.05 was used (two-sided).

**Results**

Figure 1 shows a subject inclusion flowchart. Table 1 shows the baseline characteristics of the subjects in the final sample.
The medical records of 1064 cardiac surgical cases that took place from February 2013 to January 2015 and from January 2016 through December 2017 were reviewed for the existence of abdominal CT scans without contrast within a 12-month window before or after their index cardiac surgery.

999 ineligible for inclusion due to:
- No CT scans
- CT scans with contrast only
- Imaging not including the renal arteries

65 subjects included and calcium scores obtained

FIGURE 1: Sample Development Flowchart

| Preoperative Characteristics | Frequency | Percent of population |
|------------------------------|-----------|-----------------------|
| Age                          |           |                       |
| ≤50                          | 7         | 11                    |
| 51-60                        | 11        | 17                    |
| 61-70                        | 22        | 34                    |
| 71-80                        | 17        | 26                    |
| >80                          | 6         | 12                    |
| Gender                       |           |                       |
| Male                         | 34        | 52                    |
| Female                       | 31        | 48                    |
| BSA                          |           |                       |
| <1.50                        | 3         | 5                     |
| 1.50-2.00                    | 37        | 57                    |
| >2.00                        | 25        | 38                    |
| Medical History              |           |                       |
| Prior MI                     | 16        | 25                    |
| Diabetes mellitus            | 29        | 45                    |
| Hypertension                 | 58        | 86                    |
| Smoking                      | 43        | 66                    |
| Peripheral vascular disease  | 16        | 25                    |
TABLE 1: Preoperative Characteristics of the Study Subjects

BMI: body mass index (Mosteller formula); CKD: chronic kidney disease; MI: myocardial infarction; COPD: chronic obstructive pulmonary disease; CABG: coronary artery bypass graft; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker

Twenty-seven patients (41.5%) in the sample developed AKI-CPB stages 1-3 (Table 2). The mean DO₂I was 253 mL/min/m² (range, 115 - 420 mL/min/m²). In univariable analysis, pre-operative creatinine and BB use, BSA, PP, CS-Aorta, and DO₂I were significantly associated with the development of AKI-CPB. The odds ratio (OR) for CS-Aorta was 1.136 (95% confidence interval (CI): 1.022 - 1.262, p=0.0182). Age, history of congestive heart failure (CHF), diabetes mellitus, history of MI, pre-operative use of ACE-I or ARB, duration of CPB, and intraoperative inotropic agents were found not to be significantly associated with AKI-CPB. CS-LRA and CS-RRA were also not significantly associated with AKI-CPB. Table 3 summarizes the results of the univariable analysis.
### TABLE 2: Post-Operative Acute Kidney Injury Outcomes in the Study Sample

| Acute Kidney Injury Stage | Frequency | Percent |
|---------------------------|-----------|---------|
| 0                         | 38        | 58.5    |
| 1                         | 10        | 15      |
| 2                         | 5         | 8       |
| 3                         | 12        | 16.5    |

### TABLE 3: Results of the Univariable Analysis.

| Parameter                          | Odds Ratio | 95% Wald Confidence Limits | p-value |
|------------------------------------|------------|----------------------------|---------|
| Age                                | 1.038      | 0.994 - 1.084              | 0.0922  |
| History of CHF                     | 1.277      | 0.473 - 3.444              | 0.6293  |
| History of MI                      | 3.137      | 0.973 - 10.114             | 0.0556  |
| DM                                 | 1.277      | 0.473 - 3.444              | 0.6293  |
| Pre-operative BB use               | 3.286      | 1.146 - 9.338              | 0.0268  |
| Pre-operative serum creatinine     | 12.016     | 2.128 - 67.840             | 0.0049  |
| Pre-operative ACE/ARB use          | 3.577      | 0.445 - 4.125              | 0.3915  |
| BSA                                | 32.343     | 3.059 - 341.961            | 0.0039  |
| Pre-operative PP                   | 1.030      | 1.000 - 1.059              | 0.0244  |
| Duration of CPB                    | 1.006      | 0.994 - 1.019              | 0.3467  |
| Intra-operative inotropic use      | 1.058      | 0.999 - 1.019              | 0.9125  |
| CS-RRA                             | 1.280      | 0.959 - 1.707              | 0.0335  |
| CS-LRA                             | 1.004      | 0.999 - 1.009              | 0.8829  |
| CS-Aorta                           | 1.136      | 1.022 - 1.252              | 0.0182  |
| DO2 per 100 mmHg                   | 0.296      | 0.092 - 0.847              | 0.0402  |

The variables that were significantly associated with AKI-CPB were then entered into a multivariable model (Table 4). PP remained significantly associated with the development of AKI-CPB, but DO2 and the calcium scores did not (p > 0.05). For PP, the OR=1.062, (95% CI=1.012 - 1.114, p=0.0144). This would seem to indicate that for each mmHg rise in baseline PP, there was a 6.2% increase in the odds of the patient developing AKI-CPB. The other variables that were significantly predictive in the multivariable model were BSA and pre-operative creatinine.
TABLE 4: Results of the Multivariable Analysis

| Parameter                                | Odds Ratio | 95% Wald Confidence Limits | p-value |
|------------------------------------------|------------|---------------------------|---------|
| Pre-operative BB use                     | 2.189      | 0.431 - 11.110            | 0.3447  |
| BSA per 0.1 m²                           | 2.063      | 1.308 - 3.255             | 0.0018  |
| Pre-operative PP                         | 1.062      | 1.012 - 1.114             | 0.0144  |
| Pre-operative serum creatinine per 0.1 mg/dL | 1.503      | 1.110 - 2.035             | 0.0066  |
| CS-Aorta                                 | 1.000      | 1.000 - 1.000             | 0.2086  |
| DO²I                                     | 0.989      | 0.972 - 1.008             | 0.2166  |

BB: beta blocker; BSA: body surface area; PP: pulse pressure; CS-Aorta: calcium score in the abdominal aorta; DO²I: oxygen delivery index during CPB

Discussion

Our retrospective cohort study in cardiac surgical patients undergoing CABG, valve, or combined surgery with CPB found that calcium scores in the renal arteries or infrarenal aorta were not independently and significantly associated with the development of AKI-CPB, but PP, pre-operative creatinine, and BSA were associated with this outcome. This ran contrary to our initial hypothesis.

Arterial calcification has been shown to be more common in patients with CKD as demonstrated by the 1996 milestone paper by Braun et al. [20]. Subsequent studies have suggested an independent correlation between vascular calcification and renal function. A relationship similar to the one between coronary artery calcification and increased incidence of cardiac complications is hypothesized to exist for aortic calcification and the development of AKI [21]. The suspected mechanism involves arterial stiffening as a consequence of calcium deposition in the aorta, reducing the elastic compensatory reflex during times of hypoperfusion, essentially the same mechanism as the one associated with the existence of elevated PP [21]. This premise provided our rationale to study the aortic calcium score to determine if it might be an independent risk factor for AKI-CPB.

There could be several reasons why this study did not find an association between the calcium score and AKI-CPB. Our finding could be related to the small sample size and the fact that our outcome variable was AKI in the immediate post-operative period (five to seven days). The incidence of AKI or chronic renal disease later in life for the subjects in our sample is not known. Furthermore, we used the “raw” Agatston scores as predictors in this study, as opposed to a score of calcific aortic disease burden such as the one recently described by Reddy et al. [22]. This group derived a total score of abdominal aortic calcification (AASC) from sagittal CT reformats of the aorta distal to the inferior mesenteric artery (IMA) and showed it to have a high interrater agreement (interclass correlation), as well as a strong correlation with the corresponding CT calcium score. It would be interesting to examine whether this score is associated with AKI-CPB.

We used the calcium score in the infrarenal aorta because calcific deposits in the lower aorta occur earlier in life [23,24]. Furthermore, when calcific deposits are present in higher segments of the abdominal aorta, they are accompanied by extensive calcifications in the lower part of the aorta.

Our study appears to confirm the findings of other authors that PP is significantly and independently associated with the development of AKI-CPB. PP is a somewhat overlooked but well-substantiated independent risk factor for adverse renal outcomes such as AKI after surgery with CPB [5-7,25]. Elevated pulse pressure is reflective of the loss of arterial elastance in conduit arteries, and may be contributory to end-organ dysfunction (AKI, left ventricular hypertrophy, atherosclerosis, MI, CHF) [5,26-29]. DO²I did not reach statistical significance as a predictor of AKI-CPB, possibly due to the limitations of the sample size. However, other authors have shown it to be associated with AKI-CPB. Ranucci et al. demonstrated in a randomized clinical trial that maintaining DO²I at or above 280 mL/min/m² reduced AKI-CPB stage 1, but not stage 2 and 3, when defined according to the AKIN criteria [16]. Newland et al. were able to demonstrate in a sample of 19,410 CPB cases that a 10 mL/min/m² reduction in DO²I was associated with an average increase in the odds of AKI-CPB of 7% [15]. The DO²I threshold that showed optimal diagnostic accuracy for AKI-CPB in their sample was 270 mL/min/m².

Our study was not spared the shortcomings of small, retrospective studies. The sample size was limited by...
the availability of CT-scan data. Our cohort excluded emergency cardiac surgery and the use of an intra-aortic balloon pump. We did not evaluate the influence of pre-operative or intra-operative nadir hemoglobin, but assumed its effect on the odds of developing AKI-CPB to be mediated via DO₂J. The Ranucci et al. trial also found that erythrocyte transfusion in the ICU was independently associated with stage 1 AKI-CPB. Our sample did not include data on post-operative transfusion, and this was not evaluated. We did not possess data on pre-operative contrast load or inflammatory markers such as high-sensitivity C-reactive protein, and those were not taken into account in the analysis.

Conclusions
In a single-center retrospective study of cardiac surgical patients undergoing CABG, valve or combined surgery with CPB, PP, pre-operative creatinine, and BSA were significantly and independently associated with the development of AKI-CPB, while Agatston calcium scores in the renal arteries or infrarenal aorta were not.

Additional Information

Disclosures

**Human subjects:** Consent was obtained or waived by all participants in this study. Cooper University HealthCare Institutional Review Board (IRB) approved study with approval number 19-307. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

The authors wish to thank Madeline Bekier, Brian McEniry, Spencer Ng, Robert Rios and John Wallace for their assistance with data management.

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