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The Impact of Renal Artery Stenosis on Outcomes After Open-Heart Surgery

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Objectives The aim of this study was to assess the impact of atherosclerotic renal artery stenosis (ARAS) on outcomes after open-heart surgery (OHS).

Background Acute kidney injury after OHS portends significant morbidity and mortality.

Methods Data from all adult patients undergoing OHS from January 2000 to April 2010 who underwent renal duplex ultrasound were prospectively collected. ARAS was severe (60% to 99% stenosis) if peak systolic velocity was >200 cm/s. The associations between ARAS and post-operative reduction in glomerular filtration rate (GFR), need for renal replacement therapy, length of stay, and overall short-term and long-term mortality (up to 8 years) were tested using multivariate time-to-event adjusted analysis.

Results A total of 714 patients were evaluated, with a mean age of 67 ± 12 years (63% men) and a mean GFR of 52 ± 25.9 ml/min/1.73 m^2. A total of 206 (29%) had ARAS; of these, 79% (n = 163) had unilateral and 21% (n = 43) had bilateral ARAS. ARAS was associated with peripheral artery disease (p = 0.004) and lower high-density lipoprotein levels (p = 0.04). Patients with advanced age (p = 0.01) and descending aorta grafting (p = 0.004) had significant post-operative reductions in GFR. Adjusted models showed a nonsignificant trend between ARAS and reduction in GFR (p = 0.09). ARAS was not associated with need for renal replacement therapy (p = 0.4), longer length of stay (p = 0.7), or mortality (p = 0.7), but low pre-operative GFR was a strong predictor of long-term mortality.

Conclusions ARAS does not appear to be associated with post-operative change in GFR, need for hemodialysis, longer length of stay, or mortality in patients undergoing OHS. (J Am Coll Cardiol 2014;63:310–6) © 2014 by the American College of Cardiology Foundation

Acute kidney injury (AKI) after open-heart surgery (OHS) portends significant morbidity and mortality (1–3). Depending on the definitions used, post-operative AKI occurs in 3% to 30% of patients, and AKI requiring renal replacement therapy (RRT) develops in 1% to 5% of patients (1,2). The latter group has a mortality of 60% compared with an overall mortality of 2% to 8% after OHS (3). Patients with AKI have a 4-fold increased risk for short-term and long-term death. In fact, increases in serum creatinine have an exponential association with risk for 30-day mortality (<0.5 mg/dl from baseline associated with a 3-fold risk and >0.5 mg/dl increase associated with an 18-fold increased risk) (3). The underlying pathophysiology of AKI after cardiac surgery is renal ischemic injury due to a variety of factors, including intraoperative hypotension and complications that impair renal perfusion or lead to atheroembolic or thromboembolic events to the kidneys (2).

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Atherosclerotic renal artery stenosis (ARAS) is common and ranges in incidence from 25% to 38% in patients with established atherosclerotic vascular disease (4). However, the impact of ARAS on post-operative glomerular filtration rate (GFR) and clinical outcomes is unknown. We sought to study the impact of ARAS on post-operative change in GFR, AKI with need for RRT, length of stay, and overall short-term and long-term mortality.

Methods

Study population. Using the Cardiovascular Information Registry, we identified 37,000 consecutive patients age >18 years, undergoing first-time OHS from January 2000

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to April 2010. This registry contains detailed demographic, clinical, pathologic, operative, and outcome variables on all patients undergoing cardiac surgery at Cleveland Clinic, abstracted from clinical records concurrent with patient care. The Cardiovascular Information Registry follow-up information was supplemented using the Social Security Death Index for mortality data. This database was cross-referenced with a vascular ultrasound database to identify 714 patients who had undergone renal vascular ultrasound in the 90 days before or after OHS. We collected follow-up information at 30, 60, and 90 days and yearly. These registries are approved for use in research by the institutional review board.

Definitions. GFR was calculated using the Modification of Diet in Renal Disease study formula: GFR (ml/min/1.73 m^2) = 186.3 × serum creatinine (mg/dl) − 1.154 × age (years) − 0.203 (× 1.212 if black or × 0.742 if female) (5). Renal artery stenosis was defined using the renal ultrasound criteria measuring peak systolic velocity (PSV) and end-diastolic velocity and the renal/aortic resistive index (RAR). The renal ultrasound definitions used were 0% to 59% (PSV <200 cm/s and RAR <3.5), 60% to 99% (PSV ≥200 cm/s and RAR ≥3.5), >80% (PSV ≥200 cm/s, RAR ≥3.5, and end-diastolic volume >150 cm/s), and occluded (100%) in the absence of flow (6).

Endpoints. Primary endpoints included pre-discharge GFR and the degree of change in GFR over time. Secondary endpoints included in-hospital morbidy and mortality, length of stay, and long-term all-cause mortality.

Statistical analysis. Simple descriptive statistics were used to summarize the data. Continuous variables are presented as mean ± SD and as 15th, 50th (median), and 85th percentiles. Categorical data are described using frequencies and percents, and comparisons were made using Wilcoxon rank sum tests or chi-square tests. Transformations of scale were performed on continuous variables to meet statistical model assumptions, and the results of regression models are presented with their coefficients rather than odds or hazard ratios.

A number of variables examined in the multivariate analyses had missing values (ranging from 0% to 22%). A 5-fold Markov-chain Monte Carlo imputation technique was used to impute the missing values (7). Estimates of regression coefficients and their variance covariance obtained for each of the imputed datasets were then combined to yield the final regression estimates and p values using PROC MIANALYZE in SAS version 9.0 (SAS Institute Inc., Cary, North Carolina).

Factors associated with graded ARAS and need for RRT were identified using multivariate cumulative and binary logistic regression models using PROC LOGISTIC in SAS. Variables affecting length of stay were identified using multivariate linear regression using PROC REG in SAS. Temporal trend analysis and factors influencing change in pre-discharge GFR were analyzed using longitudinal regression model P-1 (PROC MIXED in SAS) (8).

Survival was assessed nonparametrically using the Kaplan-Meier method and parametrically using a multiphase hazard mode. Variable selection (with a p-value criterion for retention of variables in the model) used bootstrap bagging (bootstrap aggregation) (9,10). This was a 4-step process. First, a new dataset was created by randomly selecting patients with replacement from the original dataset. Second, risk factors were identified using an automated forward stepwise selection. Third, the results of the variable selection were stored. These 3 steps were repeated 1,000 times. Finally, the frequency of occurrence of variables related to group membership was ascertained and indicated the reliability of each variable (bootstrap aggregation step).

Abbreviations and Acronyms

AKI = acute kidney injury

ARAS = atherosclerotic renal artery stenosis

GFR = glomerular filtration rate

OHS = open-heart surgery

PSV = peak systolic velocity

RAR = renal/aortic resistive index

RFA = random forest analysis

RRT = renal replacement therapy

Random forest analysis (RFA). Random forest regression was performed as a confirmatory sensitivity analysis for the impact of renal artery stenosis on operative length of stay and need for dialysis in 714 patients using 1,000 trees. Using this machine learning tool, we were able to identify and depict the relationships of selected baseline variables with the binary (need for RRT) and continuous (length of stay) variables, as shown in Figure 1. The classification or regression tree method constructs a tree by recursive binary partitioning of the data into regions that are increasingly homogenous with respect to the binary or continuous response variables (10–12). The classification accuracy was improved by aggregating the results of many trees, each grown from a “bootstrap” dataset formed by random sampling of the data. We constructed 1,000 trees for random forest classification modeling and used 20 variables to split each node using the randomForest package in R (R Foundation for Statistical Computing, Vienna, Austria) (11). There were no pre-specified assumptions regarding variables, and randomization was introduced into this model by both random bootstrap sampling of patients from the original cohort and random sampling of variables for each tree branch. The random forest approach is preferable when it is necessary to depict a complex relationship (linear or nonlinear) between a predictor and an outcome variable. It is also used to identify the complex interaction effect (if any) among predictors and an outcome.

Power calculation. A power analysis was performed for the endpoint of need for dialysis on the basis of a sample size of 584 patients with 12% requiring dialysis using multivariate logistic regression. The calculated power of this logistic regression to detect a significant difference was >90%.

Results

Baseline characteristics. The demographic, pre-operative laboratory, and operative characteristics are listed in