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Title: Comparison of Risk of Atrial Fibrillation among Black versus White Patients Following Coronary Artery Bypass Grafting

Short Title: Obesity, race and atrial fibrillation

Jimmy T. Efird, PhD, MSc,a,b,c Preeti Gudimella, MD,a,b,d,e Wesley T. O’Neal, MD, MPH,f William F. Griffin, MD, MS,g Hope Landrine, PhD,h Linda C. Kindell, BSN, RN,a Stephen W. Davies, MD, MPH,b Daniel F. Sarpong, PhD,† Jason B. O’Neal, MD,† Patricia Crane, PhD, RN, FAHA, FNAP,c Margaret A. Nelson, PhD,c,e T. Bruce Ferguson, MD,† W. Randolph Chitwood, MD,a Alan P. Kypson, MD,a Ethan J. Anderson, PhD,b,d,e

aEast Carolina Heart Institute, Department of Cardiovascular Sciences, Brody School of Medicine, East Carolina University, Greenville, NC
bCenter for Health Disparities, Brody School of Medicine, East Carolina University, Greenville, NC
cCollege of Nursing, East Carolina University, Greenville, NC
dDepartment of Pharmacology and Toxicology, Brody School of Medicine, East Carolina University, Greenville, NC
eEast Carolina Diabetes and Obesity Institute, Divisions of Health Sciences and Research & Graduate Studies, East Carolina University, Greenville, NC
fDepartment of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC
gDepartment of Internal Medicine, Medical University of South Carolina, Charleston, SC
hDepartment of General Surgery, University of Virginia School of Medicine, Charlottesville, VA
†Center for Minority Health and Health Disparities Research and Education, Xavier University of Louisiana, New Orleans, LA
jDivision of Cardiothoracic Anesthesiology, Department of Anesthesia, Vanderbilt University Medical Center, Nashville, TN

Corresponding Author:
Jimmy T. Efird, PhD, MSc
Director, Center for Epidemiology and Outcomes Research
East Carolina Heart Institute
Brody School of Medicine, East Carolina University
115 Heart Drive
Greenville, NC 27834
Phone: +1.650.248.8282
Email: jimmy.efird@stanfordalumni.org
Abstract

Obesity has been identified as a risk factor for postoperative atrial fibrillation (POAF) following coronary artery bypass grafting (CABG). However, no studies have addressed the influence of race on this association. A total of 13,594 patients undergoing first-time, isolated CABG without preoperative atrial fibrillation between 1992 and 2011 were included in our study. The association between body mass index (BMI) and POAF was compared by race. Relative risk and 95% confidence intervals were computed using maximum likelihood log-binomial regression. Increasing levels of BMI were associated with higher POAF risk following CABG among black but not white patients (P\text{interaction}=0.0009).

Key Words: postoperative atrial fibrillation; coronary artery bypass grafting; obesity; race
**Introduction**

Postoperative atrial fibrillation (POAF) is a common complication following coronary artery bypass grafting (CABG), and obesity is a well-established risk factor for developing POAF.(1) However, no studies have addressed the differential influence of race on this association (Figure 1). Recently, increased body mass index (BMI) has been shown to be a stronger predictor for incident atrial fibrillation (AF) in blacks compared with whites in the general population.(2) To our knowledge, a similar finding has not been examined in patients undergoing CABG. This is important as black patients who develop POAF are at increased risk for mortality following CABG.(3) Identifying high risk groups for POAF will allow for the development of targeted interventions to reduce mortality, hospital readmissions, and total hospital costs among CABG patients.(4) Similar to the general nonsurgical obese population, we hypothesized that obese black patients undergoing CABG are at a higher risk for developing POAF.

**Methods**

This was a retrospective cohort study of patients undergoing first-time, isolated CABG at the East Carolina Heart Institute (ECHI) between 1992 and 2011. Patient demographics, prior medical history/comorbidities, preoperative medications and operative data were collected at the time of surgery. Patients with POAF were compared with those without POAF. Only black and white patients were included to minimize the potential for residual confounding (~1% other races). Racial identity was self-reported. The study and a waiver of participant consent for the period from 1992 to 2011 was approved by the Institutional Review Board at the Brody School of Medicine, East Carolina University (UMCIRB 12-002107).
Clinical variables were defined according to standard Society of Thoracic Surgeons (STS) protocol and documented by hospital notes, medication reports, outpatient medical records, radiology readings, and physician documentation.(5)

POAF denoted a first-time episode of AF (chaotic/irregular atrial rhythm with a variable rate and irregular ventricular rhythm) lasting longer than 1 hour following surgery and requiring treatment. Patients with a history of preoperative paroxysmal, persistent, or permanent AF/atrial flutter were excluded.

The World Health Organization (WHO) classification of BMI was used to group obesity into 3 classes.(6) Non-obese patients were designated as the reference group for statistical comparisons. Underweight patients have a known risk profile for adverse cardiac outcomes and mortality and were excluded from our analysis to minimize confounding bias (n=102).(7)

Data for this study were obtained from the STS Adult Cardiac Surgery Database and the electronic medical record (EMR) at the Brody School of Medicine. Cardiovascular surgery information at our facility was first reported to the STS in 1989 with routine data submission starting in 1992. An EMR was introduced at the Brody School of Medicine in 1997. Patient information and clinical data from 1989 to 1997 were retrospectively scanned into the EMR. The STS database is linked to the EMR through a unique patient medical record number. The National Death Index, using social security numbers, was used to validate operative mortality information in our EMR. However, in accordance with §205(r) of the Social Security Act, the use of social security numbers was proscribed within our university system at the end of 2011.

Categorical variables were expressed as frequency and percentage, whereas continuous variables were reported as median and interquartile range. Statistical significance (P<0.05) for categorical variables was computed using the Fisher’s exact test and the Deuchler-Wilcoxon
procedure for continuous variables. Trend across categories of obesity was computed using an exact Cochran-Armitage trend test.(8) An iterative expectation-maximization algorithm was used to account for missing BMI values (<0.01%; imputation efficiency >99.9%).(9)

Log-binomial regression was used to directly estimate relative risk (RR) and 95% confidence intervals (CI) for POAF.(10) Goodness-of-fit was assessed by examining Akaike’s Information Criteria and leverage/casewise diagnostic statistics, generalized to log-binomial regression.(11) P-values for the interaction between race and obesity level was computed using a likelihood ratio test by entering the appropriate cross-term into our regression models. All models achieved convergence and satisfied admissibility criteria (i.e., linear predictor constrained to be negative).(10)

The initial multivariable models included variables in our dataset that have been previously associated with POAF in the literature, regardless of their statistical significance in the current analysis (e.g., patient age, diabetes mellitus, heart failure, hypertension, obesity, peripheral artery disease, sex, and three-vessel coronary disease). Post-hoc inclusion of other prior medical history/comorbidities and preoperative medications into the model was performed in a pairwise fashion. P-values for point estimates were computed assuming asymptotic normality. Rounding was performed using the method of Holly and Whittemore.(12) SAS Version 9.4 (Cary, NC) was used for all analyses.

Results

A total of 13,594 patients were included in the study (48% age >65 years, 70% males, 17% blacks) (Table 1). A greater percentage of black patients were diabetic, hypertensive, and used angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARBs),
beta-blockers, diuretics, and lipid lowering agents as preoperative medications (P<0.0001). In contrast, a greater percentage of white patients were male and preoperatively used antiplatelet agents (P<0.0001). A decreasing trend of digitalis use and an increasing trend of ACEi/ARB and beta-blocker use with increasing obesity severity was observed for white (P_trend<0.0001) but not black patients (P_trend>0.05). Adjusting for age and sex in our total sample, POAF was significantly associated with obesity (P=0.0019) and white race (P<0.0001), which is consistent with previous research (not shown in tables).(1)

Approximately 91% of patients underwent cardiopulmonary bypass (Table 2). The median length of hospital stay following surgery was 5 days (IQR=3.0). Increasing severity of obesity was associated with an increasing percentage of patients with renal failure (P_trend=0.0022) and POAF (P_trend=0.0021) among black but not white patients (P_trend>0.5).

Similarly, the relative risk for POAF, adjusted for demographics and prior medical history/comorbidities, increased with obesity severity among black (P_trend<0.0001) but not white (P_trend=0.33) patients (P_interaction=0.0009) (Table 3). The adjusted interaction effect remained statistically significant when the analysis was further stratified by age group, a known risk factor for POAF (≤65 years: P_interaction=0.022; >65 years, P_interaction=0.013) (not shown in tables).

The pairwise addition of other variables listed in Table 1 did not substantively change our results. Adjusting for year period of surgery (<2000 vs. ≥2000) also had little effect.

Discussion

In both the general population and following cardiac surgery, blacks have a lower incidence of AF than whites, despite having more cardiovascular risk factors and increased incidence of stroke.(2, 13) However, in a recent population-based study of 5,685 community-
dwelling adults ≥65 years, increasing BMI was linearly associated with chronic/persistent AF risk among blacks but not whites (P_{interaction}=0.01), prompting the current stratified analysis by race.(2) While the association of obesity and POAF is well established in the CABG literature, our study, to our knowledge, is the first to examine and demonstrate a differential influence of race on this association.(1)

Obese patients, owing to their generally increased blood pressure levels, are believed to tolerate higher doses of certain medications known to be cardioprotective against AF with a side effect of hypotension (e.g., beta-blockers, renin-angiotensin-aldosterone-system inhibitors, and aldosterone antagonists).(14) However, their use in black patients is frequently questioned, especially among hypertensive and heart failure patients.(15) Thiazide diuretics or calcium channel blockers, for example, are the preferred first-line therapy for hypertension (HTN) among black patients compared with thiazide diuretics or beta-blockers among white patients.(16) Accordingly, POAF risk may be higher among black CABG patients because of their lower use of prophylactic AF medications.

Chronic, low-grade inflammation has been reported to play a role in the pathogenesis of obesity and its relationship to cardiovascular disease.(17, 18) Acute phase proteins (e.g., C-reactive protein (CRP)) and proinflammatory cytokines (e.g., IL-1, IL-6, TNF-α) are commonly increased in obesity.(17, 18) For example, obese individuals have greater plasma concentrations and more than ten times the amount of IL-6 in adipose tissue than their leaner counterparts.(18) The enlarged adipose tissue is a major site of inflammatory mediators and releases an abundance of proinflammatory cytokines and CRP into circulation.(17) Increased postoperative levels of IL-2, IL-6, IL-8 and CRP have been observed to be associated with AF among CABG patients.(19-21) In theory, obese blacks, who tend to manifest higher levels of serum IL-6 and CRP than
obese whites, may be more susceptible to POAF following CABG.(22) Future research efforts will benefit from the collection of inflammatory biomarkers associated with obesity and POAF.

Our results may be explained by factors not completely controlled for in our analysis. For example, the left ventricular septum is more hypertrophic in the black population, which is believed to represent cardiac remodeling related to HTN.(23) To minimize the potential confounding effect of this risk factor for POAF, we excluded patients with preoperative AF and adjusted our multivariable models for HTN. While this strategy was effective, some residual confounding may still exist given that preoperative HTN was recorded as a dichotomous variable.

In contrast, increased left atrial diameter, a known risk factor for AF, is more prevalent among the white population and also is associated with obesity.(23) Again, by excluding pre-operative AF, we likely reduced the predominance of patients with increased left atrial diameters. However, because left atrial diameter measurements were not routinely documented in the health records during the study period, we cannot rule out that some of these patients remained in our analysis. Nonetheless, such bias probably would have been towards the null given that increased left atrial diameter is less commonly associated with being black.

Additionally, increased levels of b-type natriuretic peptide (BNP), which has been shown to confer a significant risk for POAF, is associated with diastolic dysfunction and a subsequent enlarged left atrium, independent of signs or symptoms of cardiac dysfunction.(24, 25) We were unable to adjust our results for preoperative levels of BNP, which was only collected if a patient manifested fluid overload. However, our multivariable analysis was adjusted for unstable heart failure.
The increased risk of POAF observed among obese black patients could be attributed to an overall lower use of certain cardioprotective medications. In our data, there was a linearly increasing trend of ACEi/ARB and beta-blocker use with respect to obesity, but only among white patients (Table 1). Nonetheless, the pairwise post-hoc inclusion of preoperative medications into our multivariable model did not substantively change our results.

BMI has been criticized as being a less than ideal surrogate marker for body fat in coronary heart disease patients and lacking broad construct validity. Specifically, this measure fails to take into account fat mass/fat-free mass ratio, cardiorespiratory fitness, and body fat distribution. Categorization by BMI also may have contributed to internal validity bias. However, BMI was grouped according to the widely implemented WHO classification scheme. Furthermore, BMI is generally recommended as a practical approach for assessing body fat in the clinical setting and has been shown to be a better gauge of total body fat than body weight alone.

Newly identified genetic polymorphisms, such as rs10504554 (LY96) and rs2200733 (PITX2), have been associated with increased POAF risk. While such markers may be important to our findings, DNA was not collected in our study.

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Conflict of Interest

The authors of this manuscript have no conflict of interest to disclose.

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Figure 1 legend. Summary of the preoperative (Day-1) and intra/postoperative risk factors known to be associated with POAF. The schematic shown above highlights the major question addressed by the present study, namely the unknown interacting role of obesity and race (shown at left in blue text) as preoperative risk factors for POAF. The time-scale at top illustrates the increasing prevalence of POAF (red shading of arrow) that peaks within postoperative day +2 and +3 following surgery. In the boxes in red text are the intra-and postoperative variables that we and others have shown to play a role in determining whether a patient is likely to have sinus rhythm or POAF following heart surgery. ACEi=angiotensin converting enzyme inhibitors; AF=atrial fibrillation; CPB=cardiopulmonary bypass; CVD=cardiovascular disease; HF=heart failure; PAD=peripheral artery disease.