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Plasma Catecholamine Levels on the Morning of Surgery Predict Post-Operative Atrial Fibrillation

Ethan J. Anderson, PhD,[a,b] Jimmy T. Efird, PhD, MSc,[c,d,e,f] Andy C. Kiser, MD,[d] Patricia B. Crane, PhD, RN,[e] Wesley T. O'Neal, MD, MPH,[g] T. Bruce Ferguson, MD,[d] Hazaim Alwair, MD,[d] Kendal Carter,[c] J. Mark Williams, MD,[d] Anil K. Gehi, MD,[h] Alan P. Kypson, MD[i]

ABSTRACT

OBJECTIVES This study sought to determine whether plasma catecholamines and monoamine oxidase-B (MOA-B) are associated with post-operative atrial fibrillation (POAF) in patients undergoing elective cardiac surgery.

BACKGROUND Although intra- and post-operative adrenergic tone has been demonstrated to be an causative factor for POAF, the role and association of pre-operative plasma catecholamines remains unclear.

METHODS Prior to administration of anesthesia on the morning of surgery, blood samples were obtained from 324 patients undergoing nonemergent coronary artery bypass graft and/or aortic valve surgery with cardiopulmonary bypass at East Carolina Heart Institute. The concentrations of norepinephrine (NE), dopamine (DA), epinephrine (EPI), and enzyme MAO-B were assessed in platelet-rich plasma. A log-binomial regression model was used to determine the association between quartiles of these variables and POAF.

RESULTS Levels of NE ($p = 0.0006$) and EPI ($p = 0.047$) in the 4th quartile ($Q4^{+}_{NE}$) were positively associated with POAF, whereas DA ($p = 0.0034$) levels in the 4th quartile ($Q4^{+}_{DA}$) were inversely associated with POAF. Adjusting for age, heart failure (HF), and history of atrial fibrillation, the composite pre-operative (adrenergic) plasma marker ($Q4^{+}_{NE} \vee Q4^{-}_{DA}$) was associated with a 4-fold increased occurrence of POAF (adjusted $p = 0.0001$). No association between plasma MAO-B and POAF was observed.

CONCLUSIONS Our results suggest that pre-operative adrenergic tone is an important factor underlying POAF. This information provides evidence that assessment of plasma catecholamines may be a low-cost method that is easy to implement for predicting which patients are likely to develop POAF. More investigation in a multicentric setting is needed to validate our results. (J Am Coll Cardiol EP 2017;■:■–■) © 2017 by the American College of Cardiology Foundation.

Atrial fibrillation (AF) is a prevalent and costly complication of open-heart surgery (1). The benefits of patients remaining in sinus rhythm include lower hospital readmission rates, reduced length of stay, and fewer post-operative complications (e.g., stroke, myocardial infarction, heart failure, ventricular arrhythmias, and death) (2-6). Thus, there is a need for a convenient,

From the [a]Department of Pharmaceutical Sciences and Experimental Therapeutics, College of Pharmacy, Fraternal Order of Eagles Diabetes Research Center, University of Iowa, Iowa City, Iowa; [b]Department of Pharmacology and Toxicology, Brody School of Medicine, East Carolina University, Greenville, North Carolina; [c]Center for Epidemiology and Outcomes Research, East Carolina Heart Institute, Greenville, North Carolina; [d]Department of Cardiovascular Sciences, Brody School of Medicine, East Carolina University, Greenville, North Carolina; [e]Office of the Dean of Research, College of Nursing, East Carolina University, Greenville, North Carolina; [f]Center for Clinical Epidemiology and Biostatistics, School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, Australia; [g]Department of Medicine, Division of Cardiology, Emory University, Atlanta, Georgia; [h]Department of Medicine, Division of Cardiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and the [i]REX Cardiac Surgical Specialists, University of North Carolina Health Care, Raleigh, North Carolina. This study was supported by U.S. National Institutes of Health grant R01HL122863 to Drs. Anderson, Efird, and Kypson. Dr. Gehi is a speaker for St. Jude Medical and Biotronik. All the other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

ACEi = angiotensin converting enzyme inhibitor

AF = atrial fibrillation

ARB = angiotensin receptor blocker

CCB = calcium channel blocker

COPD = chronic obstructive pulmonary disease

DA = dopamine

ECG = electrocardiogram

ELISA = enzyme-linked immunosorbent assay

EPI = epinephrine

HF = heart failure

HTN = hypertension

ICU = intensive care unit

LOS = length of stay

MAO = monoamine oxidase

MI = myocardial infarction

MV E/A = ratio of early to late ventricular filling velocities across the mitral valve

NE = norepinephrine

PACU = peri-anesthesia care unit

POAF = post-operative atrial fibrillation

Q_4^+ = fourth quartile

Q_4^- = not fourth quartile

noninvasive, and cost-effective means for predicting which patients may develop post-operative atrial fibrillation (POAF). This is especially important during the pre-operative window when maximum benefit of pharmacologic therapy management of POAF can still be achieved.

Catecholamines are vital to cardiac electromechanical function owing to regulation of intracellular Ca^{2+} through β-adrenoceptor activation. Increased catecholamines are arrhythmogenic and have been reported to be key factors underlying POAF (2,7,8). Although anesthesia dampens the effect of catecholamines on the heart during surgery, a rebound effect is thought to occur following cardiopulmonary bypass, leading to a sympathetic surge that can propel the heart into AF (7,9,10). For this reason, contemporary post-operative standard of care includes use of β-blockers following cardiac surgery.

In the intra- and post-operative states, catecholamine overload, inflammatory cytokines, metabolic imbalance, and impaired cardiomyocyte energetics have been implicated as causal factors in POAF (8,11-13). Independent of their inotropic effects, catecholamines also are capable of generating substantial oxidative stress through their metabolism by monoamine oxidase (MAO) (14,15). In a previous study, we established that MAO activity in atrial tissue is associated with POAF in patients undergoing cardiac surgery (16). Because MAO is the principal enzyme responsible for catecholamine metabolism in the myocardium, we hypothesized that pre-operative plasma MAO isoform B (MAO-B), expressed in platelets and catecholamine levels (dopamine, epinephrine, norepinephrine), also would be associated with POAF.

METHODS

The study was approved by the Institutional Review Board of Brody School of Medicine at East Carolina University (UMCIRB09-0669). Study design followed STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for observational cohort studies (17).

PATIENT ENROLLMENT. A total of 324 consecutive patients undergoing on-pump elective (nonemergent, nonurgent) coronary artery bypass graft or aortic valve replacement surgeries between August 2014 and January 2016 at the East Carolina Heart Institute were included in the analysis. This cohort included patients who received routine concurrent procedures (such as coronary endarterectomy, internal cardiac defibrillation, femoral-femoral cardiopulmonary bypass, pacemaker insertion, pericardiectomy, repair or restoration of the heart or pericardium, or transmyocardial laser revascularization). Patients undergoing surgical or catheter maze procedures and those with pre-operative shock were excluded from the study. Participants gave written consent in person to 2 members of the research team experienced in hospital patient care. Basic demographics were recorded for patients who did not give consent.

BLOOD SAMPLE COLLECTION. Pre-operative blood samples were obtained prior to anesthesia through central intravenous lines placed upon arrival to the perianesthesia care unit (PACU) on the morning of surgery (to account for potential diurnal and nutritional variations in plasma catecholamine levels). Vacutainer tubes containing sodium citrate were used to collect the blood samples. The tubes were placed in a bag of ice and transported to the laboratory within 30 min. The samples were centrifuged for 10 min at 4,000 rpm. The plasma and buffy coat were transferred to another tube and centrifuged at 8,000 rpm for an additional 10 min. Two-thirds of the plasma volume was divided into 2-ml cryotube aliquots for storage. The other one-third of the plasma volume was mixed with the protein-rich pellet and transferred to a 2-ml cryotube. To prevent degradation, ethylenediaminetetraacetic acid was added to the protein-rich plasma. Samples were stored at −80°C.

DIAGNOSTIC CRITERIA FOR AF, POAF, HF, AND RENAL FAILURE. Atrial fibrillation was defined in accordance with American Heart Association/American College of Cardiology (AHA/ACC) 2014 AF Guidelines as any chaotic or irregular supraventricular rhythm that included the absence of a P wave before the QRS complex, a variable rate and rhythm in the atria, and may include an irregular ventricular rhythm (18). Atrial fibrillation was confirmed by 12-lead electrocardiography (ECG). Post-operatively, cardiac rhythm and rate were continuously monitored by ECG in the cardiac intensive care or step-down unit until hospital discharge. POAF was defined as any episode of AF confirmed by ECG lasting >5 min. Cases of POAF occurring after hospital discharge were not recorded in our database. Because some patients with a history of AF do not develop POAF, history of AF was considered an important prognostic variable for POAF in our analysis. Heart failure (HF) was similarly defined in accordance with AHA/ACC-2013 HF Guidelines as impaired left