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Defining the Links Between Oxidative Stress–Based Biomarkers and Postoperative Atrial Fibrillation

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Atrial fibrillation (AF) is the most common form of cardiac arrhythmia. In 2010, an estimated 2.7 to 6.1 million patients in the United States displayed AF.[1] The prevalence of AF continues to grow, with an estimated prevalence in the United States between 5.6 and 12 million cases by 2050.[1,2] Many epidemiological characteristics alter AF risk, with age being the most striking. In fact, sporadic AF affects ≈2.3% individuals over the age of 40, and greater than 10% of individuals over the age of 80 years.[3,4] Due to the high prevalence of AF, national healthcare costs associated with AF treatment are estimated at ≈$26 billion annually.[5] Despite this prevalence, the mechanisms of AF are not well understood and are a critical area for translational research.

AF is associated with a 1.5- to 1.9-fold increased mortality risk.[6] This increase is primarily due to thromboembolic events, particularly stroke.[6] Treatment of AF can be either pharmacologic or procedural. Pharmacologically, treatment is generally geared towards rate control as rhythm control has not been shown to improve outcomes.[7] Anticoagulation is also utilized in patients with AF to mitigate thromboembolic risk.[7] Procedurally, AF may be resolved with ablation of triggering sites, often near the pulmonary veins.[8] Unfortunately, this treatment may not be 100% successful in preventing AF and carries risk of complications including stroke, puncture of the heart, damage to the esophagus, diaphragmatic paralysis, and stenosis of the pulmonary veins.[8]

While AF commonly occurs in the absence of known triggers, it also arises as a postoperative complication in 30% to 50% of cardiac surgeries.[9] These postoperative arrhythmias may be transient and cause little morbidity, but in some cases may lead to lengthened hospital stays, increased healthcare costs, and thromboembolic events. In fact, postoperative AF (PoAF) has been shown to independently correlate with longer, more expensive hospital stays.[9] Additionally, patients with postoperative AF are more than twice as likely to suffer a stroke when compared to cardiac surgery patients who did not develop AF.[10] While most PoAF is self-limited, ≈3% continue to have persistent AF 6 weeks postsurgery.[11] Risk factors for the development of postoperative AF include age, structural heart disease, extracardiac comorbidities, and conditions relating to the surgery itself. The treatment for these arrhythmias is similar to that for other incidences of AF and includes antithrombotic and anti-arrhythmic therapy.

While the cause of postoperative AF is multifactorial, oxidative stress is thought to be a contributing factor. During cardiac surgery, reperfusion of the heart following ischemia leads to increases in oxidative stress, with NADPH oxidase being an important contributor.[12,13] This oxidative stress, along with other factors, may contribute to PoAF. Supporting this hypothesis, NADPH oxidase activity in the right atrium during cardiac surgery is a predictor of development of PoAF.[14] Furthermore, serum peroxide levels and atrial myocardial protein oxidation are elevated in patients who develop PoAF.[15] Modulation of the oxidative stress pathway may be a potential therapeutic strategy, as ascorbate reduces atrial effective refractory period in a canine model of AF, patients with the highest dietary antioxidant capacity display reduced incidence of PoAF, and antioxidant administration prior to surgery reduces incidence of PoAF.[16–18]

In this issue of the *Journal of the American Heart Association*, Wu et al measured levels of 3 highly sensitive and robust lipid oxidation markers in OPERA trial patients before, after, and during recovery from cardiac surgery to further investigate the link between oxidative stress and PoAF.[19] F_2-isoprostanes (F_2-isoP), isofurans (IsoF), and F_3-isoprostanes (F_3-isoP) are nonclassic eicosanoids formed by free radical oxidation of arachidonic acid or eicosapentaenoic acid, and reflect lipid oxidation in vivo. These markers

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were measured in the blood and urine at baseline, at the end of surgery, and at 2 days following cardiac surgery. Their relationship to PoAF incidence during hospitalization or for 10 days following surgery was analyzed. The study aimed to determine whether increased levels of oxidative stress markers can predict occurrence of PoAF. Importantly, Wu et al found that F_2-isoP and IsoF in the urine were 20% and 50% higher in those patients who developed PoAF, respectively. These important data add to the growing field of evidence that oxidative stress contributes the mechanism of PoAF development; however, there remain many unanswered questions due to the large number of variables associated with this specific pathophysiology. In the future, additional biomarkers may be utilized to expand the findings of this article to reflect other forms of cellular damage, as F_2-isoP and IsoF are markers only of lipid oxidation. Additionally, it will be interesting to consider the factors contributing to the small subset of patients who develop persistent AF following PoAF, as this article limited analysis of patients for 10 days postsurgery.

In summary, this new study utilizes reactive oxygen-based biomarkers that assess the link with PoAF with the goal of defining new diagnostic and therapeutic approaches. These markers may be used to identify patient with a high risk of developing PoAF, allowing more aggressive therapy. Additionally, this article supports the idea of new treatment strategies that target the oxidative stress mechanism of AF.

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Disclosures

None.

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