Post-operative Atrial Fibrillation and Oxidative Stress

A Novel Causal Mechanism or Another Biochemical Epiphenomenon?*

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Over the last decade there has been substantial progress in understanding the pathogenesis of atrial fibrillation (AF), primarily due to the recognition of the role of the pulmonary veins and their antral regions in the initiation and perpetuation of AF (1,2). Much work has focused on the electrophysiological (3,4), anatomical, and histological properties of the pulmonary veins (5); how they initiate and perpetuate AF; and also on the potential role of the left atrium in the perpetuation of AF (6–8). However, little is known about why and how pulmonary veins (and/or the left atrium) become arrhythmogenic in some patients and remain dormant in others. It also is not clear whether the pulmonary veins are electroanatomically different in patients with AF than in normal subjects. For example, in one study the effective refractory period within the pulmonary veins was found to be shorter in patients with than without AF (3), whereas in another study no significant difference was observed (4).

Isoproterenol, adenosine, acetylcholine, parasympathetic stimulation, and rapid atrial pacing have been used to promote AF both in vitro and in vivo. It is possible that neurohormonal activation, changes in parasympathetic/sympathetic tone, stretch, and proinflammatory cytokines facilitate AF, specifically in the presence of a genetic and/or acquired predisposition such as certain channelopathies; genetic polymorphisms; changes in gap junctions; and/or extracellular matrix with fibrosis, stretch, and left atrial dilatation, etc.

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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Post-operative AF may provide a model to better understand at least some of the mechanisms that promote AF. As widely reported, post-operative AF may develop in up to 65% of patients after cardiac surgery, usually within 2 to 5 days, and often resolves within several weeks. The majority of the patients who develop post-operative AF never experience AF again, suggesting that a set of reversible factors resulted in AF. A genetic and/or acquired electroanatomical abnormality of the atrium and/or pulmonary veins may not necessarily be sufficient for the development of recurrent AF in these patients. Moreover, such an electroanatomical predisposition may not even be necessary for the genesis of AF in these patients.

Increasing age, male gender, history of AF, left atrial dilatation, low left ventricular ejection fraction, hypertension, chronic obstructive pulmonary disease, and obesity have been identified as predictors of post-operative AF (9). The technique and complexity of cardiac surgery, and peri-operative treatment with beta-blockers or antiarrhythmic agents such as amiodarone or sotalol, have also been demonstrated to influence the probability of post-operative AF (10).

Catecholamines, inflammation, release of proinflammatory cytokines, and activation of tissue oxidases with an increase in oxidative stress have been implicated as potential mechanisms that facilitate post-operative AF. Prior in vitro studies have demonstrated that oxidative stress may lead to electroanatomical remodeling and increase the vulnerability to AF by decreasing atrial effective refractory period and by altering the extracellular matrix with progressive fibrosis (11,12). Steroids and statins have been shown to attenuate profibrillatory effects of oxidative stress.

A few clinical studies have demonstrated the beneficial effects of pre-treatment with corticosteroids and statins for the prevention of post-operative AF. A recent randomized study demonstrated that perioperative treatment with hydrocortisone in conjunction with metoprolol was associated with a significant decrease in post-operative AF (13). In another randomized study, pre-operative therapy with atorvastatin was associated with a 61% reduction in the risk of post-operative AF (14).

In this issue of the Journal, Kim et al. (15) report on the association between nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity in the human atrium and the development of AF after cardiac surgery. In this study, the authors measured basal and NADPH-stimulated superoxide production in the right atrial appendage samples obtained from 170 consecutive patients who underwent coronary artery bypass surgery. The authors also measured plasma markers of lipid and protein oxidation.

Patients who developed post-operative AF were found to have a significant increase in atrial NADPH oxidase activity. Although reperfusion during surgery was associated with an increase in plasma markers of lipid and protein oxidation, this increase was not associated with the devel-
Development of post-operative AF. On multivariate analysis, an increase in NADPH oxidase activity was identified as the strongest independent predictor of post-operative AF. Based on these observations, the authors propose that the atrial NADPH oxidase system may be a critical pathway in the development of post-operative AF. This report is a natural follow-up of a series of previous studies by the authors. They first demonstrated the presence of NADPH oxidase in human atrial myocytes, and then found increased levels of this oxidase system in patients with paroxysmal or chronic AF.

The premise of the study is that plasma markers of oxidative stress may not have sufficient specificity to accurately reflect changes that occur in the human atrium, particularly when robust activation of a number of oxidases may occur in the course of cardiac surgery. Therefore, the authors measured both plasma markers of oxidation and tissue oxidase activity. The study demonstrates that there is no association between myocardial oxidase activity and plasma markers of oxidation and also no association between the plasma markers and the probability of post-operative AF.

On multivariate analysis that included the variables of age, diabetes, post-operative therapy with beta-blockers, treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, or statins, and NADPH-stimulated superoxide levels, oxidase activity was the only independent predictor of AF.

The authors should be commended for meticulously conducting experiments in a large number of samples of human cardiac tissue. Demonstrating the role that atrial oxidases may play in the genesis of AF in the human heart with a large sample size and recognizing the need to study potential mechanisms at the tissue level rather than assessing systemic parameters are the major strengths of this important study.

However, the findings of this study are hypothesis-generating instead of conclusive and should be carefully interpreted. First, this study demonstrates an association between oxidase activity in the atrium and the development of post-operative AF. Causality is not demonstrated by these findings. It is possible that NADPH oxidase activity is one of the many biochemical changes that occur during the development of post-operative AF and is not the primary causal event. When complex interactions between the neurohormonal system, proinflammatory cytokines, and oxidative stress are considered, it may be quite difficult to dissect the primary biochemical abnormality. Nicotinamide adenine dinucleotide phosphate oxidase may simply be a surrogate for one or more of the complex changes that occur during and after cardiopulmonary bypass and cardiac surgery.

It should also be noted that left atrial size was not included in the multivariate analysis, due to the unavailability of these data. Although it did not appear to be an independent predictor, age was closely associated with an increase in oxidase activity and development of post-operative AF, raising the possibility that an increase in oxidase activity may be one of the mechanisms by which aging may facilitate AF.

Despite the descriptive nature of the findings, the study provides another piece of information in the quest to better understand mechanisms of AF and devise therapeutic strategies. These observations may not be limited to post-operative AF, but may also point to potential biochemical mediators that activate mechanisms involved in the genesis of other types of AF. These initial observations hopefully will prompt additional studies to further investigate the specific pathways involved in the initiation and perpetuation of AF.

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REFERENCES