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EDITORIAL COMMENT

Removing the Stress From Hypertension-Induced Atrial Fibrillation*

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The incidence of atrial fibrillation, the most common arrhythmia, is increasing as our population ages. Traditionally, systemic and cardiac disorders have been regarded as the causes of atrial fibrillation, leading to electrical and structural remodeling of the atria. In only 10% to 20% of cases, atrial fibrillation is primarily an electrical disorder and is not associated with underlying systemic and cardiac disorders such as hypertension. Yet, most of the pharmacological and ablative therapies currently used for atrial fibrillation, which are limited by the suboptimal efficacy, toxicities, and relatively high rates of recurrence, are targeting electrical activity within the heart rather than the upstream underlying pathophysiological processes. Despite remarkable progress, mechanistic insights into the signaling pathways that promote the substrate for the pathogenesis and maintenance of atrial fibrillation are still required.

Oxidative stress, an imbalance between the generation and neutralization of reactive oxygen species (ROS), is believed to be one mechanism through which atrial fibrillation is initiated and sustained (1). In the atrial appendages of patients with atrial fibrillation, compared with those patients in normal sinus rhythm, increased inflammation and oxidative injury were noted. The change in redox state leads to gene programming changes and activation of matrix metalloproteinases leading to activation of atrial myofibroblasts. Atrial myofibroblasts secrete extracellular matrix and, through the production of cytokines and chemokines, trigger an inflammatory response. Inflammatory cells produce ROS. Additionally, under hemodynamic stress, noninflammatory cells, including cardiomyocytes can produce ROS, typically through nicotinamide adenine dinucleotide phosphate oxidases or mitochondrial dysfunction. Increased ROS in cardiomyocytes alters electrophysiological properties of atrial ion channels, promoting arrhythmias.

Attenuating oxidative stress either by blocking the formation of ROS with antioxidants or blocking protein adduction with scavenger molecules has been tested as therapeutic approaches for atrial fibrillation. In general, ROS scavengers have not yielded protection against atrial fibrillation. Multiple antioxidants have been studied, including N′acetyl-cysteine, ascorbic acid (vitamin C), and tocopherol (vitamin E), as well as apocynin, which directly inhibits nicotinamide adenine dinucleotide phosphate oxidase. In a meta-analysis, antioxidant treatment reduced the risk of post-operative atrial fibrillation, although subanalysis showed that only N′acetyl-cysteine and ascorbic acid had a beneficial effect (2). The trials were small, and it is unclear whether it was a direct effect of the drug itself, especially because the oral availability of these drugs, specifically ascorbic acid, is low compared with that of intravenous administration. Perhaps suboptimal therapeutic targets have been studied and treatment of atrial fibrillation with more specific antioxidative therapies is possible.

When the redox state is unbalanced, polyunsaturated fatty acids can become oxidized to form highly reactive γ-ketoaldehydes (KAs), the most

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reactive of which are the isolevuglandins (IsoLGs). These highly reactive aldehydes adduct proteins essentially immediately, leading to protein misfolding and crosslinking and the formation of pre-amyloid oligomers in the atria. In the absence of normal protein homeostatic mechanisms to refold or recycle these misfolded proteins, proteotoxicity occurs, leading to downward spiral of cellular and cardiovascular health. During aging, proteotoxicity naturally occurs, and many proteins that are responsible for maintaining proteostasis are implicated in cellular aging. Both hypertension and atrial fibrillation are diseases more frequently observed in older individuals.

In humans with atrial fibrillation, pre-amyloid oligomers (precursors to amyloid deposition formed from protein adduction) have been found in the atria. Previously, the Murray laboratory demonstrated that rapid pacing of cultured atrial cells in vitro caused the generation of superoxide and cytosolic pre-amyloid oligomers, which were inhibited by salicylamine, a small molecule scavenger of γ-KAs, but not by the antioxidant curcumin, which is incapable of scavenging γ-KAs (3). They also found that formation of pre-amyloid oligomers in atria was independently associated with hypertension in patients undergoing elective cardiac surgery without a history of atrial arrhythmias, congestive heart failure, cardiomyopathy, or amyloidosis (4). These results offer a mechanistic link between a specific type of oxidative stress and atrial cell injury.

In this issue of *JACC: Basic to Translational Science*, Prinsen et al. (5) proposed the hypothesis that IsoLGs may be the final common pathway for atrial remodeling and atrial fibrillation in the setting of hypertension. To test this hypothesis, the Murray laboratory used a well-established model of hypertension in which mice were rendered hypertensive by minipump infusion of angiotensin II. Similar to humans with hypertension, the mice developed a diffuse accumulation of IsoLGs and pre-amyloid oligomers, occurring before the development of significant atrial structural abnormalities, which were absent in control animals and in mice treated with a scavenger of IsoLGs, 2-hydroxybenzylamine, starting 3 days prior to angiotensin II infusion. In hypertensive mice, the total amount of inducible atrial fibrillation was increased in the hypertensive mice, but decreased within 2 weeks of stopping angiotensin II, demonstrating reversibility of the process. Remarkably, cotreatment with 2-hydroxybenzylamine, compared with angiotensin II alone, significantly reduced the burden of atrial fibrillation. Using atrial HL-1 cells, they demonstrate that stretch caused a substantial increase in IsoLG adducts and pre-amyloid oligomers, which was attenuated by 2-hydroxybenzylamine. Finally, the Murray group demonstrates that the atrial oligomers may contain atrial/brain natriuretic peptides, which can induce cytotoxicity by reducing adenosine triphosphate production in atrial HL-1 cells. Taken together, the study fills in many gaps from the original in vitro studies, strongly supporting the concept that an increase in IsoLGs may initiate dysfunction within the atria leading to atrial fibrillation. Furthermore, the investigators propose that scavenging reactive downstream mediators of oxidative stress, namely IsoLGs, rather than targeting the generation of ROS may be a better therapeutic target to prevent atrial fibrillation. Given the dearth of new therapies for atrial fibrillation, the findings offer some hope that more precise targeting of this abnormally regulated pathway may yield a new therapeutic for at least some patients with atrial fibrillation.

Naturally, as in any study of this design, there are limitations. Is the relatively short burst of inducible atrial fibrillation in mice equivalent to atrial fibrillation in humans? Probably not, but it is a sign of an underlying propensity to develop an atrial arrhythmia. At minimum, the presence of IsoLGs and pre-amyloid oligomers correlate with hypertension in humans. In this 2-week study, the IsoLG scavenger was administered 3 days prior to initiating the induction of hypertension, which appears to be an unlikely treatment scenario in humans. The more likely timeline would be that a patient would have hypertension for years prior to developing structural abnormalities including atrial enlargement and fibrosis. Whether scavenging IsoLGs at a later stage of this multifactorial disease process will be beneficial cannot be assessed based on the current data. Yet, the findings certainly support additional studies in other animal models of atrial fibrillation.

What might be the downstream targets that cause a change in the susceptibility to develop atrial fibrillation in this hypertension animal model? Do IsoLGs affect the abundance, folding, and/or function of ion channels that modulate the cardiac action potential, and are these ion channels conserved in humans? It is likely that angiotensin II causes a multitude of changes in the atria, some dependent on and others independent of increased oxidative stress. It is conceivable that IsoLGs and pre-amyloid oligomers are necessary, but not sufficient, for the induction of atrial fibrillation. Sorting through these important

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details may take substantial time and effort, but the potential of developing a new pharmacological approach for the prevention and potentially treatment of atrial fibrillation should stimulate substantial interest from the electrophysiology community.

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