Published in final edited form as:

Heart. 2012 November ; 98(22): 1615–1616. doi:10.1136/heartjnl-2012-302328.

Antioxidant therapy for atrial fibrillation: lost in translation?

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Atrial fibrillation (AF) is the most common clinical arrhythmia, the incidence of which is rising. More than 15.9 million people in the USA will have AF by 2050.¹ Current therapies for AF, antiarrhythmic drugs and catheter ablation, have significant limitations. Most current antiarrhythmic drugs target one or a few of the cardiomyocyte ion channels. Current drugs have considerable proarrhythmic and non-cardiac adverse effects. In the treatment of AF, a lack of a significant difference in the outcome of a rhythm control strategy using current antiarrhythmic drugs and a rate control strategy points to the limited efficacy of these drugs. Catheter ablation is based on creation of scar tissue in the heart in order to prevent focal discharges from propagating, or to block the re-entrant circuits of AF. Ablation has somewhat debatable long-term success in management of AF. In addition, catheter ablation of AF is an expensive treatment that probably cannot meet the growing demand for AF therapy and is associated with significant complications. A major reason for the limited success with the aforementioned therapies may be the fact that neither antiarrhythmic drugs nor catheter ablation addresses the upstream underlying pathophysiologies of AF. Current antiarrhythmic drugs block target ion channels, while the ion channel abnormality is often downregulated as a result of upstream signalling events. Similarly, catheter ablation provides an anatomically fixed treatment for focal discharges and re-entry circuits, while the reasons for those abnormal electrical activities remain unaddressed, and while the location of the arrhythmic substrates can change over time.

The pathophysiology of AF is complex and is not completely understood, but many studies suggest oxidative stress as a mediator of AF. An elevated level of reactive oxygen species (ROS) has been linked with increasing age, heart failure, diabetes mellitus, coronary artery disease, obesity and alcohol intoxication; all conditions associated with AF.² In addition, clinical studies have shown an association between oxidative stress markers and AF.³ For example, MM-CK activity, which is a redox marker, is decreased, and immunodetectable 3-nitrotyrosine, a marker for the presence of peroxynitrite, is increased in the right atrial appendage of patients with AF compared with those in normal sinus rhythm.³ We have shown that derivatives of reactive oxidative metabolites and ratios of oxidised to reduced glutathione and cysteine are increased in the blood of patients with AF.⁴ Many pro-oxidant genes are overexpressed, and many antioxidant genes are downregulated in AF.⁵ Direct addition of oxidants to the heart supports a causal role for oxidative stress in AF.⁶

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Dr Dudley has applied for the following patents: (1) Method for Predicting Onset/Risk of Atrial Fibrillation, (2) Prevention of sudden death by modulation of Src family, (3) Modulating mitochondrial-reactive oxygen species to increase cardiac sodium channel current and mitigate sudden death, (4) Biomarkers for Prediction of Stroke Risk in Atrial Fibrillation, and (5) Mitochondrial antioxidants for prevention of sudden death by raising connexin43 levels.

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Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.

Several experimental studies have provided possible mechanisms for oxidative stress to cause AF. Oxidative stress increases the late Na^+ current and the L-type Ca^{2+} current. AF causes leak of Ca^{2+} from sarcoplasmic reticulum (SR), and decreases peak Na^+ current and sarcoplasmic/endoplasmic reticulum calcium uptake (SERCA)-mediated SR Ca^{2+} uptake.² In addition, ROS can decrease connexin43 and impairs gap junction function probably via activation of c-Src tyrosine kinase.⁷ In summary, there are a constellation of ion abnormalities, including abnormal intracellular Ca^{2+} handling, reduced repolarisation reserves, decreased peak sodium current, and weakened cardiomyocyte coupling. Moreover, ROS increases cardiac fibrosis by enhancing fibroblast proliferation and type I collagen gene expression,⁸ and fibrosis is a known cause of AF. Oxidative stress may also play a key role in pathogenesis of thromboembolism in AF by affecting all three elements of Virchow triads in causing thrombosis: stasis, endothelial injury and coagulopathy.²

Despite considerable evidence from clinical and experimental studies for a central role for ROS in many cardiovascular disorders including AF, clinical trials have not shown an impressive result with using general ROS scavengers.⁹ Those results may be because of the nature of ROS molecules possibly exerting their effects by quickly reacting with proteins and lipids before a general scavenger can neutralise them. Another issue is that oxidants can exist in multiple redox states and forms. For example, superoxides can easily convert to hydrogen peroxide, and hydrogen peroxide can convert to peroxynitrate and hydroxyl radical. A general scavenger can usually neutralise one or a few forms of ROS, but other forms of ROS remain to exert the arrhythmic effects of ROS.

A different therapeutic approach may be targeting the sources of excess ROS. Of the numerous cellular sources of ROS generation, mitochondria, the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and uncoupled nitric oxide synthase (NOS) are considered the major ROS production systems in the human heart. The major source of oxygen radical production in mitochondria is the electron transport chain. The NADPH oxidase is an enzyme that uses NADPH to reduce molecular oxygen and produces large amounts of superoxide radicals as its main product. The basic function of NOS is oxidising the terminal guanidine nitrogen atom of L-arginine by using electrons from NADPH to produce NO; however, uncoupled or dysfunctional NOS produce oxygen and nitrogen-reactive species. Those sources of cardiac ROS are inter-related, and often, the activation of one results in the activation of the others. For example, mitochondrial function differentially modulates NADPH oxidase expression and activity, and the Nox4 isoform of NADPH oxidase exists in mitochondria.¹⁰ In addition to cardiac cells, inflammatory cells, such as macrophages and polymorphonuclear cells that are recruited to the heart during AF, may be important sources of excess ROS causing arrhythmia.

Among all sources of ROS, mitochondria and NADPH oxidase seem the most attractive therapeutic targets for management of AF. NADPH oxidase activity has been shown to increase in AF.¹¹ The NADPH oxidase is upregulated in early stages of AF but not in chronic AF.¹² The NADPH oxidase is associated with development of postoperative AF.¹³ Therefore, inhibition of the NADPH oxidase could be an effective treatment for primary prevention of AF and for postoperative AF.¹⁴ A large portion of cardiomyocytes are occupied by mitochondria, and they are major sources of cardiac ROS. We tested the effect of seven different antioxidant therapies on prevention of ventricular arrhythmia in an angiotensin II activation mouse model with increased levels of ROS.¹⁵ ROS were highly compartmentalised in mitochondria, and only a mitochondria-targeted antioxidant prevented ventricular arrhythmias. While promising, whether this result can be applied to AF remains to be tested.

In designing an antioxidant agent that inhibits sources of ROS, a few factors should be considered. Different sources of ROS can be activated under different pathologic conditions and at different stages of AF; therefore, an antioxidant against a specific source of ROS may be effective in the prevention of AF only under certain conditions. In addition, because of positive feedback loops among the sources of cardiac ROS, the simultaneous targeting of several important sources of ROS may be required to decrease ROS level effectively. Moreover, normal amounts of ROS are required for various physiologic signalling cascades, and too much suppression of ROS should be avoided. Finally, oxidative stress refers to an imbalance between production and neutralisation, resulting in an excess amount of ROS, and activating natural antioxidant defence mechanisms of the cell is another potential therapeutic approach which could be exploited.

In summary, treatment of AF requires a search for new modalities targeting upstream pathologies, such as oxidative stress. Many experimental studies support a critical role for oxidative stress in the genesis of AF; however, clinical trials using general antioxidants have not shown the expected therapeutic result. A more effective antioxidant therapeutic approach may be targeting the sources of ROS. Among cardiac sources of ROS, mitochondria and NADPH oxidase seem to be promising therapeutic targets for the management of AF. Clinical studies using NADPH oxidase inhibitors and mitochondria-targeted antioxidants are required to evaluate this hypothesis.

Acknowledgments

Funding This work was funded by RO1 HL1024025, T32 HL072742, P01 HL058000, R01 HL106592, a VA MERIT grant, and an American Heart Association Midwest Affiliate Postdoctoral Fellowship # AHA10POST4450037.

References

1. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006; 114:119–25. [PubMed: 16818816]
2. Sovari, AA.; Dudley, SC. Atrial fibrillation and oxidative stress. In: Sauer, H.; Ajay, MS.; Laurindo, FR., editors. *Studies in Cardiovascular Disorders*. 1. Humana Press; 2010. p. 373–89.
3. Mihm MJ, Yu F, Carnes CA, et al. Impaired myofibrillar energetics and oxidative injury during human atrial fibrillation. *Circulation*. 2001; 104:174–80. [PubMed: 11447082]
4. Neuman RB, Bloom HL, Shukrullah I, et al. Oxidative stress markers are associated with persistent atrial fibrillation. *Clin Chem*. 2007; 53:1652–7. [PubMed: 17599958]
5. Kim YH, Lim DS, Lee JH, et al. Gene expression profiling of oxidative stress on atrial fibrillation in humans. *Exp Mol Med*. 2003; 35:336–49. [PubMed: 14646586]
6. Morita N, Sovari AA, Xie Y, et al. Increased susceptibility of aged hearts to ventricular fibrillation during oxidative stress. *Am J Physiol Heart Circ Physiol*. 2009; 297:H1594–605. [PubMed: 19767530]
7. Sovari AA, Iravanian S, Dolmatova E, et al. Inhibition of c-Src tyrosine kinase prevents angiotensin II-mediated connexin-43 remodeling and sudden cardiac death. *J Am Coll Cardiol*. 2011; 58:2332–9. [PubMed: 22093512]
8. Murrell GA, Francis MJ, Bromley L. Modulation of fibroblast proliferation by oxygen free radicals. *Biochem J*. 1990; 265:659–65. [PubMed: 2154966]
9. Sesso HD, Buring JE, Christen WG, et al. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *J Am Med Assoc*. 2008; 300:2123–33.
10. Dikalov S. Cross talk between mitochondria and NADPH oxidases. *Free Radic Biol Med*. 2011; 51:1289–301. [PubMed: 21777669]

11. Dudley SC Jr, Hoch NE, McCann LA, et al. Atrial fibrillation increases production of superoxide by the left atrium and left atrial appendage: role of the NADPH and xanthine oxidases. *Circulation*. 2005; 112:1266–73. [PubMed: 16129811]
12. Reilly SN, Jayaram R, Nahar K, et al. Atrial sources of reactive oxygen species vary with the duration and substrate of atrial fibrillation: implications for the antiarrhythmic effect of statins. *Circulation*. 2011; 124:1107–17. [PubMed: 21844076]
13. Kim YM, Kattach H, Ratnatunga C, et al. Association of atrial nicotinamide adenine dinucleotide phosphate oxidase activity with the development of atrial fibrillation after cardiac surgery. *J Am Coll Cardiol*. 2008; 51:68–74. [PubMed: 18174039]
14. Sovari AA, Morita N, Karagueuzian HS. Apocynin: a potent NADPH oxidase inhibitor for the management of atrial fibrillation. *Redox Rep*. 2008; 13:242–5. [PubMed: 19017463]
15. Sovari AA, Iravanian S, Mitchell D, et al. Mitochondria-Targeted antioxidant, Mito-TEMPO, prevents angiotensin II mediated connexin 43 remodeling and sudden cardiac death [abstract]. *J Investig Med*. 2011; 59:692–730. (P6).