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Editorial

What is the impact of endothelin receptor blockade on atrial remodeling in a hypertensive model?

Endothelin-1 (ET-1) is a potent vasoconstrictor, hypertrophic stimulant in cardiac muscle, and promoter of cardiac and renal fibrosis. Via activation of its G-protein coupled receptors encoded by EDNRA and EDNRB, endothelin-1 signaling is implicated in the etiology of pulmonary hypertension, hypertension, atrial fibrillation (AF) and heart failure (HF). In a study in my laboratory, we evaluated changes in endothelin-1 mRNA and protein levels in the left atria of patients with AF, mitral valve disease and HF [1]. These conditions were associated with increased expression of ET-1, CTGF, collagens and other pro-fibrotic genes. As our study was observational, we could only assess the association of ET-1 and its receptors with atrial substrate changes. In this issue, Bukowska and colleagues directly explore the transcriptomic and functional impact of blockade of ET-1 signaling using the ET-1 receptor antagonist macitentan on left atrial remodeling in the spontaneously hypertensive rat (SHR) model relative to normotensive control rats of the Wistar-Kiyoto (WKY) strain [2]. To determine if the effects of ET-1R blockade are due primarily to attenuation of hypertension, the authors compared the effects of macitentan (MAC) with those of the anti-hypertensive drug doxazosin (DOX, an α_1-adrenergic receptor blocker), with a primary focus of the effects of these drugs on atrial calcium handling and inflammatory signaling pathways. In an effort to mimic the rate effects of AF, the authors used rapid pacing of left atrial tissue slices to further evaluate the impact of these drugs on the atrial response to high rate activity.

This was a well designed, well powered and well executed study in a well studied animal model. Somewhat surprisingly, Bukowska and colleagues found that chronic (2 month) treatment with DOX reduced systemic blood pressure in the SHR rats, while MAC was ineffective. In untreated rats, pre-pro-endothelin-1 levels were increased 4.7-fold in SHR vs WKY rats, and angiotensin converting levels were increased 1.6-fold. The ET1AR mRNA levels were also increased in SHR vs WKY rat left atria; ET1BR levels were not assessed. Protein levels of ET-1 and A-II peptides were also increased. Treatment with MAC reduced levels of ET-1 peptide but not pre-pro-ET1 mRNA levels; neither drug impacted ET1AR mRNA or protein levels. In response to high frequency pacing (5 Hz vs 0.6 Hz), mRNA levels of pre-pro-ET-1 and ACE increased in both SHR and WKY left atrial tissue slices. MAC reduced attenuated the pacing induced increment in pre-pro-ET-1 levels to control levels in SHR rats, but DOX had no effect. Both MAC and DOX reduced pacing-increased ACE mRNA expression, close to that of unpaced left atrial tissues.

As inflammatory changes underlie the development of an atrial substrate for AF, the authors evaluated the impact of MAC and DOX on mRNA and protein expression of intracellular adhesion molecule 1 (ICAM-1) and interleukin 8 (IL-8); these molecules were upregulated in the SHR vs WKY rat atria. Both MAC and DOX attenuated the increase of ICAM-1 and IL-8 mRNA. Relative to WKY rats, SHR rats had increased phosphorylation of NF-κB, p38 and ERK1/2. In SHR atria, MAC but not DOX attenuated the increase in phospho-NF-κB; both drugs attenuated the increase in phospho-p38 and phospho-ERK1/2. The changes in these inflammatory signals affected by rapid pacing were similarly attenuated by both MAC and DOX. Inflammatory changes are often bi-directionally linked with oxidative stress. Here, the authors show that the arachidonic acid oxidation product isoprostane 8-$PGF_{2\alpha}$ was approximately twice as abundant in the SHR vs WKY atria, and effectively attenuated by both MAC and DOX treatment. NADPH oxidases 2 and 4 (NOX2, NOX4) contribute to the generation of oxidative stress in muscle and other tissues. Here, the authors show that NOX4 was significantly elevated, and there was a trend for increased NOX2; at the mRNA level, neither drug impacted these oxidant generating proteins. No functional studies were performed to specifically assess the sources of oxidant generation.

Atrial fibrotic changes are associated both with hypertension and AF, and are likely an important component of the substrate for persistent AF [3]. Here, the authors report that while hypertension in SHR rats promotes typical changes in pro-fibrotic mRNA expression TGF-β, collagens 1a and 3), neither MAC nor DOX attenuated the increase in mRNA abundance of these genes, or that of MYH7 or NPPB (which encodes brain natriuretic peptide, BNP). Fibro-fatty changes in the atria associated with obesity have been shown to contribute to an AF substrate. In an ovine model of overeating, it has been shown that endothelin-1 signaling likely contributes to the AF substrate [4], and that the relevant signaling is via the ET1BR. Here, the authors did not explore changes in ET1BR.

While fibrosis is likely critical for AF persistence, abnormal calcium cycling contributes to impaired contractility and ectopy that promotes AF initiation. Changes in calcium cycling reflect changes in the abundance and / or phosphorylation of key calcium handling genes. These include the alpha-subunit of the L-type calcium channel (encoded by CACNA1C), the calcium release channel (RYR2), the sarcoplasmic reticulum calcium ATPase (SERCA2a), phospholamban (PLB) and calcium-calmodulin dependent kinase II delta (CaMKIIδ). The authors report that, in a manner similar to that observed in AF, in the SHR atria the abundance of the α1C subunit of L-type Ca^{2+} channels and of RyR2 were reduced, and RYR2 phosphorylation at S2808 was increased. However, treatment with either MAC or DOX had no impact on the expression or phosphorylation of these proteins. One notable change was that SHR expression of CaMKIIδ was significantly reduced in both MAC and DOX treatment groups.

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This study reflects a significant effort to assess AF-related changes in the SHR rat model, potentially a useful model system for screening drugs beyond MAC and DOX. It would be of interest to monitor these animals beyond eight months, to an older age to see if the untreated animals develop spontaneous AF, and to assess whether treatments such as MAC or other candidate AF drugs can attenuate the development of a substrate for AF. The use of pacing to further stress the atria from this model was helpful, as the role of metabolic stress in AF is likely quite important, perhaps revealing the need for metabolic reserves that can help the atria to deal with the increased demand for energy in response to increased electrical activity and hemodynamic load. The authors note that mitochondrial ROS are a likely source in response to increased ET-1; studies that evaluate the impact of a mitochondrially-targeted antioxidant in parallel with MAC might also be of interest.

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