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EDITORIAL

Targeting atrial fibrillation promoting atrial structural remodeling: is this a viable strategy in patients with heart failure?

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Atrial fibrillation (AF) is the most common cardiac arrhythmia in adulthood, affecting millions of people worldwide (Andrade et al. 2014). Heart failure (HF) is also an epidemic cardiovascular disease that similarly exhibits an increase in prevalence. Most important, both AF and HF are disproportionately common in the elderly population. A growing body of epidemiological, clinical, and experimental data has demonstrated an interrelationship between AF and HF (Woods and Olgin 2014; Batul and Gopinathannair 2017). For example, AF is often an adverse prognostic outcome in HF patients, especially in the patients with mild-to-moderate left ventricular dysfunction. Conversely, HF per se increases the risk of AF (Lubitz et al. 2010). The prevalence of AF increases in HF with reduced ejection fraction (HFrEF) patients, from 10% in New York Heart Association (NYHA) class I to 50% in NYHA class IV patients (Batul and Gopinathannair 2017). AF and HF also share common risk factors such as hypertension, obesity, diabetes mellitus, and ischemic heart disease (Lubitz et al. 2010; Batul and Gopinathannair 2017). In addition, several pathological features coexist in both AF and HF, such as structural remodeling, neuro-hormonal imbalance, and increased level of inflammatory cytokines. However, besides being induced by AF itself, atrial fibrosis, a prominent feature of atrial structural remodeling (ASR) underlying AF development (Burstein and Nattel 2008), could be secondary to the enhanced wall stress, increased formation of inflammatory cytokines, and circulating neuro-hormonal factors seen in HF patient (Patel et al. 2017). Enhanced renin-angiotensin-aldosterone system axis in HF patients can promote atrial fibrosis (Batul and Gopinathannair 2017; Khan et al. 2017), which could act synergistically with oxidative stress and inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and transforming growth factor-β1 (TGFβ1) to promote ASR. Overall, the evolution of such very complex changes in atrial structure has made the treatment of AF in HF patients extremely challenging, with many patients being resistant to current AF treatment (Heijman et al. 2013). Although "upstream therapy" aiming to reverse the AF-maintaining substrate including ASR has been pursued for many years (Woods and Olgin 2014), the efficacy of such approaches for secondary prevention is rather low and it remains largely unknown, whether correcting or preventing the ASR-promoting factors is sufficient to prevent AF onset or reduce AF recurrence in HF patients (Nattel and Dobrev 2017).

In the current issue of *Naunyn-Schmiedeberg's Archives of Pharmacology*, Qiu and colleagues (Qiu et al. 2017) determined whether a novel compound, DL-3-n-butylphthalide (NBP), can prevent the development of AF in an established rat model of ischemic cardiomyopathy resembling the atrial phenotype of HF patients. The authors evaluated the impact of NBP on ASR in a left-anterior-descending-coronary-artery ligation induced myocardium infarction (MI) rat model. The results revealed that NBP treatment for 4 weeks reduced both the inducibility and the duration of inducible AF episodes in MI-induced HF versus control rats, which was associated with an improvement of ventricular function along with a reduction

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in both ventricular and atrial dilatation. The alleviated structural remodeling was accompanied with less interstitial fibrosis and normalized localization and expression of the gap junction protein connexin-43, which might further contribute to an improved electrical conduction and could help maintain sinus rhythm.

Since the molecular mechanisms underlying AF pathophysiology are multifactorial (Heijman et al. 2014; Nattel and Dobrev 2016), a potential anti-AF reagent that targets the ASR-promoting mechanisms by a multimodal action is expected to be more effective against AF in patients with structural heart disease (Heijman et al. 2016). Previous work has demonstrated that NBP can prevent stroke and can protect the heart against ischemic-reperfusion injury, by promoting anti-oxidant and anti-inflammatory effects (Wang et al. 2013, 2014, 2016). Consistently, the anti-AF actions of NBP in the present study were associated with profound effects on oxidative stress and inflammatory signaling (Qiu et al. 2017). There is ample evidence for involvement of oxidative stress in the pathophysiology of AF (Jalife 2016). Thus, it is not surprising that reducing oxidative stress via elevating the nuclear factor erythroid 2-related factor 2/heme oxygenase-1 signaling and increasing the level of anti-oxidants such as catalase and superoxide dismutase with NBP should exert beneficial cardiac effects (Qiu et al. 2017). NBP could prevent atrial fibrosis or prevent oxidation-mediated posttranslational modifications of ion-channel and calcium-handling proteins. While inflammation and particularly inflammatory cytokines such as TNF-α and TGFβ1 clearly facilitate ASR by promoting atrial fibrosis (Jalife 2016), emerging evidence point also to a critical involvement of inflammatory signaling in the evolution of electrical remodeling which accompanies atrial arrhythmogenesis during AF. Specifically, recent work from our group revealed that the activation of a canonical inflammatory signaling pathway called inflammasome is sufficient to promote both atrial electrical and atrial structural remodeling (Yao et al. 2016). NBP's ability to directly or indirectly reduce the levels of the inflammatory signaling mediators such as TNF-α, TGFβ1, and nuclear factor-kappa B (Qiu et al. 2017) suggests that anti-inflammatory efficacy could be a key feature for the development of future anti-AF approaches that properly target the AF-maintaining atrial structural substrate.

The work of Qiu et al. (2017) raises many questions. It remains unclear whether the amelioration on AF inducibility by NBP is a primary action in atria or a secondary effect following an improved left ventricular function, which deems further investigation. In addition, the different types of HF, for instance, pressure overload-induced HF versus ischemic HF or HFrEF versus heart failure with preserved ejection fraction (HFpEF) (Patel et al. 2017), are likely to produce different cellular and molecular signatures in atria. Therefore, whether the different types of HF respond similarly to NBP treatment remains to be determined in subsequent studies. Regardless of these limitations, it is very encouraging to establish that a compound can reverse structural remodeling in both atria and ventricles of a HF animal model and ultimately prevent AF development. Thus, such drugs might provide a lead structure for the development of novel anti-AF approaches, which target inflammatory and oxidative signaling pathways that critically contribute to the AF-promoting substrate, particularly in the context of HF.

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