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EDITORIAL

Chronic kidney disease-induced atrial structural remodeling and atrial fibrillation: more studies on the pathological mechanism are encouraged

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Dear Editor,

It is well known that chronic kidney diseases (CKD) increase the prevalence of atrial fibrillation (AF). Epidemiologic studies suggest CKD induce two- to threefold likelihood of AF, especially the end-stage renal disease (Soliman et al., 2010; Liao et al., 2015), yet the underlying mechanisms of AF pathogenesis in the case of CKD still remain unclear. As CKD is always accompanied with other risk factors of AF, such as hypertension, electrolyte disturbance, heart failure, and atrial enlargement, and complex pathological factors, such as inflammation, renin-angiotensin-aldosterone system (RAAS) activation and autonomic nervous system dysfunction, and the occurrence and development of atrial fibrillation, are considered multifactorial (McManus et al., 2012).

RAAS, transforming growth factor β1 (TGF-β1), and oxidative stress play important roles in atrial structural remodeling and in the development of AF (Everett 4th & Olgin, 2007). RAAS can induce the activation of TGF-β1/Smads pathway, and the latter can further induce ROS and oxidative stress in various disease situations (Everett 4th & Olgin, 2007). Recent studies emphasize the important role of oxidative stress in the genesis of AF in the setting of CKD. A study by Fukunaga et al. successfully investigated the role of oxidative stress which mediated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in the genesis of in the setting of 4 weeks post-5/6 nephrectomy rats, and demonstrated the antioxidant agent, sodium zinc dihydrolipoylhistidinate, is effective in reducing atrial oxidative stress, fibrosis, and AF inducibility (Fukunaga et al., 2012). In the similar animal setting, Aoki et al. reported that renal dysfunction-induced uremic toxin indoxyl sulfate is also associated with increased oxidative stress, inflammation, profibrotic factors, and AF (Aoki et al., 2015). However, the role of TGF-β1/Smads pathway in CKD-induced AF is still not fully understood, and further research is needed.

Though it is likely that oxidative stress mediated by NADPH oxidase plays a role in AF genesis, it is still inadequate to explain the whole pathological mechanism of AF in CKD. NADPH oxidase activity which is regulated by Rac1 is critical to the generation of oxidative stress (Adam et al., 2010; Satoh et al., 2006). Previous studies indicated that Ang II increases the protein expression of connective tissue growth factor (CTGF) via the activation of Rac1, resulting in the abnormal gap junction remodeling evidenced by the up-regulation of N-cadherin and connexin43 (Cx43) (Adam et al., 2010). However, it is unknown whether gap junction would be affected by CKD. Since gap junction remodeling is highly associated with AF, any alterations in atrial Cx43 expression, phosphorylation, and distribution are considered proarrhythmogenic by affecting cell-to-cell electrical coupling, which will help solve a part of puzzles pointing to CKD-induced atrial remodeling and AF.

Calcium-handling abnormalities are known to play an important role in the pathophysiology of AF. Many pathological states are contributed to atrial Ca2+ overload and spontaneous Ca2+ leakage, leading to the delayed after depolarizations, triggered activity, re-entry, and atrial remodeling (Heijman et al., 2015). Recent studies reported that calcium-handling

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abnormalities are involved in uremic toxin indoxyl sulfate (IS)-induced AF. Chen et al. showed that treatment with IS increased pulmonary vein (PV) delayed after depolarizations and burst firings, reduced the sinoatrial node (SAN) spontaneous beating rate, and shortened the action potentials (AP) of isolated rabbit left atrium (LA). Similarly, after treatment with IS, the PV cardiomyocytes had a larger calcium transient, sarcoplasmic reticulum calcium content, and calcium leak. However, using antioxidant ascorbic acid attenuated the effects of IS on the LA, PV, and SANs (Chen et al., 2015). Besides, Huang et al. demonstrated that rabbits with CKD, induced by intraperitoneal injection of a mixture of neomycin sulfate and cefazolin for 4 weeks, developed PV arrhythmogenesis with an enhanced calcium-handling abnormalities—a larger calcium transient amplitudes, calcium contents in sarcoplasmic reticulum, and a denser current of sodium/calcium exchanger and late sodium currents, but smaller L-type calcium current densities were found in PV cardiomyocytes—via protein kinase A and ROS (Huang et al., 2017). Indeed, oxidative stress can induce calcium-handling abnormalities, leading to the pathogenesis of AF. However, there are no specific studies investigating the role of calcium-handling abnormalities in CKD-induced AF in a point of mechanism to date.

What is more, recent studies indicated that the nucleotide-binding domain leucine-rich repeat-containing receptor (NLR) pyrin domain-containing protein 3 (NLRP3) inflammasome also plays a role in the genesis of atrial fibrosis (Li et al., 2017), and CKD participates in organ NLRP3 activation (Gong et al., 2016; Chin et al., 2017). NLRP3 inflammasome, a multiprotein complex, mediates the maturation of caspase-1, interleukin (IL)-1β, and IL-18, boosting pathological inflammation. Previous studies have found an increased NLRP3 inflammasome activity in atrial tissue of both clinical AF patients and a mice model of spontaneous AF induced by CREM-IbΔC-X Tg mice (Li et al., 2017; He et al., 2016). Further studies have demonstrated that the specific expression of NLRP3 develops premature atrial contractions and severe AF by constituting a CM-specific knock-in murine model which can express a constitutive active NLRP3. However, NLRP3 inhibition by using a selective inflammasome inhibitor significantly prevented AF (Li et al., 2017). Besides, emerging evidences indicated that the NLRP3 inflammasome is involved in CKD-induced kidney fibrosis, whereas NLRP3 deletion inhibits renal fibrosis in the 5/6 nephrectomy (5/6 Nx) disease model (Gong et al., 2016). Furthermore, CKD induces the activation of NLRP3 not only in kidney but also in extrarenal organ. Chin et al. demonstrated that CKD-induced uremic toxin, the IS, is associated with the upregulation of NLRP3 inflammasome in ventricle and results in ventricular dysfunction (Chin et al., 2017). However, in the disease setting of CKD, the status of NLRP3 inflammasome/caspase-1/IL-1β and IL-18 axis in atria is unknown.

Therefore, some questions are raised: (1) does TGF-β1/Smads signaling involve in CKD-induced atrial fibrosis; (2) whether gap junction would be affected by CKD, and how does the Cx43 change; (3) would atrial NLRP3 inflammasome/caspase-1/IL-β1 and IL18 axis also be activated by CKD; (4) are calcium-handling abnormalities targets for the prevention of AF in CKD? We have reasons to believe that the characteristics of CKD-induced atrial structural remodeling and AF are systemic and multifactorial. Further studies would be encouraged to investigate these pathological changes of CKD-induced AF.

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