Letter to the Editor

Angiotensin-(1-7): A new therapeutic strategy in the management of atrial fibrillation

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Atrial fibrillation (AF) is one of the most common cardiac arrhythmia, especially in the elderly population, and contributes substantially to cardiac morbidity and mortality [1,2]. In spite of the development of novel therapeutic approaches, including the radiofrequency catheter ablation, the management of AF remains an important and difficult task. During the past decades, accumulating evidence has suggested that the development and perpetuation of AF depends on the structural and electrical remodeling of the atria [3]. Currently, the pharmacologic therapeutic strategies have shifted to non-channel blocking drugs with the potential properties to alter the underlying atrial remodeling without concomitant proarrhythmic effects [4–7].

In the past few years, experimental animal models of AF and human AF studies have demonstrated that the hyperactive renin–angiotensin system (RAS) is associated with the electrical and structural remodeling, which provide an arrhythmogenic substrate for the development and recurrence of AF. Thus, the inhibition of RAS with angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) may be an effectual approach to prevent the occurrence and recurrence of AF.

The electrophysiological changes, including shortening of the atrial effective refractory period (AERP), dispersion of AERP and loss of the normal rate adaptation of refractoriness, have been considered as the atrial electrical remodeling (AER) [8,9] in AF. AF results in a reduction in the wavelength of atrial depolarization, inducing multiple microreentry circuits and vulnerability to AF. Nakashima et al. [10] indicated that angiotensin (Ang) II was involved in the atrial electrical remodeling in dogs with rapid atrial pacing and blockade of endogenous Ang II with captopril or candesartan prevented shortening of the AERP and attenuation of rate adaptation on AERP. These findings for the first time confirmed the role of RAS in the setting of AER. The underlying mechanism is probably due to the activation of the Ang II type 1 (AT1) receptor by Ang II stimulating the phospholipase C, leading to diacylglycerol-mediated activation of protein kinase C (PKC) and to inositol 1,4,5-trisphosphate-mediated release of calcium from intracellular stores. The sustained elevation of cytosolic calcium results in the downregulation of calcium channel density and expression, consequently leading to the AERP shortening.

In addition, RAS may play a critical role in the atrial fibrosis and structural remodeling in the advanced stage of AF. Ang II, the major effector peptide of the classical RAS, is generated from Ang I by angiotensin-converting enzyme (ACE). Ang II exerts its actions via Ang II type 1 and 2 receptors which mediate opposite functions. Through its interactions with the G proteins coupled AT1 receptor, Ang II induces a phosphorylation cascade that activates the mitogen-activated protein kinases (MAPKs) signal transduction pathways. The extracellular signal-regulated kinases 1/2 (ERK1/2), members of the MAPK subfamily, are activated by phosphorylation in this signaling cascade and then transferred into the nucleus, stimulating the activation of the transcription factors such as c-fos, c-Jun, Elk-1 and c-myc, which are responsible for the proliferation of fibroblasts, cellular differentiation and hypertrophy. Goette et al. [11] demonstrated that an ACE-dependent increase in the expression of atrial ERK1/ERK2, as well as the atrial interstitial fibrosis were found in patients with AF and ACEI treatment can reduce the activated ERK1/ERK2.

In recent years, a number of large clinical trials and meta-analysis have shown the anti-arrhythmic effect of RAS inhibition. The trandolapril cardiac evaluation (TRACE) study [12], a randomized double-blind placebo-controlled study, indicated that trandolapril treatment, compared with placebo, was associated with a significantly lower risk of new-onset AF in patients with acute myocardial infarction and left ventricular dysfunction (2.8% vs. 5.3%, relative risk (RR) 0.45, 95% confidence interval (CI) 0.26–0.76). A recent post hoc analysis of the losartan intervention for end point reduction in hypertension (LIFE) study [13] showed a significant 33% reduction in the incidence of new-onset AF in patients with hypertension and left ventricular hypertrophy treated with losartan compared to those treated with atenolol (6.8% vs. 10.1 per 1000 person-years, RR 0.67, 95% CI 0.55–0.83). A recent meta-

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analysis including 56,308 patients from 11 randomized controlled trials of RAS inhibition with an ACEI or an ARB in cardiac dysfunction, hypertension, post-myocardial infarction and post-cardioversion of AF demonstrated a 28% relative risk reduction of AF (RR 0.72, 95% CI 0.60–0.85) [14]. All of these findings are consistent with the statement that RAS inhibition is most effective in preventing the occurrence of AF in high risk population for AF. A newly discovered enzyme in the RAS pathway, ACE2, cleaves vasoconstrictor/hypertrophic peptide Ang II to vasodilator/anti-hypertrophic peptide angiotensin-(1–7) [Ang-(1–7)]. These discoveries give rise to the novel concept of the RAS. ACE2 is regarded as an essential regulator of heart function. Crackower et al. [15] reported that the deletion of the ACE2 gene in mice resulted in a severe impairment in cardiac function, including the left ventricular dilatation and cardiac contractility defect. Whereas genetic ablation of ACE in ACE2 null mice completely normalized the cardiac function, suggesting the counterbalance roles for the ACE/Ang II and ACE2/Ang-(1–7) arms of the RAS.

Tallant et al. [16] and Iwata et al. [17] showed that Ang-(1–7) inhibited the growth of rat cardiac myocytes and reduced collagen synthesis and growth factors expression in fibroblasts. These antifibrotic and antifibrotic effects of Ang-(1–7), via binding to the specific Mas receptor, contrasted with the effects of Ang II. These responses by Ang-(1–7) could be blocked by [d-Ala2]-Ang-(1–7), the selective Ang-(1–7) receptor antagonist, whereas the AT 1 and AT 2 receptors were ineffective. Ang-(1–7) level was elevated after treatment with ACEI or ARB, suggesting that Ang-(1–7) may contribute to their beneficial effects on cardiac remodeling.

Ang-(1–7) has been established to be a multiple cardioprotective peptide. Ang-(1–7) could prevent the cardiac remodeling by attenuating the hypertrophy and fibrosis induced by chronic infusion of Ang II [18] or deoxytocosterone acetate (DOCA)-salt treatment [19]. De Mello et al. [20,21] have demonstrated the anti-arrhythmia effect of Ang-(1–7). They showed that in the rat heart under ischaemia/reperfusion, Ang-(1–7) could reduce the incidence of arrhythmias by activating the sodium pump, hyperpolarizing the heart cell, re-establishing the impulse conduction and prolonging the cardiac refractoriness. Pan et al. [22] suggested that the downregulation of ACE2, the key enzyme of Ang-(1–7) formation, was associated with pacing-induced AF. Our previous studies also indicated that in long-term atrial tachycardia dogs, Ang-(1–7) could prevent the action potential duration shortening, suppress the decrease of bP0 and bLa and reduce the inducibility and duration of AF, as well as attenuate the interstitial fibrosis and Ang II-mediated ERK1/ERK2 expressions [23,24]. The new axis ACE2-Ang-(1–7)–Mas receptor provides a counterbalance effect in RAS regulation. ACE2 and Ang-(1–7) expression may be enhanced by each other in a positive feedback loop [25], thereby strengthening the cardioprotective effect. Therefore, we propose that Ang-(1–7) may become the novel strategy of therapeutic interventions in atrial fibrillation because of its cardioprotective effects.

In conclusion, it is reasonable to assume that Ang-(1–7) may reduce the incidence of AF by the anti-arrhythmic and anti-remodeling characteristics. Ang-(1–7) may become a new therapeutic strategy in the prevention and treatment of AF. Undoubtedly, further research is required to elucidate the impact of Ang-(1–7) on atrial remodeling as well as to evaluate the potential clinical benefits in the management of AF.

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References
