Archives of Medical Research 45 (2014) 351–355

Archives of Medical Research

OPINION

Relationship Between Two Arrhythmias: Sinus Node Dysfunction and Atrial Fibrillation

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Received for publication February 12, 2014; accepted April 21, 2014 (ARCMED-D-14-00089).

We reviewed recent advancements in the relationship between sinus node dysfunction (SND) and atrial fibrillation (AF) and propose some underlying mechanisms in regard to ion and molecular aspects. The amount of clinical and animal experiments have proven the structural and electrophysiological remodeling of sinoatrial node (SAN) and atrium may be related significantly between SND and AF. Atrial remodeling was often related to RAS activation. RAS inhibitors and statin, which resist in atrial fibrosis, may be novel strategies to prevent or treat both SND and AF. Besides, funny current (I_f) and Ca^{2+} clock mainly contributing to the SAN automaticity may be another link between SND and AF. Gap junctions such as Cx40, Cx43 and Cx45 were proven to participate in both automaticity and conductivity of electrical impulses in SAN and atrial tissue, which was accepted as another link between SND and AF. Common genetic mutations such as the emerin gene, SCN5A gene and HCN4 gene mutation were also the mechanism for the correlation between SND and AF.

Key Words: Sinus node dysfunction, Atrial fibrillation, Remodeling.

Both sinus node dysfunction (SND) and atrial fibrillation (AF) are "hard nuts to crack" in clinical practice. Remarkably, the incidence of AF was up to 53% in a previous study including 100 patients with SND (1). Recently, two consecutive studies have indicated that there may be a possible link between these two common arrhythmias. We review recent advancement in the relationship between SND and AF and propose some underlying mechanisms in regard to ion and molecular aspects.

Recent studies have supported that the structural and electrophysiological changes of sinoatrial node (SAN) and atrium may be related significantly between SND and AF. First, the structural and electrophysiological remodeling related to AF may be an important substrate of SND. Elvan et al. (2) were the first to confirm that the corrected sinus node recovery time (CSNRT) was prolonged along with the decreasing of the maximal and intrinsic heart rates in the pacing-induced AF canine model, which was related to the occurrence of SAN remodeling. In other words, AF increased the susceptibility to SND. A recent observation from Chang et al. (3) seemed to provide further evidence to support the specific electrophysiological changes related to SND in 34 patients with AF. They found that local atrial voltage change near the SAN region was associated with a prolonged sinus node recovery time, a longer right atrial activation time, a decreased voltage of the SAN area, and a slower conduction velocity along the crista terminalis (3). Also, the SAN structure itself may be recognized as a substrate for the macro-reentry participated by neurohormonal activation, which has been regarded as an important basis of maintaining AF. Fedorov et al. (4) demonstrated acetylcholine (Ach) and isoproterenol (Iso) were shown to facilitate the pacing-induced AF/AFL by shortening the SAN and atrial repolarization period. ACh/Iso was also confirmed to regulate the filtering properties of the sinoatrial conduction pathways by regulating the degree of the entrance block. It reminded us that some electrophysiological changes of SAN in SND may increase the inducibility of AF. Recently, we investigated the inducibility of AF in a canine model of SND. Compared with baseline, the atrial effective refractory periods (ERPs) were shortened following the establishment of the canine SND model. After rapid atrial pacing, atrial ERPs were further decreased

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0188-4409/$ - see front matter.
http://dx.doi.org/10.1016/j.arcmed.2014.04.005

remarkably, and the dispersion of atrial ERPs measured at different pacing cycle lengths (PCLs) showed significant variations. The average duration and inducibility of AF after SND was increased. It seemed that the decreased automaticity and conductivity of sinus node was associated with the shortening of atrial refractoriness, which may increase the inducibility and duration of AF (5).

Obviously, there have been some animal experiments to investigate the link between SND and AF. Recently, several clinical investigations tried to reveal that electro-anatomical remodeling of the atria associates with SND and AF. Park et al. (6) included 117 patients with long-standing persistent AF (L-PeAF) who underwent radiofrequency catheter ablation (RFCA). Post-shock sinus node recovery time was proven to be an independent predictor of clinical recurrence of AF after RFCA. The recent study of Chung et al. (7) consecutively enrolled 319 nonvalvular AF patients with SND and without SND who had undergone RFCA for drug refractory AF to investigate the relationship between the type of SND and AF recurrence after RFCA. They confirmed that AF patients with SND without tachycardia-bradycardia (TB) syndrome suffered significantly more bradycardia compared to both AF patients with SND and with TB or those without SND, which was correlated with severe structural and electrical remodeling of the atria. These results suggest that the type of SND might predict the degree of atrial remodeling and predict the outcome after RFCA of AF (7). In contrast, De Sisti et al. (8) found that the right atrial effective refractory period was not changed significantly in the enrolled patients with SND (8). However, the AERP measurements were performed only at a single site and the control group was not age-matched in their study.

As mentioned above, numerous studies are apt to admit the association between SND and AF, no matter which one promotes the other clinically and experimentally. However, the potential mechanism between these two common arrhythmias is not fully understood. Recent remarkable progress in molecular biology gives us some novel understandings.

The structural remodeling of atrium and SAN in both SND and AF is mainly referred to as fibrosis (9,10), which may be promoted by the renin-angiotensin system (RAS) activation. There is novel evidence to indicate angiotensin II (Ang II) as another participator in the occurrence of AF and SND, respectively. Ang II was confirmed to upregulate connective tissue growth factor (CTGF) and TGF-β gene expression, which proposed SAN and atrial fibrosis as the important substrate of maintaining AF in a canine model of AF (11). In a recent clinical study, 80 patients scheduled for mitral valve replacement surgery were enrolled, whose tissue samples of the left atrial appendages were obtained to detect the degree of fibrosis. It was shown that local expression of Ang II was increased in AF patients, which was correlated with the duration of AF and the expression of collagen type I. mRNA expressions of the angiotensin type 1 receptor (AT1R) and angiotensin-converting enzyme (ACE) genes were observed to be markedly upregulated in AF patients (12). It suggested that the blockers of RAS including the antagonists of AT1R and ACE may be effective drugs to treat AF and prevent atrial fibrosis induced by AF. CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) trials has provided the evidence. It was shown that adding candesartan to conventional congestive heart failure (CHF) therapy in 6379 patients with symptomatic CHF and without a history of AF at enrollment led to a lower incidence of new-onset AF (13). Later, Belluzzi et al. (14) proved that ACE inhibitor was also effective in preventing relapses of lone atrial fibrillation in the absence of hypertension and/or heart disease. Meanwhile, another study attempted to reveal the association of SND with RAS. It was shown that in wild-type mice, Ang II infusion activated NADPH oxidase, leading to increased oxidized calmodulin kinase II (ox-CaMKII), SAN cell oxidative stress, apoptosis, even SND (15). In addition, statin was also recently accepted as a novel strategy to prevent AF. Several retrospective studies (16,17) and meta-analysis of RCTs (18) have reported that statin therapy was associated with a lower incidence of postoperative AF and shorter hospital stay. The study of Marin et al. (19) seemed to reveal the potential mechanism of the antifibrillatory effect of statins. As was reported, statin was associated with increased tissue inhibitor of matrix metalloproteinase-1, which was mainly responsible for degrading collagen type I and III (19). Although there is currently a lack of direct clinical evidence that angiotensin receptor blockers and statins can effectively prevent SND, it is believed that the inhibition of atrial fibrosis is effective to prevent or treat both SND and AF. According to a recent study, both RAS inhibitors and statins could prevent and inhibit atrial fibrosis via regulating platelet-derived growth factor/Rac1/nuclear factor-kappa B axis (20). Thus, inhibitors of RAS and statin may be novel strategies to prevent or treat both SND and AF.

Until now, expression of over 120 ion channels and associated proteins within the human sinus node and right atrium has been comprehensively characterized (21). Among them, the funny current (I_f) and Ca^{2+} clock mainly contributing to the SAN automaticity have recently been paid more attention. Hyperpolarization-activated inward current I_f is the mixture consisting of K^+ and Na^+ channels modulated by intracellular cyclic nucleotide. I_f encoded mainly by the HCN2 and HCN4 genes is normally responsible for electrical automaticity in sinus node. Impaired I*f* was confirmed to participate in the occurrence of SND and result in both brady- and tachyarrhythmias (22,23). Furthermore, Yeh et al. (24) provide further evidence in a canine model of AF. It was shown that rapid pacing downregulated SAN HCN2/4 and minK subunit expression to reduce currents I_f and I_{ks} by 48% in SAN. I*f* played much more significant role than I_{ks} in the prolongation of SAN recovery time. Also, no changes are shown in voltage dependence or kinetics I_{Kr}, I_{caL}, and I_{caT} (24).