EDITORIAL COMMENT

Blockade of Atrial Angiotensin II Type 1 Receptors

A Novel Antiarrhythmic Strategy to Prevent Atrial Fibrillation*

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Atrial fibrillation (AF) is known to cause significant changes in atrial tissue architecture and atrial electrophysiology (1). In recent years, it has become clear that preexisting alterations (autonomic dysbalance, degenerative tissue changes, fibrosis, and so forth) can provide an electrophysiologic and morphologic substrate, which increases the likelihood of AF onset in response to triggering events. Alterations of the interstitial matrix in atrial tissue seem to be especially significant contributing factors (1,2). Increased amounts of fibrous tissue in fibrillating human atria were described 30 years ago (3). However, only recently potential molecular mechanisms responsible for collagen accumulation in atrial myocardium have been elucidated (4,5).

One of the mediators responsible for the development of atrial fibrosis is angiotensin II. Recent studies have shown an increased atrial expression of the angiotensin-converting enzyme (ACE) and activation of the angiotensin II–related intracellular signal transduction pathway in fibrillating human tissue (4). In dogs, activation of the atrial angiotensin II system has been described in a tachycardia-induced heart failure (HF) model (5). It could be demonstrated that inhibition of the ACE can reduce the generation of angiotensin II in this HF setting, which is also characterized by less atrial fibrosis and a decreased inducibility of AF. The molecular effects of ACE inhibitors may also explain the reduced incidence of AF found in patients with left ventricular dysfunction after myocardial infarction (6).

The study presented by Kumagai et al. (7) in this issue of the Journal is the first to describe the impact of the angiotensin II type 1 receptor blocker candesartan on electrical and structural remodeling in canine atria. Using a rapid atrial pacing model, the authors demonstrate that blockade of the angiotensin II type 1 receptor reduces the development of atrial fibrosis in dogs undergoing four weeks of rapid atrial pacing, when compared with untreated controls. In addition, candesartan shortened the duration of induced episodes of AF. Angiotensin II receptor blockers seem to have advantageous effects in this atrial pacing model that are comparable with the described effects of ACE inhibitors. Candesartan might offer a significant antiarrhythmic potential by reducing the amount of fibrous tissue formation in the atria, avoiding heterogeneity and delay of atrial activation. Thus, the results of the present study are of potential clinical importance.

However, from the study by Kumagai et al. (7) it remains unclear to what extent ventricular dysfunction might have contributed to the development of atrial fibrosis in their rapid atrial pacing model, because the ventricular rate was not controlled by atrioventricular (AV) node ablation. The development of tachycardia-induced ventricular myopathy in this model may help to explain that four weeks of rapid atrial pacing was accompanied by the development of atrial fibrosis, resembling morphologic findings by Li et al. (2,5) in an HF model. In contrast, atrial fibrosis has not been observed in previous studies during rapid atrial pacing, in which rapid AV-conduction was prevented by AV node ablation (1,2). In patients with permanent AF, angiotensin II type 1 receptors are down-regulated, whereas the amount of the “antifibrotic” angiotensin II type 2 receptors are up-regulated. This may limit the therapeutic effect of angiotensin II type 1 receptor blockers in patients with long-lasting episodes of AF (8). It might be possible, however, that the down-regulation of “profibrotic” angiotensin II receptors is preceded by a period during which type 1 receptors are temporarily up-regulated. Unfortunately, the time course of changes in angiotensin II receptor expression has not been analyzed in the study by Kumagai et al. (7). Despite its methodological limitations, this study supports the significance of angiotensin II–dependent signal transduction for interstitial accumulation of collagen in the atria during AF. In contrast to most animal models, activation of the atrial angiotensin II system and development of interstitial fibrosis have been described in atrial myocardium in patients without HF but with concomitant cardiovascular disease—mainly systemic hypertension and valve disease (1,9). Animal models of AF with at least some extent of ventricular structural abnormalities represent the morphologic atrial changes (e.g., fibrosis) found in the majority of patients with AF. In contrast, atrial fibrosis is absent in AF models with complete normal ventricular function (1), which suggests that activation of the atrial angiotensin II system is of minor importance during lone AF. The observed “antiarrhythmic actions” induced by inhibition of the angiotensin II–related effects seem to be related to their influence on the interstitial matrix. A significant impact of ACE inhibitors and angiotensin II receptor blockers on atrial action potentials and on electrical remodeling has not been demonstrated in the long-term (10).

Our insight into the specific interaction between the interstitial matrix and electrophysiological properties in atrial tissue is far from complete. Increased amounts of
collagen and cellular hyperplasia of fibroblasts cause separation of atrial myocytes—which slows atrial conduction—and induce regional conduction block, which is the ideal condition for the onset and perpetuation of AF (1,2,9). However, the total amount of collagen per mm³ can be only a rough estimate for related alterations of impulse conduction, because the orientation of collagen fibers with respect to the alignment of myocytes may affect the conduction to a far greater extent than just the overall amount of measured fibrous tissue (11). Furthermore, disturbed cell-matrix interaction by membrane-bound proteases can increase cell mobility and weakens the mechanical resistance of the myocardial architecture. This results in cell slippage, dilation of the atria, and consecutive mechanical dysfunction of the atrium (9). Thus, changes in the interstitial matrix are linked to electrophysiological, mechanical, and morphologic alterations (9). Whether all these interstitial changes are related to the angiotensin II system is unclear. Further studies are mandatory to prove which changes can be produced by AF itself.

At the molecular level, several AF-related alterations of atrial tissue are due to activation of different signal transduction systems. For example, increased endothelin levels, reduced amounts of bradykinin, and altered levels of tissue proteases or cytokines can contribute to degenerative changes of atrial myocardium, collagen accumulation, cellular hypertrophy, and cell death (1,9). These mechanisms may act synergistically to affect the spread of electrical activation and beget AF. In addition to fibrotic changes, deposits of other extracellular proteins or fibrils can also contribute to conduction inhomogeneity. A recent study (12) indicates that atrial amyloid deposition can be found in patients with AF, mainly in patients with valve disease. Interestingly, the amount of atrial amyloid is inversely related to the amount of fibrous tissue, suggesting that, at least in this selected group of patients, a therapeutic approach applying “antifibrotic” strategies may be ineffective.

Further studies are needed to define the role of different molecular pathways and their dynamic interactions on alterations of atrial electrophysiology. Better knowledge about these fundamental mechanisms can help to identify novel targets for pharmacologic interventions, which may be even more effective than conventional antiarrhythmic therapy. In this perspective, the presented study by Kumagai et al. (7) provides interesting experimental evidence that can-desartan reduces the accumulation of atrial collagen formation during AF. Their data help to explain the finding of the study by Madrid et al. (13), who reported a beneficial effect of irbesartan after electrical cardioversion.

Besides the growing body of experimental evidence demonstrating the impact of angiotensin II on atrial myocardium, prospective clinical trials are needed to confirm the therapeutic effect of ACE inhibitors/angiotensin II type 1 receptor blockers in patients with AF. We have to define clinical parameters that help to anticipate the presence of an activated atrial angiotensin II system. Furthermore, we have to determine the optimal therapeutic dose of ACE inhibitors/angiotensin II type 1 receptor blockers as well as the necessary duration of therapy for the treatment of patients with “fibrosis-related” AF.

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