Inhibition of angiotensin II type 1 receptors reduces atrial stunning and spontaneous echo contrast after electrical cardioversion of atrial fibrillation

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Atrial fibrillation (AF) is known to be an important risk factor for thrombo-embolism.1,2 AF has been shown to induce a prolonged mechanical dysfunction of the atria, which becomes apparent after successful conversion of AF to normal sinus rhythm.1-4 The reduced mechanical function after termination of AF has been termed atrial stunning. Atrial stunning has been described after electrical (DC shock, overdrive pacing, catheter ablation), pharmacological, and spontaneous cardioversion of AF, which demonstrates that AF itself, rather than the mode of conversion, induces mechanical dysfunction. Pathophysiologically, the transient dysfunction of the atria appears to be due to abnormalities in cellular calcium handling and reduced calcium transient through L-type calcium channels.1,3 Furthermore, destruction of contractile proteins by calcium-dependent proteases such as calpains and functional alterations of the contractile proteins may contribute to prolonged mechanical alterations.5 In previous studies, verapamil, acetylstrophenathidine, isoproterenol, and dofetilide have been reported to reduce the amount of atrial stunning.2,3

Dagres et al.6 show that pre-treatment with the angiotensin II type 1 receptor blocker, Irbesartan, reduces left atrial stunning in patients undergoing electrical cardioversion of persistent AF. From a total of 50 patients, 25 received Irbesartan at a dose of 228 ± 93 mg/day for at least 14 days prior to cardioversion. Although the trial was non-randomized, the two patient groups were matched with regard to clinical parameters including duration of AF, blood pressure, heart rate, cardiac dimensions, and ejection fraction. Transoesophageal and transthoracic echocardiography were used to determine the left atrial appendage emptying velocity (LAAEV), spontaneous echo contrasts (LASEC), and peak velocity of the A-wave as markers of atrial mechanical function. The authors can show that Irbesartan treatment significantly reduced the amount of atrial dysfunction. LAAEV declined by 9% in the Irbesartan group compared with 48% in untreated patients and LASEC occurred substantially less after Irbesartan pre-treatment (Irbesartan group: 32% vs. 64% in untreated patients). In contrast, peak velocity of the A-wave increased similarly in both groups after cardioversion, showing that a more global mechanical performance of left atria was less affected by Irbesartan. Of note, atrial stunning was not related to AF recurrence during follow-up. Effects of Irbesartan on left ventricular pump function and atrial size were not reported.

What can we learn from the study by Dagres et al. and how can their findings be explained? The authors provide a new piece of information about the potential impact of the cardiac (atrial) angiotensin system in the process of mechanical dysfunction during AF. The results suggest that the use of Irbesartan may be helpful to reduce atrial stunning, and thereby thrombo-embolic complications after cardioversion. Several reports have shown an activation of the atrial angiotensin II system in patients with AF.1,7,8 Angiotensin II can influence structural as well as electrophysiological atrial changes. Angiotensin II induces the cellular response by activation of two different receptors. Qualitatively, the two types of angiotensin II receptors (AT-1/AT-2) induce different responses that oppose one another. Activation of AT-1 receptors induces a cascade of phosphorylations that activate the so-called mitogen-activated protein kinases, which stimulate proliferation of fibroblasts, cellular hypertrophy, and apoptosis. Activation of AT-1 also stimulates 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. PKC can phosphorylate L-type calcium channels, which may alter calcium influx and can affect potassium channels, such as Ito and the delayed rectifier.7,8 Furthermore, the AT-1 receptor is described to form complexes with Kv4.3, leading to internalization of the receptor-channel complex. Overall, angiotensin II has multiple effects on cardiac electrophysiology.
including ionic currents and gap junction expression. Irbesartan has been reported to inhibit currents carried by hKv1.5 (I_{hKv1.5}), Kv4.3 (I_{Kv4.3}), HERG (I_{HERG}), and KvLQT1 (I_{KvLQT1}). These electrophysiological effects may be more relevant in remodelled/diseased atria.1,7,8 Thus, similar to anti-arrhythmic drugs ( dofetilide, AVE0118, verapamil), which have been reported to effect atrial contractility by their ability to block ion channels, Irbesartan may also reduce atrial mechanical dysfunction by influencing the shape of the action potential, and thereby affecting calcium transients, cellular calcium handling, and contractility. Furthermore, angiotensin II stimulates via AT-1 receptors the production of O_2\(^{2-}\) by NADPH oxidases. Increased oxidative stress induced by NADPH oxidase activity has been shown to cause oxidative changes of structural proteins and contractile filaments in fibrillating atria.9,10 Thus, oxidative stress induced by AT-1 receptor activation may contribute to the development of atrial contractile dysfunction. Increased oxidative stress is also of relevance for pro-thrombogenic endocardial changes.7,11 Interestingly, sartan therapy affected the development of LASEC in the study by Dagres et al.6 LASEC are shown to be a marker for thrombo-embolic stroke in patients with AF. In general, the occurrence of LASEC appears to be related to atrial flow velocities. Thus, attenuation of atrial stunning by blockade of the angiotensin II type 1 receptor may help to explain the lower likelihood for the development of LASEC during Irbesartan therapy, which supports the potential clinical implication of the present report.

In contrast to these cellular changes, it appears unlikely that a brief Irbesartan pre-treatment phase (14 days) causes an improvement of morphological alterations such interstitial fibrosis or atrial size. Enlarged atrial size is an important factor for the development of AF as well as for the occurrence of LASEC and thrombo-embolic complications. Alterations of atrial size, however, were not reported in the present study. Persistent ‘unloading’ of the heart by antihypertensive drugs or by restoring normal left ventricular function has been shown to reduce atrial size, which corresponds to a lower risk in long term for thrombo-embolic complications. Nevertheless, the impact of long-term Irbesartan therapy on atrial architecture and function still needs to be defined.

Overall, the underlying pathophysiological mechanisms of how Irbesartan affects atrial stunning and LASEC need further investigations. In addition, some results of the present study are unclear and in contrast to previous reports. Madrid et al.11 could show that Irbesartan reduces the recurrence rate of AF after electrical cardioversion, which was not the case in the study by Dagres et al. Furthermore, several reports have shown a correlation between the amount of atrial dyscontractility after cardioversion and AF recurrence.1,2,4 Thus, the present results are still preliminary and definite conclusions cannot be drawn at this point. Randomized studies on larger, and more homogeneous, patient cohorts have to validate the present findings.

Nevertheless, the study by Dagres et al. provides very first clinical information about the effects of Irbesartan on atrial contractility after cardioversion. Therefore, the present prospective study adds a new and important piece of information, which supports the use of sartans in patients with AF, as already suggested by retrospective clinical trials (TRACE, ValHeFT, SOLVD, CHARM) as well as experimental data.1,7,8 Indirectly, the present study can also help to explain recent results of the LIFE study, showing that losartan therapy reduced the risk of stroke in patients with new-onset AF. Results from still ongoing clinical trials (ACTIVE-I, ANTI-PAF) may provide more insights into the impact of sartan therapy on atrial architecture/function and the risk of thrombo-embolic stroke.

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References