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Treatment of Atrial Fibrillation with Calcium Channels Blockers

Tajiri K, Guichard JB, Qi X, Xiong F, Naud P, Tardif JC, et al. An N-/L-type calcium channel blocker, cilnidipine, suppresses autonomic, electrical, and structural remodelling associated with atrial fibrillation. **Cardiovascular Research** 2019;115:1975–85. <http://doi.org/dgp2>

Atrial fibrillation (AF) is the most frequent sustained arrhythmia, and is associated with complications as ischemic stroke and heart failure decompensation, which generate morbidity and mortality in patients suffering from this condition. The pathophysiology of AF is complex and multifactorial, as reflected by the scant progress in effective new treatment options for this arrhythmia. Although catheter ablation appeared in the last years as a useful option for some types of AF, such as paroxysmal AF, pharmacological therapy has still few alternatives and with high collateral effects. Persisting AF promotes myocardial changes, known as structural remodelling, the most studied being atrial wall interstitial fibrosis. At the same time, modifications in ion channel and intercellular gap junction expression alter myocardial electrical conduction, a condition known as electrical remodelling. Currently, it is known that sympathetic hyperactivity plays an important role in the onset and maintenance of AF, and is a common factor in the generation of structural and electrical remodelling of the heart. Laboratory animals and human studies have shown hyper-innervation and increased catecholamine release in the atrial walls of hearts with AF. In addition to this neural remodelling, the activation of the renin-angiotensin-aldosterone system significantly contributes to the emergence of fibrosis.

Tajiri et al. studied the effects of N and L voltage-dependent calcium channel blockade with cilnidipine on myocardial remodelling induced by AF. At the cardiovascular level, N-type calcium channels are found in sympathetic nerve endings and induce noradrenaline release through calcium entry and depolarization of the presynaptic terminal button. In an experimen-

tal model in dogs with AF induced with an external high-frequency pacemaker, the authors studied the effects of oral cilnidipine administration on the atrial walls during 7 or 21 days, compared with administration of the selective L-type channel blocker nifedipine. They observed that blockade of the L-type calcium channels inhibits the electrophysiological, autonomic and structural consequences of AF remodelling, and also reduces arrhythmia vulnerability and duration. Cilnidipine reduced fibrosis and attenuated the decrease in sodium channel and connexin expression in right atrial samples, reflected as mitigation in the reduction of electrical conduction velocity and the effective refractory period. Interestingly, some protective effects on remodelling were associated with inhibition of catecholamine release in sympathetic nerve endings, as shown by lower noradrenaline levels and improved heart rate variability. None of these benefits was observed in the nifedipine group, which strengthens the concept of a benefit mediated by reduced sympathetic stress.

Cilnidipine is a calcium channel blocker approved in some Asian and European countries for the treatment of hypertension, with scarce collateral effects. In this study, Tajiri et al. studied for the first time the use of an N calcium channel blocker in atrial remodelling caused by arrhythmia, demonstrating sympatholytic effects independent of beta-adrenergic receptor blockade. Although it is a preclinical study, the beneficial results seem solid and encouraging, in view of a potential complementary use for the treatment of AF. In addition, the data of this work reinforce once again the central role of dysautonomia in the pathophysiology of cardiovascular diseases. Moreover, other previous studies showed that cilnidipine may have additional beneficial effects, such as reduction of serum angiotensin II levels and inhibition of aldosterone in the supra-renal medulla. Further experimental studies are necessary to better understand the protective mechanism conferred by calcium blockade, as well as controlled clinical trials demonstrating the safety and efficacy of cilnidipine in the prevention of AF-associated recurrences and remodelling.