

Letters to the Editor

Ivabradine as an Atrioventricular Node Modulator. Promise or Reality?



Ivabradina como modulador del nódulo auriculoventricular. ¿Promesa o realidad?

To the Editor,

We read with great interest the article published in your journal by Fontenla et al.¹ It was particularly thought-provoking, as it goes against what seemed evident regarding the action of ivabradine in selective If channel inhibition. We completely agree that the findings of these authors and the others described would imply conducting *ad hoc* clinical trials. However, we would like to mention some concerns.

Specifically, we would like to know about the patient's functional status and the temporal relationship between this factor and implantation of the cardiac resynchronization therapy defibrillator. To our mind, this point is especially important, as the patient's heart failure, in itself, could imply increased adrenergic activity and therefore, faster baseline conduction of atrial fibrillation (AF). It is reasonable to think that the simple fact of providing a cardiac resynchronization device would improve the patient's heart failure, and decrease adrenergic activity and the baseline heart rate. This is a common situation in clinical practice when patients with permanent AF and decompensation due to heart failure receive vasodilator and diuretic therapy, which lowers heart rate and obviates the need for higher doses of their rate-reducing medication. To affirm that the favorable heart rate management was due to ivabradine, we believe that resynchronization-related improvement would have to be ruled out, as well as changes in the remaining heart failure therapies. In addition, we wonder whether ivabradine therapy was also considered before biventricular pacemaker implantation, as the indication for the device might have been questionable if the patient had fast AF. In this regard, it could also be interesting to evaluate whether the patient would again show a low percentage of biventricular pacing on discontinuation of the drug.

The findings described contrast with those of authors reporting that the action of ivabradine is highly specific for the If channel. Inhibition of If channel activity induces changes in the slope of the diastolic depolarization current (automatism), but not in other action potential or conduction system parameters.^{2,3} Of note, in descriptions of families with mutations in the *HCM4* gene (which codes for the most common If channel in human cells), the clinical presentation is sinus bradycardia, sinus arrhythmia, or AF without changes in node conduction (effects similar to those seen with ivabradine).⁴ As the authors rightly state, this channel is present in

all cells of the human heart, not only the sinus node, which leads to their debate about whether If channel inhibition may help to control heart rate during AF (or even provide other, unknown effects). It is also important to mention that ivabradine use has been reported to increase the risk of developing AF,⁵ and that discontinuation of the drug is currently indicated when this occurs. For this reason, we believe that it should not be used in patients with paroxysmal AF and cardiac resynchronization devices in order to improve the percentage of biventricular pacing, as the primary objective should be to avoid AF development.

We are enormously grateful to the authors for their article. The ionic functioning of the heart is extremely complex and what once seemed evident and fully demonstrated may appear in a new light as additional evidence emerges and leads to reconsideration of the action of drugs such as ivabradine.

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