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New Therapeutic Strategies for Diastolic Dysfunction

De Angelis A, Cappetta D, Piegari E, Rinaldi B, Ciuffreda LP, Esposito G. Long-term administration of ranolazine attenuates diastolic dysfunction and adverse myocardial remodeling in a model of heart failure with preserved ejection fraction. **Int J Cardiol 2016;217:69–79.**

Approximately half of the patients with signs and symptoms of heart failure present with preserved ejection fraction, a condition known as diastolic heart failure. Although the pathophysiological mechanisms underlying this entity are not fully elucidated, there is general agreement that hypertrophy, changes in extracellular matrix and altered Ca2+ homeostasis contribute to diastolic dysfunction, worsening ventricular relaxation and increasing myocardial stiffness.

The increase of cardiomyocyte Na+ concentration as a result of higher Na+ current (INa+) has been described as a potential mechanism of diastolic dysfunction. This leads to the activation of the Na+/Ca2+ exchanger (NCX) with the ensuing Ca2+ overload (Figure 1). Based on this knowledge, and with the need of finding new therapeutic targets, De Angelis et al. essayed the effects of ranolazine administration in hypertensive rats with diastolic dysfunction.

Ranolazine is a compound which selectively inhibits its INa+ and could consequently decrease intracellular Na+-dependent Ca2+ accumulation. Preliminary data obtained from animal experiments have shown that ranolazine improves diastolic function, and these positive results have been confirmed by small studies in patients with coronary artery disease. Both animal and patient results support chronic ranolazine administration effects in diastolic dysfunction models, as Dahl SS rats. As expected, hypertensive animals developed diastolic dysfunction with preserved ejection fraction. Ranolazine administration decreased left ventricular end-diastolic pressure and improved ventricular relaxation. Interestingly, ranolazine did not modify ventricular hypertrophy observed in hypertensive animals, but induced significant changes at the extracellular matrix level. In this sense, it attenuated interstitial fibrosis, reduced collagen type I/III ratio and type 2 metalloproteinase (MMP-2) expression and activity.

Thus, the results of De Angelis et al. extend previous knowledge provided by data from other authors, demonstrating that ranolazine inhibits INa+ current and improves diastolic function without changing blood pressure.

Treatment with ranolazine has a positive impact on passive myocardial components, which define, at least in part, the diastolic properties of the ventricle, increasing animal survival. However, further studies are necessary to identify the precise mechanisms underlying these results.

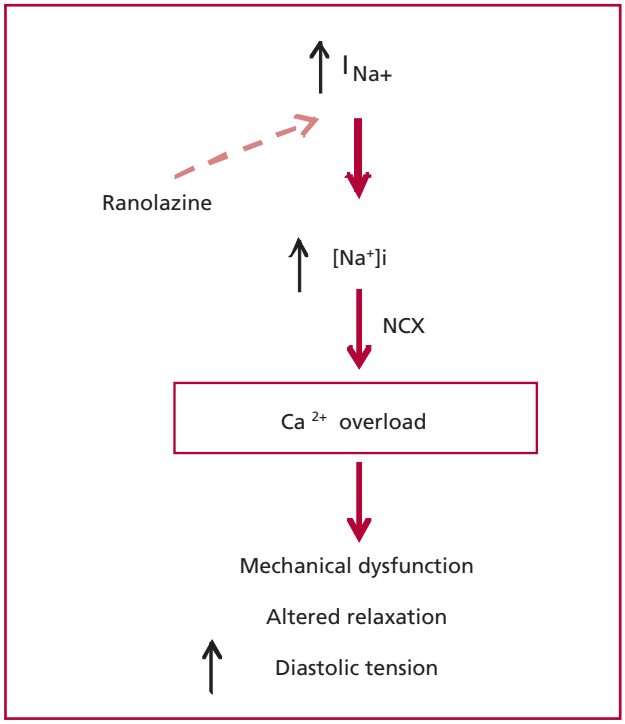

Fig. 1. Increased Na+ current (INa+) leads to higher intracellular Na+ concentration ([Na+]i). These changes lead to Na+/Ca2+ exchanger (NCX) activity with concomitant Ca2+ overload, which would be responsible for diastolic dysfunction. Ranolazine by inhibiting INa+ current would attenuate mechanical dysfunction.