

### Pharmacologic Modulation of Parasympathetic Activity in Heart Failure

Lataro RM, Silva CAA, FazanR Jr, Rossi MA, Prado CM, Godinho RO, Salgado HC. Increase in parasympathetic tone by pyridostigmine prevents ventricular dysfunction during the onset of heart failure. **Am J Physiol Regul Integr Comp Physiol** (August 15, 2013). (In press). doi:10.1152/ajpregu.00102.2013

Heart failure is characterized by the presence of an imbalance between the sympathetic and parasympathetic tone. The alteration of vagal heart rate control becomes evident in the early stages of ventricular dysfunction and is related to adverse outcome in patients with heart failure due to myocardial infarction. In this sense, different experimental evidence suggests that parasympathetic tone increase could be a therapeutic alternative to attenuate heart failure evolution. Chronic vagal stimulation has proved to increase survival in rats with heart failure.

Because acetylcholine is the primary neurotransmitter of parasympathetic nerve endings, the use of drugs that increase its bioavailability might have a similar effect to that described for the electrical stimulation of the vagus nerve. Therefore, parasympathetic neurotransmission could be improved by acetylcholinesterase inhibition. In this sense, the authors investigated long-term (4 weeks) effects of an acetylcholinesterase inhibitor (pyridostigmine) on sympathovagal balance, cardiac remodeling, and cardiac function in a heart failure model following myocardial infarction.

Myocardial infarction was elicited in adult male Wistar rats by left anterior descending coronary artery ligation. The infarcted animals were randomized to a control group and to a second group which underwent 4 weeks of pyridostigmine administration. After 4 weeks evolution, sympathetic and parasympathetic

tone was evaluated by changes in heart rate produced by methylatropine (vagal tone) and propranolol (sympathetic tone) administration.

In conscious rats with heart failure, pyridostigmine reduced baseline heart rate, increased vagal tone and reduced sympathetic tone. Pyridostigmine treatment reduced myocyte diameter and collagen density and increased vascular endothelial growth factor (VEGF) in the left ventricular myocardium, suggesting pro-angiogenic activity. Finally, cardiac function was assessed by constructing a pressure-volume loop. Four-week treatment with pyridostigmine increased stroke volume, ejection fraction and dP/dtmax, without modifying ventricular relaxation.

The authors concluded that long-term pyridostigmine administration, after coronary artery occlusion, increases vagal tone and decreases sympathetic tone, improving ventricular function and thereby attenuating cardiac remodeling and progression of heart failure.

*The Lataro et al.'s study is interesting, because in patients with heart failure, 6-month stimulation of the vagus nerve was associated with significant improvement of NYHA functional class, quality of life, ejection fraction and stroke volume. However, many questions remain unanswered:*

*Are the beneficial effects of vagus nerve stimulation independent of heart rate changes?*

*What are the adequate stimulation parameters necessary to achieve a benefit with minimal side effects?*

*Should vagal stimulation be synchronized with cardiac cycle?*

*Are vagal stimulation effects independent of ventricular dysfunction etiology?*

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