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Could the inhibition of microRNAs be a treatment option for heart failure in the future?

Hinkel R, Ramanujam D, Kazcmarek V, Howe A, Klett K, Beck MPharm C, et al. AntimiR-21 prevents myocardial dysfunction in a pig model of ischemia/reperfusion injury. **J Am Coll Cardiol 2020;75:1788–800. https://doi.org/10.1016/j.jacc.2020.02.041**

Myocyte hypertrophy and interstitial fibrosis are key components of left ventricular remodeling that can lead to heart failure and death in a large number of patients with ischemic heart disease. In recent years, a group of molecules strongly involved in gene regulation of postischemic myocardial remodeling, called micro ribonucleic acids (microRNAs), have been studied. MicroRNAs are a wide family of very small non-coding RNA molecules with the ability to modulate the gene expression of many proteins that are involved in pathological and physiological cellular processes. Modifications in the expression of microRNAs have been associated with various pathological processes such as cardiac fibrosis, hypertrophy and angiogenesis. A strongly expressed molecule in heart disease is microRNA-21, which has been identified in most cells of the cardiovascular system, but with a high preference in the cells involved in myocardial fibrosis. Pharmacological inhibition or genetic manipulation of microRNA-21 has been found to produce antifibrotic effects in different organs. In addition, murine studies have demonstrated that microRNA-21 inhibition prevents fibrosis and cardiac dysfunction in pressure overload hypertrophy.

In this new study, Hinkel et al. seek to demonstrate the applicability and efficacy of the local intracoronary use of a microRNA-21 inhibitor (LNA-antimiR-21) in pigs, a large animal experimental model with more clinical relevance, subjected to 60-minute ischemia by anterior descending coronary artery occlusion with intracoronary balloon, followed by reperfusion and evolution for 33 days. Intravascular administration of LAN-antimiR-21 in the descending and circumflex coronary artery at 5 and 19 days of reperfusion inhibited the marked increase of microRNA-21 expression in the ischemic hearts, measured at the end of the experimental protocol. Histological and immunohistochemical studies revealed a reduction in macrophage infiltrate, lower fibroblast proliferation and a significant anti-fibrotic effect. Finally, the animals treated showed lower increase of left ventricular weight and improved ventricular function evaluated by cardiac catheterization.

Although the current treatment of postischemic heart failure, mainly based on the use of renin-angiotensin-aldosterone system inhibitory drugs and vasodilator agents, has meant a great progress in patient evolution, in recent years it has been suggested that the clinical efficacy of these therapeutic strategies has reached a level where it is very difficult to achieve significant additional improvements. MicroRNA dysregulation in ischemic heart disease leads to myocyte hypertrophy and interstitial fibrosis, which often ends in heart failure and death. In this work, the authors demonstrate, for the first time in a large animal model, that intracoronary administration of a microRNA-21 inhibitor prevents adverse ventricular remodeling and improves cardiac function. These positive results in a heart failure model with greater proximity to the clinical scenario confirm what had already been clearly seen in rodent models. For this reason, the family of microRNAs are potential therapeutic targets that generate interest and should be studied more deeply in view of their clinical projection. The cardiac benefit of microRNA-21 inhibition is mainly due to its action on non-myocyte cells, which are present throughout the body. Therefore, the possibility of being administered systemically without major side effects, especially outside the heart, and the duration of the long-term benefits should be analyzed. In line with the first clinical trials in kidney diseases, this preclinical study could mark the beginning of a long path in a new therapeutic exploration with anti-microRNAs as an alternative treatment option for a group of such prevalent diseases.