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Remote Perconditioning. New Benefits in Ischemic Heart Disease with Potential Clinical Extrapolation

Pilz PM, Hamza O, Gidlöf O, Gonçalves IF, Tretter EV, Trojanek S, et al. Remote ischemic perconditioning attenuates adverse cardiac remodeling and preserves left ventricular function in a rat model of reperfused myocardial infarction. **Int J Cardiol 2019;285:72-9. http://doi.org/c5sw**

Despite early reperfusion therapy, the ischemic myocardium suffers additional damage as a consequence of blood flow restoration, a condition known as reperfusion injury. In this context, myocardial protection techniques, such as ischemic preconditioning, have been studied for decades. Since the discovery that these protection strategies can be performed at a distance from the ischemic tissue (remote preconditioning), the possibilities of achieving viable clinical extrapolation of encouraging experimental results have significantly increased. Specifically, remote ischemic perconditioning consists of ischemia-reperfusion cycles performed at a distance from the heart (generally in a limb) during myocardial ischemia. Several preclinical studies have demonstrated the ability of remote preconditioning to reduce infarct size. This translates into the improved chronic evolution of reperfused infarctions, with lower maladaptive ventricular remodeling rate and progress to heart failure. However, the benefits of remote perconditioning on variables different from infarct size are less well known.

In this interesting work, Pilz et al. studied some of the mechanisms involved in the effects of remote perconditioning on myocardial remodeling and left ventricular function after ischemia-reperfusion injury. Rats, subjected to 30-minute regional ischemia by coronary artery occlusion, followed by 14-day reperfusion, received, during myocardial ischemia, three 5-minute ischemia-reperfusion cycles in a lower limb as conditioning stimulus. At the end of the protocol, the animals underwent in vivo echocardiographic ventricular function studies, following which the hearts were removed and studied in an ex-vivo model, perfused according to the Langendorff technique. Compared with the ischemia-reperfusion group without perconditioning, the perconditioning group improved left ventricular ejection fraction and diameters, as well as systolic pressure and stroke volume. Also, their heart weight was reduced and infarct size was lower, suggesting positive structural changes. By means of histological and molecular studies, the authors observed decreased macrophage infiltration, lower pro-inflammatory cytokine levels and reduced type 2 and 9 matrix metalloprotease expression. These results are in agreement with lower inflammation and favorable effects on extracellular matrix remodeling. The authors could also demonstrate epigenetic modifications following increased neuregulin 1 and H3K4me3 signaling activity, a system which has been shown to be favorable in the chronic evolution of ischemic heart disease when stimulated by other mechanisms.

Adverse ventricular remodeling may progress to heart failure and is hence associated with poor prognosis in patients with ischemic heart disease. Beta blockers, renin-angiotensin system inhibitors and angiotensin II receptor blockers are regularly used to prevent post-ischemic maladaptive ventricular myocardial remodeling. However, a significant number of patients still progresses to heart failure and, eventually, death. The study by Pilz et al. suggests additional benefits of perconditioning on left ventricular remodeling and function, particularly in its ability to modulate the inflammatory response and the metalloprotease system through the participation of neuregulin-1 and tenascin-C molecules, which reduce fibrosis and hypertrophy and thus improve cardiac function. Neuregulin 1 is a protein strongly associated with cardiac development and myocardial repair and its levels are highly reduced in infarction. Preclinical studies have demonstrated its ability to act against adverse remodeling, with strong local anti-inflammatory effects. Also, the experimental use of recombinant neuregulin suggests ventricular function improvement in heart failure.

It is encouraging that remote perconditioning, in addition to its known capacity to reduce infarct size in its acute phase in different experimental models, can achieve these preclinical results on the expression of neuregulin and its favorable consequences in chronic ischemic heart disease. Moreover, remote perconditioning is an intervention with great potential for clinical application, because it is applied during ischemia and can be performed very simply with a pressure cuff in one of the upper limbs.