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Factor Xa inhibition prevents adverse myocardial remodeling by pressure overload. A new therapeutic strategy?

Guo X, Kolpakov MA, Hooshdaran B, Schappell W, Wang T, Eguchi S, et al. Cardiac Expression of Factor X Mediates Cardiac Hypertrophy and Fibrosis in Pressure Overload. **JACC Basic Transl Sci 2020;5:69-83. doi: 10.1016/j.jacbts.2019.10.006.**

In chronic pathological stress the heart suffers structural and functional modifications associated with cardiac remodeling that could lead to heart failure and death. Several molecular and cellular changes can be observed, such as myocyte hypertrophy, interstitial fibrosis, increased oxidative stress and inflammation, and prothrombotic states, characterized by greater activation of coagulation factors and platelets, In addition to its primary functions of activating hemostasis, it is currently known that the coagulation cascade factors fulfill other physiological functions related to angiogenesis, inflammation and tissue repair.

The coagulation factor X is a serine protease synthetized in the liver and released into the circulation to be locally activated as another coagulation cascade component in response to tissue damage, thus developing activated thrombin. Recent evidence demonstrated that activated factor X (Factor Xa) also accomplishes other non-hematological functions activating protease-activated receptors PAR1 and PAR2. Both cardiac myocytes and fibroblasts increase the expression of PAR1 and PAR2 in response to different stressor stimuli, thus inducing ventricular remodeling.

In this experimental work, Guo et al. aimed to study the local extravascular generation of factor Xa in response to increased left ventricular pressure and the mechanisms of cellular growth they activate as a consequence of PAR receptor cleavage, in a mice model undergoing aortic arch stenosis to generate left ventricular pressure overload for three weeks. An additional group of animals with stenosis received a daily dose of rivaroxaban at a lower plasmatic concentration than that needed to achieve anticoagulant effects, with the intention of blocking the local myocardial factor Xa. Additional in vitro studies of neurohormonal stressor administration in myocyte and fibroblast cultures were done to demonstrate the mechanisms involved in myocardial remodeling. Results showed an increase in the local expression of factor Xa, which induces myocyte hypertrophy and fibroblast proliferation, migration and differentiation. Moreover, these factor X effects are mediated by the cleavage and activation of PAR1 and PAR2 receptors, that are overexpressed in the hearts with hypertrophy. Interestingly, low dose rivaroxaban did not modify blood coagulation states, but reduced hypertrophy, inflammation and myocardial fibrosis of mice with pressure overload. In addition, mice showed improved left ventricular diastolic function.

Direct-acting anticoagulants on factor Xa are widely used in clinical practice to treat or prevent thromboembolic events in patients with atrial fibrillation, deep vein thrombosis or pulmonary embolism. Recent clinical trials have demonstrated that the combined use of low-dose rivaroxaban and antiplatelet agents reduce the risk of death due to cardiovascular events, as myocardial infarction and stroke in patients with acute coronary syndrome or stable coronary artery disease. The results of Guo et al.'s work demonstrate the local myocardial production of factor Xa and that its inhibition with a low dose of the anticoagulant rivaroxaban prevents maladaptive ventricular remodeling and improves diastolic function. These findings add to the growing evidence of the pleiotropic role of factor Xa in physiological and pathophysiological mechanisms that go beyond their action in the coagulation cascade. Its effects are mediated by the extracellular domain cleavage of PAR1 and PAR2 receptors. Different studies have involved PAR receptors in the determination of infarct size and postischemic and hypertensive remodeling, with proinflammatory and profibrotic action in the myocardium. The present work added to previous evidence generates favorable expectations regarding the benefits of the pharmacological blockade of factor Xa/PAR receptors in cardiac remodeling due to pressure overload. Clinical studies are necessary to validate these preclinical results and to validate the doses and adequate use opportunity.