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Regional heterogeneity and posttranslational myofilament protein alterations in cardiac disease

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Modulation the Ca2+-responsiveness of cardiac myofilaments affects force production during cardiac systoles and ventricular relaxation during cardiac diastoles. To study myofilament protein alterations we perform direct force measurements in permeabilized isolated cardiomyocytes obtained from the hearts of humans or from various animal models of acute or chronic heart failure. Moreover, biochemical assays are employed to pinpoint structure to function relationships between protein alterations and sarcomeric dysfunctions. Our results suggest that at progressed stages of human heart failure beta-adrenergic down-regulation is accompanied by an increase in the Ca2+-sensitivity of force production mainly because of troponin I hypophosphorylation. Alterations in protein phosphorylation are complemented by additional ones during conditions leading to nitro-oxidative stress (e.g. reperfusion following ischemia, postischemic remodeling, doxorubicin toxicity, etc.). Under in vitro test conditions selective oxidation of sulfhydryl groups (SH) by dithiodipyridine, nitration of tyrosine residues by peroxynitrite, enzymatic cleavage by μ-calpain or carbonylation by the Fenton-reaction all decrease the Ca2+-sensitivity of force production in permeabilized cardiomyocytes. However, the sarcomeric proteins affected by these insults and the mechanisms by which they evoke sarcomeric dysfunctions are divergent. Our results suggested predominant structural alterations of the sarcomere following protein cleavage or nitration, while SH-oxidation or protein carbonylation were associated with changes in the fine regulation of sarcomeric function. Collectively, the direction of change in the Ca2+-sensitivity of force production may depend on the hierarchy of sarcomeric protein alterations and on their interactions in the diseased heart. For example, in a postischemic murine model of heart failure (with increased protein carbonylation) we found a decreased Ca2+-sensitivity of force production in cardiomyocytes at the infarcted zone despite troponin I hypophosphorylation. Moreover, our latest results suggest that the above sarcomeric protein alterations combine with each other in a region specific manner in different types of heart failure.

Prof. Zoltán Papp *is an experimental cardiologist and the head of the Division of Clinical Physiology, Institute of Cardiology, University of Debrecen, Hungary. At the moment he serves as the Vice-Dean for Educational Affairs at the Medical Faculty of the University of Debrecen, and also as a Board Member of the Heart Failure Association of the European Society of Cardiology. He acts as the chairman of the Basic Research Section of the Heart Failure Association between 2012 and 2014. Zoltán Papp is experienced in cellular physiological methods, and in particular in direct force measurements in permeabilized isolated cardiomyocytes. The research team of Zoltán Papp concentrates on myocardial contractility, myocardial ischemia/reperfusion injury, acute and chronic heart failure, myofilament proteins, and on positive inotropic agents. Zoltán Papp's research team has contributed to the characterization of various posttranslational protein modifications of cardiac myofilaments, and has elucidated their consequence on sarcomeric force production. In addition, he also studied the relationships between altered intracellular signalling (e.g. β-adrenergic myofilament protein phosphorylation) and impaired contractility of failing hearts with systolic and diastolic dysfunctions. Last but not least, Zoltán Papp has analyzed several aspects of the pharmacological mechanisms of action of levosimendan.*