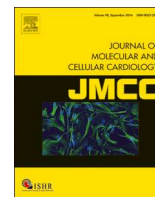




Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

journal homepage: www.elsevier.com/locate/yjmcc

Original article

Myofilament Ca^{2+} sensitivity correlates with left ventricular contractility during the progression of pressure overload-induced left ventricular myocardial hypertrophy in rats

Mihály Ruppert^{a,b,*,1}, Beáta Bódi^{c,1}, Sevil Korkmaz-Icöz^b, Sivakkanan Loganathan^b, Weipeng Jiang^b, Lorenz Lehmann^d, Attila Oláh^a, Bálint András Barta^a, Alex Ali Sayour^{a,b}, Béla Merkely^a, Matthias Karck^b, Zoltán Papp^{c,e}, Gábor Szabó^{b,1}, Tamás Radovits^{a,1}

^a Heart and Vascular Center, Semmelweis University, Budapest, Hungary^b Department of Cardiac Surgery, University of Heidelberg, Heidelberg, Germany^c Division of Clinical Physiology, Department of Cardiology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary^d Department of Cardiology, Angiology and Pulmonology, University Hospital Heidelberg, Heidelberg, Germany^e HAS-UD Vascular Biology and Myocardial Pathophysiology Research Group, Hungarian Academy of Sciences, Debrecen, Hungary

ARTICLE INFO

Keywords:

Myocardial hypertrophy

Myofilament function

 Ca^{2+} sensitivity

Contractility

ABSTRACT

Aim: Here we aimed at investigating the relation between left ventricular (LV) contractility and myofilament function during the development and progression of pressure overload (PO)-induced LV myocardial hypertrophy (LVH).

Methods: Abdominal aortic banding (AB) was performed to induce PO in rats for 6, 12 and 18 weeks. Sham operated animals served as controls. Structural and molecular alterations were investigated by serial echocardiography, histology, quantitative real-time PCR and western blot. LV function was assessed by pressure-volume analysis. Force measurement was carried out in permeabilized cardiomyocytes.

Results: AB resulted in the development of pathological LVH as indicated by increased heart weight-to-tibial length ratio, LV mass index, cardiomyocyte diameter and fetal gene expression. These alterations were already present at early stage of LVH (AB-week6). Furthermore, at more advanced stages (AB-week12, AB-week18), myocardial fibrosis and chamber dilatation were also observed. From a hemodynamic point of view, the AB-wk6 group was associated with increased LV contractility, maintained ventriculo-arterial coupling (VAC) and preserved systolic function. In the same experimental group, increased myofilament Ca^{2+} sensitivity (pCa_{50}) and hyperphosphorylation of cardiac troponin-I (cTnI) at Threonine-144 was detected. In contrast, in the AB-wk12 and AB-wk18 groups, the initial augmentation of LV contractility, as well as the increased myofilament Ca^{2+} sensitivity and cTnI (Threonine-144) hyperphosphorylation diminished, leading to impaired VAC and reduced systolic performance. Strong correlation was found between LV contractility parameters and myofilament Ca^{2+} -sensitivity among the study groups.

Conclusion: Changes in myofilament Ca^{2+} sensitivity might underlie the alterations in LV contractility during the development and progression of PO-induced LVH.

Abbreviations: AB, aortic banding; ANP, atrial natriuretic peptide; AWT_d , anterior wall thickness in diastole; $\beta/\alpha\text{-MHC}$, beta/alpha myosin heavy chain ratio; CD, cardiomyocyte diameter; cMyBP-C, cardiac myosin binding protein-C; CO, cardiac output; cTnI, cardiac troponin-I; $\text{dP}/\text{d}t_{\text{max}}$, maximal slope of systolic pressure increment; $\text{dP}/\text{d}t_{\text{min}}$, maximal slope of diastolic pressure decrement; $\text{dP}/\text{d}t_{\text{max-EDV}}$, $\text{dP}/\text{d}t_{\text{max-end-diastolic volume}}$ relationship; E_a , arterial elastance; EDPVR, end-diastolic pressure-volume relationship; ESPVR, end-systolic pressure-volume relationship; F_{max} , Ca^{2+} -saturated maximal force; F_{passive} , Ca^{2+} -independent passive tension; HW/TL, heart weight to tibial length ratio; LVEDD, left ventricular end-diastolic diameter; MAP, mean arterial pressure; pCa_{50} , myofilament Ca^{2+} sensitivity; PO, pressure overload; PRSW, preload recruitable stroke work; P-V, pressure-volume; PWT_d , posterior wall thickness in diastole; SV, stroke volume; SW, stroke work; Tau, time constant of left ventricular pressure decay; VAC, ventriculo-arterial coupling

* Corresponding author at: Experimental Research Laboratory, Heart and Vascular Center, Semmelweis University, 1122 Budapest, Városmajor u. 68., Hungary.

E-mail address: ruppertmis@gmail.com (M. Ruppert).

¹ Authors Mihály Ruppert and Beáta Bódi, Gábor Szabó and Tamás Radovits contributed equally to this work.

<https://doi.org/10.1016/j.yjmcc.2019.02.017>

Received 12 December 2018; Received in revised form 31 January 2019; Accepted 28 February 2019

Available online 04 March 2019

0022-2828/ © 2019 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).