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Hemodynamic characterization of a transgenic rat strain stably expressing the calcium sensor protein GCaMP2

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Hemodynamic characterization of a transgenic rat strain stably expressing the calcium sensor protein GCaMP2

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Background: The importance of calcium homeostasis and signaling has been intensively investigated in various tissues. A novel transgenic rat strain has recently been generated that stably expresses the genetically engineered calcium sensor protein GCaMP2 (containing a calmodulin-based calcium sensor and a fluorescent protein) in different cell types including cardiomyocytes (Sci Rep 2015; 5:12645). This animal model offers a unique possibility to directly examine calcium signaling in cells, tissues and organs, thus it might be a useful tool for assessing the effects of drugs and pathophysiological states on cardiac calcium homeostasis.

Purpose: In order to investigate whether the expression of the GCaMP2 protein itself affects cardiac function, in the present work we aimed at characterizing in vivo hemodynamics by left ventricular (LV) pressure-volume analysis in the GCaMP2 transgenic rats strain.

Methods: GCaMP2 transgenic rats (GCaMP2 group, n=10) and age-matched Sprague-Dawley control animals (Co group, n=10) were investigated. In vivo hemodynamic characterization was performed by LV pressure-volume analysis, obtaining both conventional hemodynamic parameters as well as sensitive, load-independent functional indices.

Results: Post-mortem heart weight data showed increased heart weight in the GCaMP2 group compared to controls (heart weight to tibial length ratio: 0.26±0.01 GCaMP2 vs. 0.23±0.01g/cm Co, $p<0.05$), suggesting myocardial hypertrophy. We detected elevated mean arterial pressure (MAP: 137.6±3.1 GCaMP2 vs. 127.9±3.1mmHg Co, $p<0.05$) in transgenic rats. LV systolic function was not altered in transgenic rats as indicated by conventional parameters (ejection fraction, stroke volume, dP/dtmax) and load-independent, sensitive indices (end-systolic pressure-volume relationship, preload recruitable stroke work). Regarding diastolic function we found a marked deterioration of LV active relaxation in GCaMP2 animals (Tau: 16.8±0.7 GCaMP2 vs. 11.7±0.6ms Co, $p<0.001$; dP/dtmin: -9641±247 GCaMP2 vs. -10781±420 mmHg/s Co, $p<0.05$). Parameters of LV stiffness were found to be unchanged in transgenic rats.

Conclusions: Our data indicated myocardial hypertrophy, arterial hypertension and impaired LV active relaxation along with unchanged systolic performance in the heart of transgenic rats expressing the GCaMP2 fluorescent calcium sensor protein. Myocardial expression of this genetically engineered calcium sensor protein might interfere with physiological calcium handling, resulting in the observed characteristic changes in the heart. While there were no significant changes in calcium handling in primary cardiac cell cultures (Sci Rep 2015; 5:12645), special caution should be taken when using this rodent model in cardiovascular pharmacological and toxicological studies. In addition, this rat may be a useful model for studying calcium handling in cardiac hypertrophy.