

Incomplete structural reverse remodeling from late-stage left ventricular hypertrophy impedes the recovery of diastolic but not systolic dysfunction in rats

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Objective: Pressure overload-induced left ventricular myocardial hypertrophy (LVH) regresses after pressure unloading. However, distinct structural alterations become less reversible during the progression of LVH, which might influence the restoration of cardiac function. Here, we investigated how a reverse remodeling process from early versus late-stage LVH affects different aspects of left ventricular function.

Methods: Pressure overload was induced in rats for 6, 12 and 18 weeks. Sham-operated animals were used as controls. Pressure unloading was evoked by removing the aortic constriction at week 6 (early-debanded) and week 12 (late-debanded). Echocardiography and histological analyses were carried out to detect structural alterations. Pressure–volume analysis was performed to assess left ventricular function. Molecular alterations were analyzed by quantitative real-time-PCR, and western blot.

Results: Myocardial hypertrophy regressed to a similar degree in early and late-debanded groups. Accordingly, no differences were detected in the extent of regression regarding left ventricular mass, cardiomyocyte diameter, heart weight-to-tibial length ratio and beta-to-alpha myosin heavy chain expression. In contrast, resorption of interstitial and perivascular myocardial fibrosis was only detected in the early-debanded group, whereas it persisted in the late-debanded group. Removing the aortic constriction normalized ventriculo-arterial coupling and increased systolic performance in both debanded groups. However, the residual dysfunction in active relaxation and passive stiffness was more severe in the late-debanded compared to the early-debanded group.

Conclusion: Early debanding led to complete structural reverse remodeling (reduced hypertrophy and fibrosis) and full restoration of left ventricular function. In contrast, myocardial fibrosis persisted after late debanding, which impeded the normalization of diastolic but not systolic function.

Keywords: contractility, diastolic function, interstitial fibrosis, myocardial hypertrophy, perivascular fibrosis, pressure overload, pressure–volume analysis, reverse remodeling, systolic function

Abbreviations: AB, aortic banding; ANP, atrial natriuretic peptide; ANOVA, analysis of variance; AWTd, anterior wall thickness in diastole; β/α -MHC, Beta/Alpha myosin heavy chain ratio; CD, cardiomyocyte diameter; CO, cardiac output; CTGF, connective tissue growth factor; Ea, arterial elastance; EDPVR, end-diastolic pressure–volume relationship; EF, ejection fraction; ESPVR, end-systolic pressure–volume relationship; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HR, heart rate; HW/TL, heart weight to tibial length ratio; LV, left ventricle; LVH, left ventricular myocardial hypertrophy; MAP, mean arterial pressure; MF, myocardial fibrosis; PO, pressure overload; PRSW, preload recruitable stroke work; P-V, pressure–volume; PWTd, posterior wall thickness in diastole; σ , left ventricular meridional wall stress; SV, stroke volume; Tau, time constant of left ventricular pressure decay; VAC, ventriculo-arterial coupling

INTRODUCTION

In recent years, a growing body of literature has provided evidence that the termination of the pathological insult of sustained pressure overload [e.g. by aortic valve replacement (AVR) in case of aortic stenosis or by antihypertensive medications in case of arterial hypertension] induces the regression of left ventricular myocardial hypertrophy (LVH) [1–3]. This process is termed myocardial reverse remodeling and involves the restoration of the hypertrophic left ventricular phenotype on the molecular, ultrastructural, geometrical and also functional level [4]. Nevertheless, recent experiments have indicated that the

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