

RESEARCH ARTICLE | Sex Differences in Cardiovascular and Cerebrovascular Physiology, Disease, and Signaling Mechanisms

Pressure-volume analysis reveals characteristic sex-related differences in cardiac function in a rat model of aortic banding-induced myocardial hypertrophy

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Ruppert M, Korkmaz-Icöz S, Loganathan S, Jiang W, Lehmann L, Oláh A, Sayour AA, Barta BA, Merkely B, Karck M, Radovits T, Szabó G. Pressure-volume analysis reveals characteristic sex-related differences in cardiac function in a rat model of aortic banding-induced myocardial hypertrophy. *Am J Physiol Heart Circ Physiol* 315: H502–H511, 2018. First published May 25, 2018; doi:10.1152/ajpheart.00202.2018.—Sex differences in pressure overload (PO)-induced left ventricular (LV) myocardial hypertrophy (LVH) have been intensely investigated. Nevertheless, sex-related disparities of LV hemodynamics in LVH were not examined in detail. Therefore, we aimed to provide a detailed characterization of distinct aspects of LV function in male and female rats during different stages of LVH. Banding of the abdominal aorta (AB) was performed to induce PO for 6 or 12 wk in male and female rats. Control animals underwent sham operation. The development of LVH was followed by serial echocardiography. Cardiac function was assessed by pressure-volume analysis. Cardiomyocyte hypertrophy and fibrosis were evaluated by histology. At *week 6*, increased LV mass index, heart weight-to-tibial length, cardiomyocyte diameter, concentric LV geometry, and moderate interstitial fibrosis were detected in both male and female AB rats, indicating the development of an early stage of LVH. Functionally, at this time, impaired active relaxation, increased contractility, and preserved ventricular-arterial coupling were observed in the AB groups in both sexes. In contrast, at *week 12*, progressive deterioration of LVH-associated structural and functional alterations occurred in male but not female animals with sustained PO. Accordingly, at this later stage, LVH was associated with eccentric remodeling, exacerbated fibrosis, and increased chamber stiffness in male AB rats. Furthermore, augmented contractility declined in male but not female AB animals, resulting in contractility-afterload mismatch. Maintained contractility augmentation, preserved ventricular-arterial coupling, and better myocardial compliance in female rats contribute to sex differences in LV function during the progression of PO-induced LVH.

NEW & NOTEWORTHY We investigated sex differences in pressure overload-induced left ventricular myocardial hypertrophy for the first time on the functional level by pressure-volume analysis. We

found that left ventricular hypertrophy was initially characterized by prolonged active relaxation, increased contractility, and maintained ventricular-arterial coupling in both sexes. However, at a later stage, augmented contractility declined in male but not female rats, resulting in contractility-afterload mismatch. Furthermore, in male rats, increased myocardial stiffness also contributed to hypertrophy-associated diastolic dysfunction.

cardiac function; contractility; left ventricular hypertrophy; pressure-volume analysis; sex differences; ventricular-arterial coupling

INTRODUCTION

In recent decades, sex differences have been reported to influence the development of many cardiovascular pathologies, including pressure overload (PO)-induced pathological left ventricular (LV) myocardial hypertrophy (LVH). In accordance, numerous aspects of LVH were taken under investigation to explore potential sex-related disparities. As a result, sexual dimorphisms in LV volumes, geometry, function, structural composition, and molecular background were also recognized. To summarize these key findings, in women with long-lasting hypertension or aortic stenosis as well in female rodents with aortic constriction, smaller LV dimensions (2, 4, 26), more concentric LV geometry (2, 4, 6), better systolic function (2, 4, 6, 9, 26), less interstitial fibrosis (10, 26), less apoptosis (7), and different regulation of genes encoding mitochondrial factors (28) were documented compared with their male counterparts with comparable mechanical overload.

Despite the above-mentioned extensive clinical and experimental research, potential sex-related differences with regards to LV hemodynamics have not yet been investigated. In recent years, the technique of LV pressure-volume (P-V) analysis became the “gold standard” method to assess numerous aspects of *vivo* cardiac function in animal models accurately (21). Particularly, in pathological conditions associated with sustained PO [aortic banding (AB), aortic stenosis, and arterial hypertension], the significance of P-V analysis is given by the fact that the robust increment in afterload makes the conventional load-dependent parameters inappropriate to characterize

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