Jasmine B Matsuda
Undergraduate
Mount San Antonio College, Walnut, CA

Parnia Mobasheran[1,2], Qinglin Yang[1,2]
[1.]LSU Health Sciences Center, Department of Pharmacology & Experimental Therapeutics
[2.]Cardiovascular Center of Excellence, LSUHSC

"Left atrial dysfunction is an early and transitional driver in the development of heart failure with preserved ejection fraction"

Heart failure with preserved ejection fraction (HFpEF) constitutes over 50% of HF cases in the United States, with growing incidence in aging and metabolically burdened populations. The left atrium (LA) plays a crucial role by acting as a reservoir during ventricular contraction. Impaired LA function leads to reduced left ventricle (LV) filling or elevated filling pressures, the latter has recently proposed as a hallmark of HFpEF progression. However, it is impossible to establish LA's roles in the development and progression of HFpEF in patients. To address this, we developed a novel pre-clinical mouse model to investigate how LA plays a critical role in initiating and sustaining HFpEF. Using a fine-tip cautery pen, we applied controlled epicardial burns to the left atrial (LA) surface of 5–6-month-old male C57BL/6J mice to induce localized atrial dysfunction (AD). Burns were distributed across multiple non-overlapping regions to achieve widespread injury. Mice were assigned to three groups, including sham (no injury), mild AD (3 burns), and moderate AD (5 burns). Over the following 4 weeks, we evaluated cardiac function (transthoracic echocardiography), pulmonary function (whole-body plethysmography), and exercise capacity (treadmill test) to monitor disease progression. Mice with moderate LA injury showed reduced left ventricular ejection fraction (LVEF) and fractional shortening (LVFS), enlarged left atrial (LA) area, impaired LV longitudinal strain, worsened LV diastolic function, and reduced exercise capacity, without evidence of pulmonary dysfunction. In contrast, mice with mild LA injury preserved both LVEF and LAEF with decreased LA and LV time to peak strains of radial and longitudinal, exhibited LA enlargement, developed LV diastolic dysfunction and pulmonary congestion, and demonstrated impaired exercise tolerance. Our LA injury model demonstrates severity-dependent pathophysiological outcomes, with mild injury replicating the classic HFpEF phenotype. Moderate LA injury impaired LV filling and reduced preload, resulting in EF without signs of pulmonary dysfunction, likely LA and LV failure did not reach the point causing pulmonary congestion. However, the resulting systolic impairment limited the cardiac capacity to meet increased metabolic demands during treadmill testing. In contrast, mild LA injury preserved EF, likely due to the compensatory hyper-contraction to maintain normal LV filling with increased filling pressure, which compromises LV compliance of the healthy part of LA, leading to diastolic dysfunction. On the other hand, the increased LA pressure increases pulmonary venous pressure and reduced lung compliance. Consequently, these changes culminated in diminished exercise tolerance. Mild AD findings closely resemble the HFpEF phenotype, emphasizing LA dysfunction as a critical early and transitional driver. The above results provide strong evidence supporting the hypothesis that LA is a crucial hallmark in the development and progression of HFpEF. Moreover, this highly innovative preclinical model provides a valuable platform to study the pathogenesis and pathological mechanisms of HFpEF, explore therapeutic targets, and identify biomarkers for early detection.