Editorial

Aortic regurgitation and heart valve disease in mice

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Heart valve disease, in both congenital and acquired forms, is an important and growing public health problem. Epidemiologic studies in the United States have revealed an overall prevalence of 2.5%, and the incidence increases with age. Heart valve disease has a growing clinical impact and significant economic burden (1,2). In patients with aortic stenosis (AS) or aortic regurgitation (AR), morbidity and mortality is increased because of heart failure from chronic left ventricle (LV) disfunction (3,4). An analysis of the mechanism by which chronic LV volume overload leads to heart failure due to AR or AS is important and a useful mice model is timely.

Epidermal growth factor receptor (EGFR) is one of the most physiologically important receptor tyrosine kinases. It plays important biological roles in developmental biology and tissue homeostasis (5,6). EGFR signaling regulates the embryonic formation of semilunar heart valves. Mice homozygous for a single-nucleotide substitution mutation in *EGFR* showed a global 90% reduction in EGFR-tyrosine kinase activity. $Egfr^{Wa2/Wa2}$, or waved-2 (Wave), mice have histological and functional abnormalities in the aortic valve (7,8).

In this issue, Hajj and colleagues provide comprehensive functional, histological, and molecular characterization of spontaneous valvular-volume-overload cardiomyopathy in a mouse model (9). The authors first examined the aortic function and structure and found a significant transvalvular gradient in Wave mice with AR, even when AS was not present. Other researchers have reported fibrosis, calcification, and elevated transvalvular gradients in aortic valves of Wave mice and interpreted the results as indicative of calcific AS (8). For Hajj and colleagues, aortic cusp separation (ACS) was normal in Wave mice at all ages. However, in 3 of 55 Wave mice, ACS was <0.66 mm; the mice had hemodynamically important AS and also severe AR. On color Doppler echocardiography, the prevalence of moderate or severe AR was 70%, 81%, and 73% in Wave mice at 1.5, 6, and 12 months of age, respectively. Aortic valve regurgitant fraction was significantly increased in all Wave mice. However, interestingly, mitral regurgitation was trivial or absent in all mice. Despite the presence of normal ACS, Wave mice showed substantial systolic pressure gradients across the aortic valve. The increased transvalvular gradient was associated with increased aortic pulse pressure, which is consistent with AR but not AS. Increased transvalvular gradient and ACS were not correlated. Mice without AS showed a remarkable quadratic relationship between LV stroke volume and transvalvular systolic gradient, which implies that the gradient is produced by AR. The findings are exciting for two reasons. First, they provide novel information of significantly increased aortic-valve regurgitant fraction and trivial or absent mitral regurgitation in all mice. Second, they confirm that the transvalvular systolic gradient was produced by the AR.

Then Hajj and colleagues examined histological changes in the aortic valve. Valve collagen levels, valve calcification and lipid deposition were undetectable in Wave mice at 1.5 months of age but were significantly increased at 6 and 12 months. Levels of proteoglycans in the aortic valve were significantly elevated in Wave mice at 1.5, 6, and 12 months of age. All these data provide an interesting observation that aortic valve dysfunction occurs in the presence of excess proteoglycans level, including versican, in valve cusps, but precedes fibrosis, calcification, apoptosis, and lipid deposition in the valve.

The authors investigated the mechanism of valve dysfunction in Wave mice. They identified myxomatous structural incompetence and consequent diastolic prolapse of valve cusps as major mechanisms of AR, features that are common in humans with isolated AR (10). A novel finding was that deficient proteoglycan breakdown occurs

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postnatally in Wave mice. Despite significant increases in polymeric intact versican level, level of cleaved versican was reduced in Wave mice at 6 months of age.

In investigating ventricular morphology and function, Hajj and colleagues found significant LV chamber enlargement, consistent with volume overload, in Wave mice with AR. LV stroke volume and LV mass, indexed to body mass, was elevated. LV ejection fraction was normal in mice at 1.5 and 6 months of age but was significantly decreased by 12 months, which indicated the onset of LV dysfunction. In mice with AR, the features of LV mass, LV end diastolic volume, and LV ejection fraction were similar in males and females at 6 months of age. The authors further examined myocardial fetal gene expression and collagen isoforms, which occurs early and persists essentially unchanged for months (11). Myocardial expression of β-myosin heavy chain, myocyte-enriched calcineurin-interacting protein-1.4, collagen-1, and collagen-3 was significantly increased in Wave mice at 6 months of age. Mice at 12 months old showed fibrosis in the myocardium. Then, authors examined structural changes in individual cardiomyocytes in this mouse model. Cardiomyocyte transverse tubules (TTs) critically regulate excitation–contraction coupling by facilitating Ca^{2+} release from the sarcoplasmic reticulum. TT disruption leads to disease progression from hypertrophy to heart failure (12). At 1.5 and 3 months of age, when Wave mice demonstrated LV hypertrophy and normal LV systolic function, TT organization was normal. At 12 months of age, when both LV hypertrophy and systolic dysfunction were present, TT organization was significantly disrupted. All these data suggest that 6 to 12 months might represent the age of onset of LV dysfunction.

Hajj and colleagues have provided many exciting findings to reinforce the importance of the comprehensive characterization of aortic valve function *in vivo* when assessing the therapeutic efficacy of interventions to protect or improve valve function even in heart valve disease.

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Footnote

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