Effect of neprilysin inhibitor for ischemic mitral regurgitation after myocardial injury

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Background: After myocardial infarction (MI), mitral valve (MV) tethering and fibrosis stimulate functional mitral regurgitation (MR), resulting in high morbidity of heart failure and cardiac mortality. However, pharmacological treatment has not been proven effective in reducing ischemic MR. MV change post-MI is associated with an excessive endothelial-to-mesenchymal transition (EMT) by transforming growth factor (TGF)-β overexpression and also with left ventricular (LV) remodeling. In a recent clinical study using echocardiography, angiotensin receptor neprilysin inhibitor (ARNI) reduced functional MR to a greater extent than did valsartan, but the mechanism was not revealed.

Purpose: This study tested the hypothesis that treatment of neprilysin inhibitor attenuates functional MR after MI by facilitating LV reverse remodeling and suppressing EMT which mitigates inadequate leaflet adaptation.

Methods: In male Sprague-Dawley rats (n=31), functional MR was induced by occluding the left circumflex coronary artery. Two weeks after MI, MR and LV dilatation were confirmed by echocardiography and magnetic resonance imaging (MRI). Rats were randomly assigned to LCZ696 treatment (ARNI, 60 mg/kg/d, n=10), valsartan treatment (30mg/kg/d, n=10), or corn oil only (MR control group; n=11). After 6 weeks, LV volumes, functions and MR extent were quantified by using echocardiography, cardiac MRI and pressure-volume loop analysis. Also, excised mitral leaflets and LV were analyzed by histopathology and primary cultured valvular endothelial cells (VECs) were evaluated focusing on molecular changes.

Results: LCZ696 significantly attenuated post-MI LV dilatation after 6 weeks when compared with the control group (LV end-diastolic volume (EDV), 461.3±41.3 uL versus 525.1±78.2 uL; p<0.05), while valsartan did not (LV EDV, 471.2±26.8 uL; p>0.05 to control). There were no significant differences in the change of arterial pressure and ejection fraction between the treatment groups, however, dP/dt was greater in the LCZ696 group than in the MR control group (8203±286 mmHg/s for LCZ696 versus 6936±555 mmHg/s for MR control; p=0.01). MR extent and LA volume were significantly decreased in the LCZ696 group compared with the valsartan group. Pathological analysis showed that fibrosis was more prominent in the MR control than in the LCZ696 group. LCZ696 strongly reduced leaflet thickness, TGF-β, and downstream phosphorylated extracellular-signal-regulated kinase and EMT (25.4±11.8% vs. 53.4±12.6% α-smooth muscle actin-positive VECs; p<0.05). Leaflet area increased comparably (5%) in the LCZ696 group compared with the valsartan group.

Conclusions: Neprilysin inhibitor has positive effects on LV reverse remodeling and also directly modulates profibrotic changes of MV leaflets post-MI without eliminating adaptive growth. Understanding the mechanisms could provide new opportunities to ARNI reducing ischemic MR.