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Pressure overload evokes cardiac chemokine receptor CXCR4 upregulation, which predicts subsequent progression of heart failure

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Background. Excessive inflammation after myocardial infarction is a critical contributor to ventricular remodeling, and a potential therapeutic target. The role in non-ischemic heart failure is not well characterized.

Purpose. We sought to noninvasively evaluate temporal and spatial inflammation in mice following pressure overload by multimodality imaging.

Methods. C57Bl/6 mice underwent transverse aortic constriction (TAC, n=41) or sham surgery (n=20). PET with the chemokine receptor CXCR4 ligand Ga-68-pentixafor was conducted serially at 3d, 1wk and 3wk after TAC. CMR was used for serial measurement of left ventricular (LV) geometry and function. Immunohistochemistry assessed inflammatory cell infiltration. Masson trichrome staining revealed interstitial collagen deposition. Ventricular unloading was achieved by removal of aortic banding (reverse TAC, rTAC, n=8). Inflammation and function were non-invasively assessed at 1wk and 3wk after rTAC.

Results. CMR identified progressive LV hypertrophy after TAC (LV mass, 3wk: 131±20 vs 87±7mg for sham, p<0.001). Contractile function was persistently impaired (ejection fraction (EF), 3d: 47±12 vs 67±5%, p<0.001; 1wk: 47±13 vs 68±6%, p<0.001; 3wks: 44±12 vs 66±6%, p<0.001). Histology at 3wk post-TAC showed interstitial fibrosis, confirming LV remodeling. CXCR4 PET displayed mild diffuse inflammation throughout the LV within 1wk after TAC (%ID/g, d3: 1.02±0.19 vs 0.87±0.12 p<0.05; 1wk: 0.96±0.20 vs 0.74±0.25 p<0.001), declining by 3wk (0.86±0.14 vs 0.74 ± 0.13, p=0.06). The CXCR4 signal at 7d predicted systolic volume at 3wks (r=0.44, p=0.006). Immunostaining revealed an elevation of CD68+ macrophages in LV after TAC compared to sham (cells/field, 1wk: 74±24 vs 37±12, p<0.01; 3wk: 63±14 vs 37±12, p<0.001), which was inversely proportional to cardiac function (r=-0.82, p <0.01). rTAC resulted in rapid recovery of LV function compared to 3wk TAC in the same animals (EF: 57±13 vs 44±15%, p<0.01). Moreover, CXCR4 signal was significantly lowered by rTAC (%ID/g, 0.64±0.08 vs 0.92±0.14, p=0.013), corroborating the interplay between ventricular loading, inflammation and contractile function.

Conclusions. Ga-68-Pentixafor identifies mild diffuse inflammatory cell infiltration in pressure overload induced heart failure, proportional to functional decline. Recovery after rTAC lowered Ga-68-pentixafor signal, indicating a relationship between pressure overload and inflammation, which may emerge as a target for novel therapeutic strategies.
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