Bone morphogenetic protein 7 protects against pressure overload-induced left ventricular remodeling and facilitates its regression in mice

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Purpose: TGF-β1 and 2 exert fibrogenic and hypertrophic effects in the myocardium under biomechanical stress. Another member of the TGF-β family, Bone Morphogenetic Protein 7 (BMP7), opposes TGF-β-induced fibrogenesis. Herein, we assessed the role of BMP7 in the LV remodeling response to pressure overload and in the LV reverse remodeling after pressure overload release.

Methods: C57BL6 and BMP7+/− mice were subjected to 4 wk aortic arch banding (AB) or 4 wk banding followed by debanding surgery (DB). Echocardiography was performed using Vevo-770 equipment (VisualSonics). Histological fibrosis (Masson trichrome) and myocardial expression of fibrosis related genes (qPCR) were analyzed. Statistical analyses: ANOVA and Bonferroni test.

Results: s.c. delivery (4 wk) of recombinant BMP7 (rBMP7) to AB mice diminished LV hypertrophy (LV mass, 4wk AB: 117.3 ± 3.5 mg vs 4wk B+BMP7: 93.2 ± 2.5 mg, p<0.001) and gene and histological fibrosis. Systolic [(LVEF, 4wk AB: 39 ± 1.5% vs 4wk B+BMP7: 58 ± 3.5%, p<0.001), MAPSE, 4wk AB: 0.42 ± 0.02 mm vs 4wk B+BMP7: 0.56 ± 0.02 mm p<0.001]) and diastolic (E/E', 4wk AB: 41 ± 1 vs 4wk B+BMP7: 29 ± 1, p<0.001) dysfunctions were lesserened. Following debanding (DB), most of the reverse remodeling occurred over the first postoperative week. One week treatment with a neutralizing BMP7-Ab, starting at DB, hampered remodeling regression [LV mass (1 wk DB: 104 ± 3.6 mg vs 1 wk DB+BMP7-Ab: 114 ± 3.5 mg, p<0.005); fibrotic area (1 wk DB: 0.4 ± 0.09% vs 1 wk DB+BMP7-Ab: 2.4 ± 0.7%, p<0.001) and the recovery of LV dysfunction [(LVEF, 1 wk DB: 51 ± 1.4% vs 1 wk DB+BMP7-Ab: 45 ± 1.4%, p<0.005); (MAPSE, 1 wk DB: 0.61 ± 0.02 mm vs 1 wk DB+BMP7-Ab: 0.49 ± 0.03 mm, p<0.001)]. Similarly, the myocardium from mice deficient in BMP7 displayed a poorer remodeling regression [LV mass (1 wk DB: 104 ± 3.6 mg vs 1 wk DB+BMP7+/−: 111 ± 4 mg), fibrotic area (1 wk DB: 0.4 ± 0.09% vs 1 wk DB+BMP7+/−: 2.8 ± 0.5%, p<0.001) and less functional recovery than WT mice [(LVEF, 1 wk DB: 51 ± 1.4% vs 1 wk DB+BMP7+/−: 44 ± 1.4%, p<0.005); (MAPSE, 1 wk DB: 0.61 ± 0.02 mm vs 1 wk DB+BMP7+/−: 0.42 ± 0.02 mm, p<0.001)].

Conclusion: BMP7 attenuated the myocardial remodeling response to pressure overload and facilitated the reverse remodeling and functional recovery after releasing the aortic constriction. Strategies to modulate the activity of BMP7 signaling and its consequences on the LV remodeling regression may have putative therapeutic value after valve replacement in patients with aortic stenosis. Funding: ISCIII PI12/009999.

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