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Impaired TGF-β mediated cardiac healing in patients with right ventricular dilatation after repair of tetralogy of Fallot

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Introduction: The transforming growth factor (TGF)-β pathway plays an important role in the setting of left ventricular pressure overload and post-myocardial infarction compensatory processes with regard to cardiac hypertrophy, fibrosis, and remodeling. Our aim was to evaluate the role of TGF-β in patients with right ventricular (RV) volume overload after tetralogy of Fallot (TOF) repair.
Methods: 96 patients (22 (7–66) years) were included and underwent magnetic resonance imaging to assess RV size and function. Serum levels of TGF-β were assessed using ELISA kits; inflammatory factors (e.g. tumor necrosis factor-α and interferon-γ), cardiomyocyte growth factors (e.g. epidermal growth factor), and metalloproteinase inhibitor 2 (i.e. tissue inhibitor of metalloproteinase (TIMP) 2) were measured using protein array analysis. In 36 patients, serial follow-up measurements were available with a 5-year interval (14 ± 5 years at baseline). Results were compared to 70 healthy controls (21 (12–64) years).
Results: TGF-β tended to be lower (3.8 ± 3.3 ng/ml vs. 6.3 ± 5.7 ng/ml, p = 0.10) in patients with a large RV (RV end-diastolic volume (EDV) 171 ± 22 ml/m2) than in patients with a small RV (RVEDV 102 ± 12 ml/m2). In the serial follow-up patients, RVEDV increased (137 ± 33 ml/m2 to 148 ± 38 ml/m2, p = 0.001) over 5-years time, while TGF-β decreased (4.6 ± 2.6 ng/ml to 3.0 ± 1.9 ng/ml, p = 0.005) during this period. In controls, TGF-β remained unchanged with increasing age. Contrary to results in patients with a small RV and controls, inflammatory factors increased with increasing follow-up duration in patients with a large RV, while cardiomyocyte growth factors and TIMP 2 decreased.
Conclusions: We have linked the process of progressive RV dilatation with declining serum levels of TGF-β in patients after TOF repair. Lower TGF-β levels coincided with increased markers of immune activation and reduced markers of cardiac protection, making this subgroup of patients more susceptible to adverse RV remodeling and eventually RV failure.
A better understanding of the molecular biology that governs this process might aid in earlier recognition of patients at risk for heart failure and better treatment options.