Cell therapy to restore overloaded right ventricular function: Will the dream come true?

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Background. — Despite the prevalence of right ventricular (RV) failure in congenital heart diseases, cell therapy applied to the right ventricle is poorly studied. Our aim was to evaluate in a large animal model of overloaded RV dysfunction such therapy using cardiac progenitors issued from human embryonic stem cells.

Methods. — A model of combined (barometric and volumetric) overloaded RV dysfunction was created in piglets using a surgical procedure mimicking repaired tetralogy of Fallot. After 4 months, cell therapy was surgically administrated using either multiple trans-epicardial injections of HUES-24 derived human cardiac progenitors into right ventricle myocardium or extracellular matrix hydrogel patches seeded with cardiac progenitors and sewn after a gentle abrasion on the free wall of the right ventricle. Myocardial function was measured 3 months after cell transplantation by conductance catheter technique using maximal elastance (E_max) slope. The risk of ventricular arrhythmia was evaluated by programmed ventricular stimulation at the end of the follow-up. A histological study analyzed the structural remodelling. The fate of the progenitors was studied using antibodies directed against Ki67, CD31, CD34, GFP, Islet1 and Connexin 43. All pigs were immunosuppressed using tacrolimus.

Results. — All pigs survived and neither complication nor ventricular arrhythmia occurred. In injected animals (SHAM group: \( n = 6 \), HUES-24 group: \( n = 6 \)) the evolution of the E_max slope value was similar between the two groups. Whereas the total fibrosis increased significantly with time in SHAM, it returned to baseline values in HUES-24 group. However, the progenitors were not found into myocardium. In contrast, in patched animals, human progenitors were found not only in the patch zone, but also close to the myocardium. These progenitors were able to proliferate, to migrate, to express specific cardiac markers and to establish inter-progenitors connexions.

Conclusion. — Cell therapy using trans-myocardial injections of human cardiac progenitors seems to have a beneficial effect on overloaded RV tissue remodelling, but this mode of administration is not sufficient to obtain a significant improvement of myocardial contractility. Seeded patch seems to be more conservative for engrafted cells; their impact on overloaded RV function requires further experimentation.

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