An Interdisciplinary Multiscale Modeling Approach to Develop Right Ventricle Pulmonary Valve Replacement Surgical Procedures with a Contracting Band to Improve Ventricle Ejection Fraction

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Right ventricular (RV) dysfunction is a common cause of heart failure in patients with congenital heart defects and often leads to impaired functional capacity and premature death. Patients with repaired Tetralogy of Fallot (ToF), a congenital heart defect which includes a ventricular septal defect and severe right ventricular outflow obstruction, account for the majority of cases with late-onset RV failure. Current therapy by surgical or catheter based pulmonary valve insertion to treat pulmonary regurgitation and RV outflow patch reduction has proven inadequate to restore RV function in most patients. A new surgical option placing an elastic band in the right ventricle is proposed to improve RV function measured by ejection fraction (EF). An interdisciplinary multiscale multiphysics modeling approach is proposed to combine cardiac magnetic resonance (CMR) imaging, modeling, tissue engineering and mechanical engineering techniques to construct ventricle models, perform virtual surgery, demonstrate feasibility of the new surgical procedure with band insertion, and identify optimal mechanical conditions under which optimal surgical outcome and cell-seeded contracting band myocardium tissue regeneration could be achieved. 3D multiscale CMR-based RV/LV/Patch/Band models will be introduced to provide assessment for RV mechanical conditions and cardiac function with different band options. The models will include: band insertion with various design options; fluid-structure interactions (FSI) and active contraction; isotropic and anisotropic tissue (macro) and microthread (micro) material properties; two-layer RV/LV construction with myocardial fiber orientation; and models at organ, bundle and cell levels interacting with and informing each other. Fibrin microthreads seeded with stem-cell-derived myocytes will be used to form microthread bundles (contracting bands) for the new surgical procedure. Planar biaxial testing of fresh human myocardium will be completed using a custom-designed device. Mechanical forces generated by myocytes-seeded fibrin microthreads and bundles will be determined with cyclic uniaxial testing. These data will be used to generate micro-structure-based models of contracting biopolymer bands. Flow shear stress conditions for cell adhesion and detachment will be quantified using in vitro experiments. Macro/micro-models will be used to calculate flow shear stress for optimal band design. Our modeling results indicated that the band insertion, combined with active band contraction and tissue regeneration techniques that restore RV myocardium, has the potential to improve right ventricle ejection fraction (RVEF) by 2-7%. A 7% increase in RVEF compares favorably with recently published drug trials to treat heart failure where an improvement in LVEF of 3-4% resulted in a significant improvement in functional capacity. This research was supported in part by NIH-R01-HL 089269 (del Nido, Tang, Geva), NIH–HL63095 (PI: del Nido) and NIH-5P50HL074734 (PI: Geva; Co-Investigator: del Nido).