223

Virtual Implantation of the 50cc Total Artificial Heart

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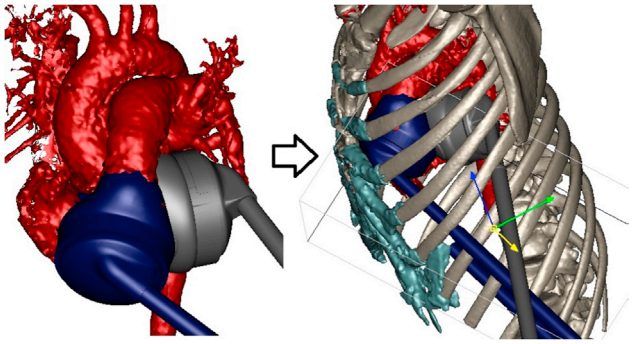
Purpose: Our group previously described successful use of virtual implantation of the 70cc Total Artificial Heart (TAH) to predict safe placement in small-size patients not meeting standard fit criteria. With the new 50cc TAH, there is an opportunity for broader use of the TAH device in pediatric patients with biventricular heart failure. The proposed fit criteria for the 50cc TAH (BSA 1.2-1.6 m2) has not been tested in actual patients. The study objective was to determine the efficacy of virtual implantation of the 50cc and 70cc TAH in a cohort of pediatric heart failure patients and compare virtual fit results with proposed fit criteria.
Methods: A chest CT of each patient was rendered for 3D display of the thoracic cage and intrathoracic structures. 3D-rendered representations of the 50cc and 70cc TAH devices were tested using virtual implantation of the device into the thoracic cage of each patient. The devices were assessed for intersection with the thoracic cage and intrathoracic structures. The results of the virtual implantation were compared to standard sizing of the 70cc device and the proposed criteria for each device.
Results: Fifteen patients (age 3-34 years; BSA 0.67-1.99 m2), being evaluated for mechanical support as bridge-to-heart transplantation, underwent virtual implantation of the 50cc and 70cc TAH. Successful virtual fit was defined as no evidence of device intersection with the thoracic cage or important intrathoracic structures. Virtual implantation of the 50cc TAH was successful in 80% of the patient cohort compared to 33% for the larger 70cc TAH. The 50cc TAH proposed criteria matched well with the virtual implantation results for this cohort with 85% concordance. The virtual implantation demonstrated device fit in 2 patients outside the proposed sizing criteria.
Conclusion: Virtual TAH device implantation previously demonstrated successful prediction of device size compatibility. With the introduction of the new 50cc TAH device, this method can establish eligibility criteria for device placement in the pediatric population.



224

Cytokine Expression in the Myocardium Correlates With Cardiac Structural and Functional Improvement Induced By Mechanical Unloading in Chronic Heart Failure

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Purpose: Inflammation plays a key role in the pathophysiology of heart failure (HF). Prior studies have shown correlation between systemic cytokines and adverse outcomes of HF patients. We hypothesized that inflammatory burden could correlate with the ability of the failing human heart to improve its endogenous function after mechanical unloading induced by left ventricular assist devices (LVAD).
Methods: We prospectively examined 68 patients supported with durable LVAD. Left ventricular function was serially evaluated using echocardiography with LVAD turn-down. LVAD- induced myocardial functional "response" was defined as a relative increase in left ventricular ejection fraction (LVEF) >50%, a final resulting LVEF>40% and a decrease in LV end-systolic volume >25% (i.e. "Responders"). LV myocardium was obtained at the time of LVAD implantation. Illumina platform was used for microarray screening of the myocardial tissue. Myocardial mRNA levels of cytokines were quantified by RT-qPCR. Phosphorylated protein levels of transcription factors were measured by Western Blot.
Results: Eleven patients met the criteria of response (i.e. 16% "Responders"). Microarray gene expression screening in the 11 Responders versus 11 age-, gender- and HF etiology- matched Non-responders showed that 20% of the differentially expressed genes were involved in inflammatory cellular pathways. The mRNA tissue levels of CCL2, CCL8 and TNFa were significantly decreased in Responders (n=11) compared to the total cohort of Non-responders (n=57). Also, phosphorylated Stat 3, a transcription factor that controls the expression of multiple cytokines was significantly down regulated at the myocardium of Responders (n=11) vs Non Responders (n=57) (0.8 ± 0.2 vs 1.9 ± 0.4 AU, respectively, p=0.02). On the contrary, phosphorylated p65-NFkB was not differentially expressed between the two groups.
Conclusion: Cytokine mRNA levels are significantly decreased in the myocardium of Responders suggesting that decreased inflammatory burden correlates with myocardial structural and functional improvement after LVAD unloading. Stat 3 could be a key coordinator of the differential inflammatory response and it could serve as a potential therapeutic target to enhance myocardial recovery following mechanical unloading of the failing heart.

225

Thymosin β4 and Its Cleavage Product Ac-SDKP Are Down-Regulated in Left Ventricular Myocardium of Patients With Advanced Heart Failure

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Purpose: Thymosin β4 (Tβ4) is a 43 amino acid peptide and has been shown to promote angiogenesis, suppress pro-inflammatory cytokines and protect cardiomyocytes from apoptosis and oxidative stress injury. The Tβ4 cleavage product Ac-SDKP is a tetrapeptide (Acetyl-Ser-Asp-Lys-Pro) that has been shown to inhibit collagen production by fibroblasts and collagen deposition in the LV of rats with hypertension or myocardial infarction. In the setting of chronic heart failure (HF), LV dysfunction and chamber remodeling are associated with interstitial fibrosis, reduced capillary density, cardiomyocyte apoptosis and increased production of reactive oxygen species (ROS). We previously showed that both Tβ4 and Ac-SDKP are down-regulated in dogs with experimentally-induced HGF. This study tested the hypothesis that protein levels of both Tβ4 and its cleavage product Ac-SDKP are down-regulated in LV myocardium of patients with advanced HF.
Methods: Fresh LV tissue was obtained from the LV free wall of 6 explanted failed human hearts (3 with ischemic cardiomyopathy, ICM, and 3 with idiopathic dilated cardiomyopathy, IDC) and from 4 donor hearts (DNR) deemed not suitable for transplantation. Protein levels of Tβ4 was determined by Western blotting and bands quantified in densitometric units (du). Levels of Ac-SDKP were determined by ELISA and expressed in ng/mg protein.
Results: Protein level of Tβ4 was significantly lower in explanted failing hearts compared to DNR hearts (0.22 ± 0.01 vs. 0.56 ± 0.02 du, $p<0.05$). Similarly, levels of Ac-SDKP were significantly lower in explanted failing hearts compared to DNR hearts (85 ± 10 vs. 207 ± 12 ng/mg protein, $p<0.05$). The magnitude of down-regulation of Tβ4 and Ac-SDKP in failing hearts was similar for both ICM and IDC (Tβ4: ICM 0.24 ± 0.02 vs. IDC 0.20 ± 0.01 du; Ac-SDKP: ICM 84 ± 20 vs. IDC 61 ± 8 ng/mg).
Conclusion: Protein levels of Tβ4 and its cleavage tetrapeptide Ac-SDKP are markedly down-regulated in LV myocardium of explanted failing human hearts regardless of the etiology of HF. These findings are in-line with the reported increase of pro-inflammatory cytokines, interstitial fibrosis, cardiomyocyte apoptosis, and ROS formation as well as reduced capillary density in failing human hearts. The findings support the therapeutic targeting of Tβ4 and Ac-SDKP as potential treatment for chronic HF.

226

Myocardial Lipid Metabolism in the End-Stage Failing: Heart: Evidence for an Energy-Starved State

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