A novel cardiac assist device (Engineered Heart Tissue) improved cardiac function and restored β-adrenergic responsiveness in dilative heart failure.

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Abstract

Aim:
We investigated the effect of implantation of engineered heart tissue (EHT) in heart failure in vivo.

Methods:
EHT was created from neonatal rat cardiomyocytes, collagen, matrigel and media. After cultivation time (14 days) electrically stimulated EHT started to contract spontaneously and developed force (0.44 ±0.13mN). Histological analysis revealed the presence of troponin I and connexin 43 positive, cross striated cardiomyocytes, besides pre-formed vessels and connective tissue. We induced DCM by application of doxorubicin in rats for 6 weeks. Cardiac function was controlled by echocardiography during the experiment. On 80 days animals were separated into 3 groups: 1. Day 80-group with animals to examine the status of DCM on day 80 (n=6), 2. EHT-group (n=13), 3. Sham-group (n=12).

In EHT-group we implanted EHT around the beating heart and in Sham-group animals underwent the same surgery without EHT-implantation.

One month after operation hemodynamic measurements were performed (Millar catheter). We examined the LV (left ventricular) +dp/dt max as measurement for contractility, under control conditions and under dobutamine (0.2mg/kg) for stimulation of β-adrenergic receptors (β-AR). Subsequently the hearts were prepared for epicardial electrical mapping analysis and finally for histological analysis.

Results:
Echocardiography revealed a significant impairment of heart function on day 80 (33.1±0.7%) measured as fractional shortening (FS) as compared to healthy animals (41.9±0.9%, p< 0.05). After surgery in EHT-group FS increased by +4.6±1.3% . In comparison, Sham-group exhibited further decrease in FS (-7.5±3.7%, p< 0.05). Hemodynamic measurements indicated a decrease in LV dp/dt max in Day 80-group (4698±370mmHg) and in Sham-group (536±246mmHg) compared to healthy animals (647±246mmHg, p< 0.05), but not in EHT-group (7840±672mmHg). Contractility analysis revealed that the dobutamine-induced increase in contractility was abolished in DCM (healthy: 12350±1619mmHg/s vs. Day 80: 7050±1045mmHg/s, p< 0.05), but was restored in EHT-group (12579±2892mmHg/s), while it further declined in Sham-group (5824±543mmHg/s). The restored dobutamine response indicated that the long-term hemodynamic situation in DCM was improved by EHT-implantation. Additionally, mapping analysis exhibited electrical coupling of EHT with the recipient heart. EHT was tightly ingrown into the native myocardium and was connected to the coronary system. In vivo EHT showed organised collagen structure, elastic fibres, and troponin I and connexin 43 positive cardiomyocytes.

Conclusion:
The restored dobutamine response indicated that DCM-induced increase in sympathetic activity with consequent β-AR down-regulation can be reversed by EHT-implantation, which demonstrated an improvement in hemodynamic regulation and cardiac function. (BMBF: 0313909)