Strip and Dress the Human Heart

Wolfram-Hubertus Zimmermann

In an average lifespan of 80 years, the heart beats ≥2.5 billion times and ejects ≈200 million liters of blood into the circulation. This amazing performance is slow, but progressively reduced with age because of a concurrent loss of cardiomyocytes without meaningful regeneration. Pathological events, most dramatically presenting as myocardial infarction, expedite cardiomyocyte loss and consequently cause contractile dysfunction leading to heart failure.

Heart failure affects ≈26 million people worldwide with 6 million patients diagnosed in the United States alone. Common treatment includes pharmacological protection from neurohumoral overstimulation and mechanical circulatory support; neither is addressing the underlying problem of cardiomyocyte loss. In end-stage heart failure and only in a stringently selected patient population, that is cardiomyocyte loss. In end-stage heart failure and only in a stringently selected patient population, that is ≈2500 patients in the United States, heart transplantation is performed with excellent results. Despite the urgent need for a broader application of heart transplantation, there is little reason to assume that these numbers will increase in the future. Hence, there is a clear unmet need for alternative strategies to advance the present state-of-the-art in the clinical management of patients with end-stage heart failure.

Therapies aiming at the biological regeneration of the heart by remuscularization address the underlying cause of the disease in a straightforward; however, clinically not yet accomplished way by (Figure) (1) implantation of cardiomyocytes, cardiac progenitor cells, or other cells with cardioprotective paracrine activity, (2) changing the fate of the myocardial scar’s stroma cells toward a cardiomyocyte lineage by in situ reprogramming, or (3) tissue engineered heart repair with the aim to create structurally and functionally defined surrogate heart muscle in vitro for precise applications in vivo.

Cell sheet and hydrogel-based tissue engineering modalities are undoubtedly most advanced toward clinical application. The arguably most comprehensive variant of tissue engineered heart repair was originally proposed by Ott et al in 2008, that is the recreation of a full heart transplant by the recellularization of a decellularized donor heart; proof-of-concept was provided in a rat model. In the present study, Guyette et al retrieved 73 nontransplantable human hearts from the New England Organ Bank and subjected 40 of them to a SDS/Triton-X100 decellularization protocol for subsequent recellularization. Together with an earlier study by Sánchez et al, which included 52 human hearts from the Spanish National Transplant Organization, there is now compelling evidence from 2 independent laboratories for the feasibility of effective decellularization of human hearts under defined conditions. Although Sanchez et al demonstrated partial recellularization with c-kit+ cardiac progenitor cells, bone marrow–derived mesenchymal stem cells, human umbilical cord endothelial cells, H9c2 rat cardiomyocytes, and mouse HL-1–derived myocytes, the study by Guyette et al demonstrated for the first time the applicability of bona fide human cardiomyocytes derived from induced pluripotent stem cells. By a rigorous experimental study design, Guyette et al demonstrated that these cardiomyocytes would adhere to the decellularized myocardium, form force-generating muscle, and in case of whole heart recellularization with 500 million cardiomyocyte contribute to left ventricular compression. Despite the low pressures generated by the recellularized left ventricle (2.4±0.1 mm Hg), Guyette et al succeeded in demonstrating that remuscularization of the decellularized human heart is feasible. However, these results also suggest low cell retention, which would be in line with studies on direct cell injection into the beating heart and suboptimal functional organization. Considering that the human heart contains ≈4 billion cardiomyocytes, structurally organized to overcome diastolic pressures of at least 80 mm Hg, Guyette et al are facing a paramount challenge in the re-engineering of hemodynamically relevant function. Additional challenges include (1) the decoration of the denuded vascular bed, including large vessels and most importantly capillaries, with the appropriate surface lining by endothelial cells and in case of the larger arteries and arterioles smooth muscle cells, (2) recreation of a conduction system for coordinated electrical activation, and (3) development of pliable heart valves with documented longevity under the physiologically relevant hemodynamic load.

Taken together, it seems fair to conclude that stripping the human heart off its cellular components is a relatively easy task, whereas recellularization in a tissue-specific context with appropriate function is less trivial. The Ott laboratory will without doubt continue to pioneer the field of organ decellularization followed by recellularization to overcome the above-mentioned caveats. Not only the tissue engineering community will be looking forward with interest and excitement to the solutions, addressing the fundamental challenges on the way to a fully remuscularized heart transplant. Whether this has to involve the decellularization and recellularization...
of a human heart or may alternatively involve readily accessible large animal hearts to meet the increasing clinical demand remains to be elucidated. In addition, the suggestion of an autologous therapy will likely have to be reconsidered for an allogeneic approach because of the anticipated, and recently in the first clinical autologous induced pluripotent stem cells study documented,15 attrition in the development of autologous induced pluripotent stem cell–based cell therapeutics.

Sources of Funding
W.H. Zimmermann is supported by the German Center for Cardiovascular Research (DZHK), the German Research Foundation (DFG ZI 708/10-1, SFB 1002 TP C04/S, and SFB 937 A18), the Foundation Leducq, the German Federal Ministry for Science and Education (BMBF FKZ 13GW0007A [BMBF/CIRM ETIII Award]), the Cardiovascular Research (DZHK), the German Research Foundation W.H. Zimmermann is supported by the German Center for Cardiomyocyte Remuscularization, addressing the underlying fundamental disease mechanism—the progressive loss of cardiomyocytes.

Figure. Schematic summarizing the current state-of-the-art in heart failure therapy and evolving strategies for myocardial remuscularization, addressing the underlying fundamental disease mechanism—the progressive loss of cardiomyocytes.

Key Words: Editorials ■ heart ■ heart failure ■ myocytes, cardiac ■ stem cells ■ tissue engineering
Strip and Dress the Human Heart
Wolfram-Hubertus Zimmermann

Circ Res. 2016;118:12-13
doi: 10.1161/CIRCRESAHA.115.307938

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/118/1/12

An erratum has been published regarding this article. Please see the attached page for:
/content/118/6/e33.full.pdf

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/
It was recently noticed that the first sentence of the *Circulation Research* editorial by Wolfram-Hubertus Zimmermann (Strip and Dress the Human Heart. *Circ Res.* 2016;118:12–13) contained an error. The correct sentence is as follows:

“In an average lifespan of 80 years, the heart beats >2.5 billion times and ejects ≈200 million liters of blood into the circulation.”

The error has been corrected in the online version of the article, which is available at http://circres.ahajournals.org/content/118/1/12.full