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Bio-Artificial Heart as Ultimate Treatment of End-Stage Heart Failure

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1 Francis E. Smit
ABCDEFG 1,2 Pascal M. Dohmen

1 Department of Cardiothoracic Surgery, University of the Free State, Bloemfontein, South Africa
2 Department of Cardiovascular Surgery, Charité Hospital, Medical University Berlin, Berlin, Germany

Corresponding Author: Pascal M. Dohmen, e-mail: pascal.dohmen@charite.de
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End-stage heart failure is a major health problem, but implementation of guidelines and optimizing medical therapy for this devastating disease should decrease mortality. If optimal conservative therapy is no longer sufficient, a mechanical support system may be required as final destination therapy or as bridge-to-transplant. Since the first heart transplantation in 1967, this therapy has become the criterion standard for end-stage heart failure, but is limited due to organ shortage. Tissue engineering could help overcome this limitation and provide regeneration, remodeling, and growth potential. This so-called bio-artificial heart would be available, created by a decellularized extracellular matrix and seeded with *in vitro* proliferated autologous cardiovascular cells. Results of the first experimental studies have been promising, but numerous challenges must be met before this procedure will be available.

MeSH Keywords: Heart Failure • Heart Transplantation • Tissue Engineering

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End-stage heart failure (ESHF) is a major public health problem, with at least 10 million patients in Europe and more than 5 million in the United States [1,2]. Refractory heart failure is rapidly increasing worldwide, with approximately 5% of patients being refractory to medical therapy [3]. In North America, an epidemiologic report estimated that approximately 550 000 patients annually develop heart failure, with an annual mortality of nearly 285 000 [4,5].

For Germany, the number of patients hospitalized with ESHF has increased by 2.4% from 2010 to 2011, with over 380 000 patients documented [6]. Mortality in 2011 was 12%, which means 45 428 patients died due to ESHF. Compared to 2010, however, there was a decrease of 6% due to improved treatment options such as more effective medical therapy, implementation of guidelines, improved medical diagnosis and imaging, telemedicine, automatic implantable cardioverter defibrillators, cardiac resynchronization therapy, assist support, and heart transplantation [1,2,7].

Since the first heart transplantation performed in 1967 by Christian Bernhard at Groote Schuur Hospital in Cape Town, more than 110 000 cardiac transplantations have been performed worldwide [8]. Today, heart transplantation is still considered the criterion standard for ESHF treatment, but is only available for a minority of patients due to organ shortage or patient contra-indication [9–11]. Additionally, there are a number of serious complications associated with transplantation, such as acute or chronic rejection, cardiac allograft vasculopathy, infection, and malignancy [12].

For some of these patients a mechanical support system is an option as bridge-to-transplantation or, eventually, if patients do not fulfill heart transplantation criteria, destination therapy. Unfortunately, mechanical support systems also have disadvantages such as increased risk for infection, thromboembolic complications, and bleeding [13–16].

Therefore, alternative treatments are desperately needed to overcome disadvantages of current options. Tissue engineering could help solve this problem because it has remodeling, regeneration, and growth potential. Previous studies have shown the benefits of tissue engineering for development of pulmonary heart valves [17] and pediatric conduits [18]. Tissue-engineered cardiovascular materials have been implanted into the systemic circulation with excellent results, showing earlier tissue regeneration compared with tissue-engineered heart valves implanted in the low-pressure circulation [19]. Haverich et al. [20] published experimental results of aortic root replacement with tissue-engineered aortic valves, showing favorable hemodynamic results and absence of tissue failure such as aneurysm formation, which can develop under high pressure. Dohmen et al. [21] showed in a juvenile sheep model that implantation of tissue-engineered equine pericardial patches can withstand systemic pressure without aneurysm formation of the decellularized structures. Furthermore, there was accelerated recellularization in these decellularized constructs, resulting in early tissue regeneration. Based on numerous experimental and clinical studies with these tissue-engineered cardiovascular constructs, new and more complex structures – so-called bio-artificial organs – have become a focus of investigation.

Similar to previous tissue-engineered cardiovascular materials, a scaffold, cells, and a bioreactor are needed as classic components. The complexity of the scaffold is different from heart valves, conduits, and patch materials, since it is a 3-dimensional organ-line scaffold, which needs to release cells and debridement, but without negatively affecting the mechanical and biological integrity of the extracellular matrix [22]. Additionally, it provides biochemical signals and expressing factors, allowing regeneration and remodeling potential of the tissue-engineered construct. Tissue decellularization should be smooth and sparing, so that afterwards the extracellular matrix can be reseeded with cells without compromising functionality.

For the recellularization procedure, different cell types are needed (e.g., endothelial cells, fibroblasts, smooth muscle cells, and cardiomyocytes) to seed the decellularized extracellular matrix. Enormous numbers of cells are needed for the seeding process, which makes it difficult to use and culture end-differentiated cells. Alternative cells are needed with increased *in vitro* proliferation potential, such as adult stem cells or induced pluripotent stem cells [23].

At the time a sufficient number of cells are available for seeding the extracellular matrix, a bioreactor must be available in which both components are brought together, cells can grow into the scaffold, and the endothelial cells can overgrow the inner surface of the cavities and the vessel trunk. Additionally, the bio-artificial heart should improve functionality within this bioreactor and be supported until being transplanted into the recipient.

In 2008 Ott et al. [24] introduced the first bio-artificial heart in a rat model. A 3-dimensional decellularized matrix was created, and a sufficient number of different cardiovascular cells were cultured *in vitro*, proliferated, and reseeded by using a bioreactor. Ultimately, myocardial contractility could be generated in this model. This study opens a new era of possibilities for patients with ESHF, but the rat heart is too small and larger 3-dimensional structures are needed to be seeded if this bio-artificial heart is to become available for patients.

Therefore, Weymann et al. [25] evaluated decellularization in a porcine heart, which is similar in to the human heart, thus

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the size would be sufficient, but care should be taken that the scaffold is free of DNA to avoid any reaction [26]. Histologically, this decellularization process was successful, but DNA quantification still showed some residual problems that need to be solved. Porcine scaffolds have the potential risk for immunogenic reactions and transmission of porcine endogenous retrovirus [27] or α-Gal epitopes [28].

Furthermore, the number of cardiovascular cells needed for seeding a human or porcine heart is greater than in a rat heart. Depending about the age of the individual, for an adult human heart, 2×10^9 cardiomyocytes are needed compared with a rat heart in which only 9×10^7 cardiomyocytes are needed [29].

Finally, a sufficient bioreactor must be available to allow the remodeling and regeneration process of the bio-artificial heart until transplantation into the recipient.

A new era is dawning in treating ESHF, but many hurdles have to be overcome.

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