Editorial

Tissue Engineered Heart Valves: Will a Clinical Application be Possible?

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Introduction

Artificial valves have been used as the ultimate treatment for cardiac valvular diseases with severe morphologic and functional disorders. Currently, artificial cardiac valves are the most widely used artificial organ, but there remain problems, such as materials, opening and closing mechanisms, and distal control. The best artificial organs are considered to function in the same manner as the target organ, and to have long-term durability together with high reliability, safety and biocompatibility in terms of materials, function, and control mechanisms. With the recent rapid development of tissue engineering, genetic engineering, and nanotechnology, new hybrid artificial valves using cultured tissues are being developed. In this article, new artificial valves produced by tissue engineering are reviewed, along with results of our studies.

New Artificial Valves by Tissue Engineering

Prospects of biovalves: Hybrid biovalves by tissue cellular engineering

The heart is a highly differentiated system, but is basically a pump with valves. Therefore, valvular function is essential for regeneration of the heart, but no studies on the construction of valvular function using cultured myocardial cells have been started. To obtain valvular function, use of artificial valves is currently the most practical method. Artificial valves comprise of mechanical and biovalves, both with their advantages and disadvantages. Mechanical valves have high durability, but always require anticoagulant therapy with warfarin, which accompanies thrombosis and hemorrhage in some cases, causing poor prognosis. On the other hand, biovalves require anticoagulant therapy with warfarin only in the early postoperative stage, and the incidence of thrombosis and hemorrhage is very low. However, the durability of biovalves is not high, and is considered to be about 20 years even in the most recent stentless porcine aortic valves. With the recent progress of the aging of dur society, biovalves improving the QOL of patients and having long-term durability are expected to be developed.

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Development and clinical application of hybrid pulmonary valves by tissue cellular engineering

Evaluation of the durability of stentless porcine pulmonary valves and basic studies on biovalve fixation methods have been performed by transplanting them to large animals since 1996.[1)] In collaboration with the Department of Cardiac surgery of Louvin Catholic University in Belgium, and the Department of Cardiac surgery of Humboldt University in Germany, we have been developing, since 1998, hybrid pulmonary valves by tissue cellular engineering,[2)] and have been the first in the world to succeed in their clinical application.

The 2 major techniques for the preparation of living pulmonary valves are decellularization of a donor valve and adhesion of recipient cells to the decellularized valve. The preparation of living pulmonary valves is performed by the following steps.

1) Decellularization of a donor pulmonary valve using deoxycholic acids.
2) Establishment of a three-dimensional cell adhesion method.
3) Transplantation experiments of hybrid pulmonary valves in large animals.

To produce a hybrid pulmonary valve, endothelial cells collected from the cervical vein of 3-month-old juvenile sheep were cultured, and inoculated to the matrix of a porcine pulmonary valve prepared by decellularization. The hybrid pulmonary valve was transplanted to the pulmonary artery of the juvenile sheep from which the endothelial cells were collected. One layer of endothelial cells was observed on the surface of the hybrid pulmonary valves excised 1 week, 3 months, and 6 months after transplantation. Macroscopic, radiographic, and pathological examination demonstrated no calcification, and

the calcium content was low.
4) Comparisons of hybrid pulmonary valves and conventional artificial valves[3)]
Stentless bioprostheses (Freestyle valve, Toronto SPV valve), which have been used clinically, were transplanted to large animals (juvenile sheep), and their usefulness, including their durability, was evaluated. Macroscopic, radiographic, and pathological examination revealed marked calcification on the wall of the stentless bioprostheses, and the Toronto SPV valves themselves were calcified. However, no calcification was detected on the walls of the hybrid pulmonary valves and on the valves themselves. The calcium content in the hybrid pulmonary valves was significantly lower than that in the stentless bioprostheses ($p<0.05$).

Based on these results, we performed clinical application of hybrid pulmonary valves at Charite Hospital in Berlin. Fifty patients with a mean age of 43 years underwent Ross operation and transplantation of a hybrid pulmonary valve to the position of the pulmonary valve. Postoperatively, no regurgitation was observed. In the patients who underwent transplantation of a hybrid pulmonary valve, there was no incidence of fever higher than 38℃, and early reduction of the number of white blood cells after surgery was noted, unlike patients who underwent transplantation of a homograft. These results suggested that the hybrid pulmonary valves were less antigenic.

Studies and development of hybrid aortic valves by tissue cellular engineering

Based on the studies and development of hybrid pulmonary valves by tissue cellular engineering and their clinical application, we are currently promoting studies and development of hybrid aortic valves. Since the aortic valve is exposed to faster blood flow and higher pressure than the pulmonary valve, more accurate 1) techniques of decellularization and 2) techniques of three-dimensional cell adhesion using bioreactors are required. Examination of the durability of biovalves under faster blood flow and higher pressure using an artificial pulsation apparatus is indispensable, and results of the respective techniques are collated. Currently, we are developing a biovalve with a higher degree of quality and durability.

1) Establishment of full decellularization techniques
Decellularization of donor aortic valves using deoxycholic acids was performed under the following conditions; 1) without stirring in deoxycholic acids, 2) with pulsatile flow of deoxycholic acids using a bioreactor, and 3) with pulsatile flow of deoxycholic acids using a bioreactor and microwaves. Complete decellularization was achieved by applying pulsatile flow and microwaves to the donor aortic valve.

2) Establishment of three-dimensional cell adhesion techniques using a bioreactor
First, endothelial cells were inoculated on the donor aortic valve with the scaffold alone as a product of decellularization under a static condition. Inoculated cells were scattered over the surface of the donor aortic valve. Next, pulsatile flow was applied to the inoculated epithelial cells using the bioreactor, resulting in the covering of the inoculated cells on the entire surface of the aortic valve and alignment of the epithelial cells in the direction of the flow. This pulsatile conditioning was considered indispensable.

3) Transplantation experiments with large animals
The durability of the hybrid aortic valve will be tested by transplantation experiments using juvenile sheep. By studying the results obtained, we will aim at clinical application of the hybrid aortic valve.

Conclusions

In this article, we have examined the status and problems of clinically used artificial valves. To lessen these problems, we have summarized cutting-edge research on hybrid artificial valves produced by tissue cellular engineering. Clinical application of hybrid pulmonary valves has already been successful in Europe, indicating that the development of hybrid aortic valves is possible in the near future. Further advancement of research aiming at ideal artificial valves is expected.

References

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