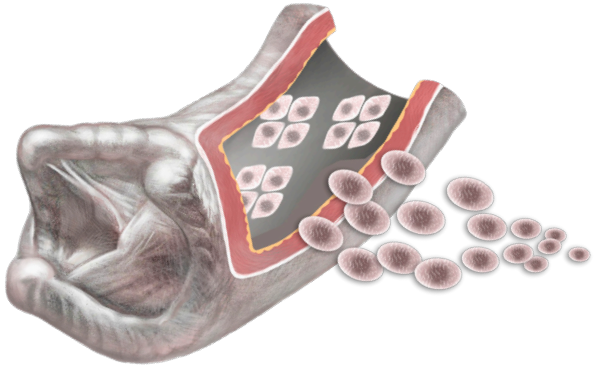
One can speak of a cure when a heart valve prosthesis has become the patient's own tissue. The cell-free allografts come closer to this goal. Sarikouch et al. were able to demonstrate a structural repopulation of the cell-free implanted tissues in tissue samples from reoperations. This is remarkable because the sample consisted mainly of clinically conspicuous implants. Whether inconspicuous, cell-free allografts heal completely, we will only find out sporadically, as a targeted control in the patient is not possible.

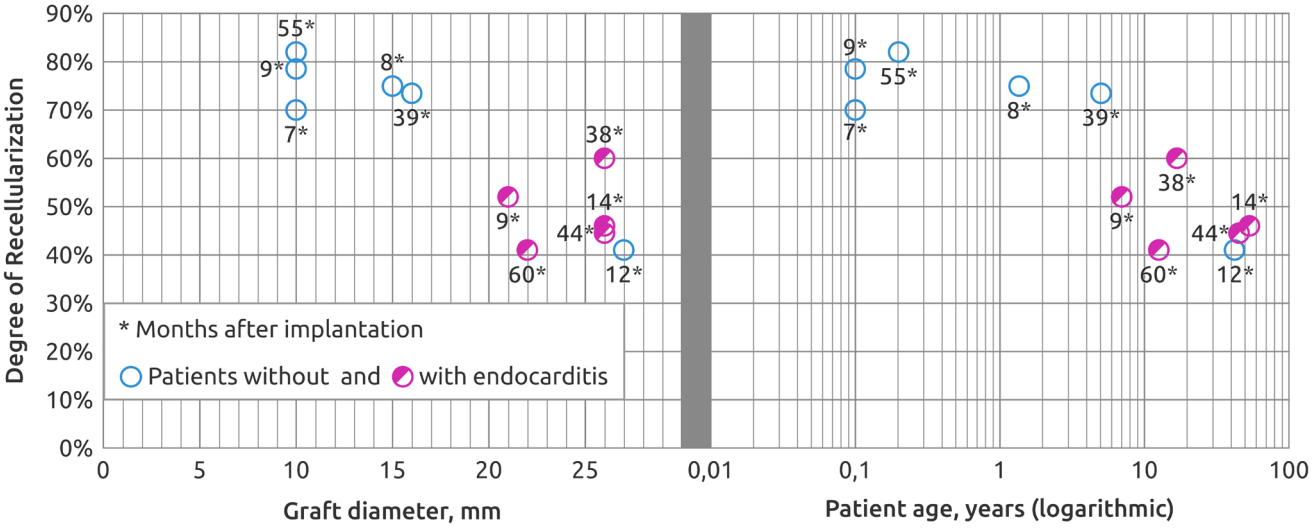


Recolonisation of cell-free allografts

Sarikouch et al.[1] studied tissue samples from heart valves that had previously been implanted as cell-free allografts. The reasons for the eleven reoperations in the context of which the tissue samples were obtained were: (suspected) endocarditis (5 cases), sub-, supra- and valvular stenosis (3 cases), two planned reoperations, and one cardiac transplantation. Two pathologists examined the histological specimens independently and came to very similar conclusions. The diversity, density and quality of the cell population were evaluated in comparison to native tissue. This means that leukocytes, for example, were not evaluated as recellularisation.

The presumably endocarditically degenerated tissue was 48±7% recellularised, the other tissues 76±4%. Intracellular pro-collagen 1 was found in mesenchymal cells. One pulmonary valve showed characteristics of immune system-mediated graft failure. Cell-free allografts implanted ≤12 months showed an uneven repopulation with decreasing cell density towards the media centre.

The sample includes clinically abnormal cases where poorer recellularisation is more likely to be expected. However, even in this difficult sample, the concept of spontaneous, structural repopulation of cell-free allografts is confirmed. The detection of pro-collagen 1 is a first indication of regeneration.



Re-colonisation of cell-free aortic and pulmonary valves as a function of valve diameter and patient age. In young patients (with small valve diameter) without (presumed) endocarditis, cell-free allografts recellularise better than in older patients, or after (presumed) endocarditis.

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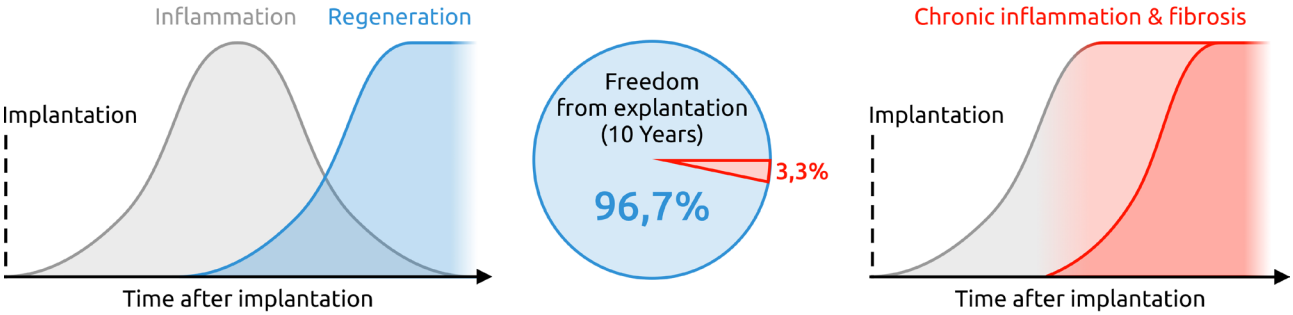
Inflammation and regeneration

In-situ remodelling takes place, in a simplified way, in two phases. After implantation of a cell-free allograft, an inflammatory reaction is triggered. Leukocytes and macrophages migrate into the extracellular matrix. In a second phase, this inflammatory reaction recedes, followed by differentiated colonisation, e.g. with myofibroblasts and endothelial cells. If the initial inflammation does not subside, but becomes increasingly chronic, the extracellular matrix degenerates and fibroses.[2]



Left: After implantation of a cell-free allograft, inflammatory processes set in and transition to a phase of differentiated re-colonisation of the extracellular matrix. Middle: Only a total of 3.3% of all cell-free pulmonary valves have to be explanted again within 10 years.[3] Right: We assume that chronic inflammation underlies graft failure, leading to fibrosis of the implanted matrix.

In vitro autologised cell-free allografts

In vitro autologisation prior to implantation requires that (i) sufficient cells of the patient are available in time, (ii) the propagation and colonisation of a suitable cell population is technically successful, (iii) the now cellular implant can be stored and transported in a vital way and (iv) the cells are not washed out after implantation. Re-colonisation is a lengthy process that prolongs the waiting time for the implant. Substantial manipulation also leads to a higher reject rate. In addition to these very complex technical requirements, many of which have not been solved for routine use, there are regulatory requirements that are no less complex. The high expenditure for preclinical and clinical development, approval, production and distribution would have to be allocated to a very small number of transplants, which would only be financially viable if the prospect of a clear superiority over the existing alternatives is very likely. However, there is insufficient evidence for this.

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2. *Fioretta ES, Motta SE, Lintas V, Loerakker S, Parker KK, Baaijens FPT, Falk V, Hoerstrup SP, Emmert MY. Next-generation tissue-engineered heart valves with repair, remodelling and regeneration capacity. Nat Rev Cardiol. 2021 Feb;18(2):92-116. doi: 10.1038/s41569-020-0422-8. Epub 2020 Sep 9. PMID: 32908285.*
3. *Boethig, D., Horke, A., Hazekamp, M., Meyns, B., Rega, F., Van Puyvelde, J., Hübler, M., Schmiady, M., Ciubotaru, A., Stellin, G., Padalino, M., Tsang, V., Jashari, R., Bobylev, D., Tudorache, I., Cebotari, S., Haverich, A., & Sarikouch, S. (2019). A European study on decellularized homografts for pulmonary valve replacement: initial results from the prospective ESPOIR Trial and ESPOIR Registry data†. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery, 56(3), 503–509.*

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