Clinical Summary

TISSUE

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NOW AND IN THE FUTURE

A Novel Tissue Treatment to Reduce Mineralization of Bovine Pericardial Heart Valves

Meuris et al., *J Thorac Cardiovasc Surg. 2018 Jul;156(1):197-206*

CORCYM

WE TAKE LIFE TO HEART

FREE tissue:

the next-generation tissue designed to reduce the causes of calcification and improve tissue durability.

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A novel tissue treatment to reduce mineralization of bovine pericardial heart valves

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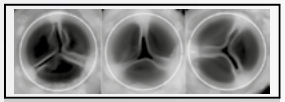
ABSTRACT

Objective: With the increasing use of bioprostheses worldwide, continuous efforts have been made to improve tissue durability. We introduce a new treatment for bovine pericardium combining octanediol-ethanol based phospholipid removal with taurine-based glutaraldehyde neutralization and storage in an aldehyde-free solution (FREE).

Methods: Treated tissues were evaluated by mechanical and biochemical characterization, phospholipid content, aldehyde levels, cell cultures on pericardial samples (L929 fibroblasts and human umbilical vein endothelial cells), rat subcutaneous implantations, and long-term juvenile sheep mitral valve implantations (n = 3). Comparisons were made to glutaraldehyde-fixed bovine pericardium or to samples from commercially available biological valves (ie, Trifecta [St Jude Medical, Saint Paul, Minn] and Perimount Magna Ease [Edwards Lifesciences, Irvine, Calif]).

Results: FREE-treated pericardium had similar mechanical strength and biochemical properties as commercially available valves. Compared with glutaraldehyde-only samples, FREE-treated samples showed lower phospholipid levels ($P < .01$), significantly better growth of L929 fibroblasts, and lower calcification levels in rat subcutaneous implants ($P < .01$). Compared with samples from Linx- (Trifecta) and ThermaFix-treated (Perimount Magna Ease) valves, similar low levels of phospholipids were observed as were similar low calcification levels in subcutaneous implants, but tissue extractions from FREE-treated samples showed the lowest levels of extracted aldehydes ($P < .01$). Mitral implants of FREE-treated valves in juvenile sheep had excellent hemodynamic behavior without any sign of degeneration or calcification at 5 months.

Conclusions: The new FREE treatment combines an adequate phospholipid reduction and aldehyde neutralization with storage in an aldehyde-free solution. This combination enhances the anticalcification properties and may thereby improve long-term durability of the tissue. (J Thorac Cardiovasc Surg 2018;■:1-10)



No calcification in FREE-treated valves after 5 months in mitral position in a juvenile sheep model.

Central Message

A new treatment for bovine pericardium combines phospholipid reduction and aldehyde neutralization with aldehyde-free storage. This combination enhances anticalcification properties and may improve tissue durability.

Perspective

With the increase in use of biological valves, also in younger patients, it is the mutual responsibility of industry, surgeons, and scientists to continue trying to improve tissue durability. We describe the strategy that LivaNova (Milan, Italy) has chosen for its new tissue technology; specifically, phospholipid reduction and free-aldehyde neutralization combined with a unique aldehyde-free storage solution.

See Editorial Commentary page XXX.

- All tissue valves are subject to structural valve deterioration (SVD), mainly due to calcification.
- Phospholipids and aldehydes are major causes of calcification.
- Phospholipids are intrinsically present in biological tissue, while aldehydes are a consequence of the fixation process. Both contribute to calcification: phospholipids directly as calcium binding sites;[1-5] aldehydes indirectly as a consequence of their toxicity to the host tissue.[6-11]
- Other valves are usually stored in liquids containing aldehydes. This, however, exposes the tissue once again to the detrimental effects of residual free aldehydes. Even pre-implant rinsing, as per instructions for use indications, does not guarantee complete removal of toxic aldehydes.

The FREE tissue treatment addresses both phospholipids and aldehydes, and enables an aldehyde-free storage that allows the valve to be ready to use, straight from the jar. This combination enhances anticalcification properties and may improve tissue durability.

METHODS

- The FREE tissue was investigated both in vitro and in vivo for safety and efficacy.
- FREE-treated tissue was evaluated in rat subcutaneous implantations and long-term juvenile sheep mitral valve implantations.
- Comparisons were made to glutaraldehyde (GA) fixed bovine pericardium (control group) or to samples from commercially available biological valves (Trifecta™ treated with Linx™ and Perimount Magna Ease™ treated with ThermaFix™).

IN VITRO RESULTS

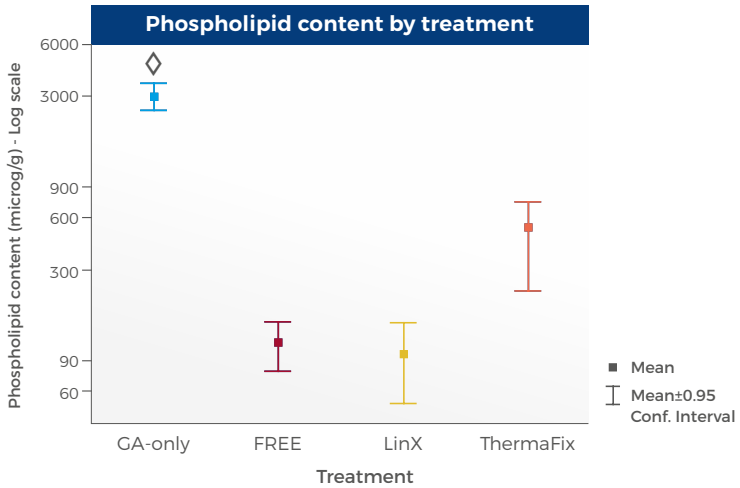
Mechanical and Biochemical Characterization

FREE-treated tissue guarantees the same mechanical and biochemical performance and stability as the tissue found in other commercially available valves.

Phospholipid Content

- Phospholipid content in FREE-treated tissue is reduced up to 96% vs control group.
- FREE-treated tissue showed similar low levels of phospholipids compared to samples from Linx™ and ThermaFix™ treated valves.

-96%
phospholipid content*



*vs control group

◊ P<.001 vs all treated samples. Between the treated samples, there were no significant differences.

Aldehyde Content

Three analyses were performed to test the aldehyde level:

1. **Qualitative: colorimetric assay**

Tissue samples from different valve models are exposed to a staining reagent that is sensitive to aldehydes. The purpose is to visually determine the level of aldehydes that remain in the valve tissue. The darker the blue, the more aldehydes are present.

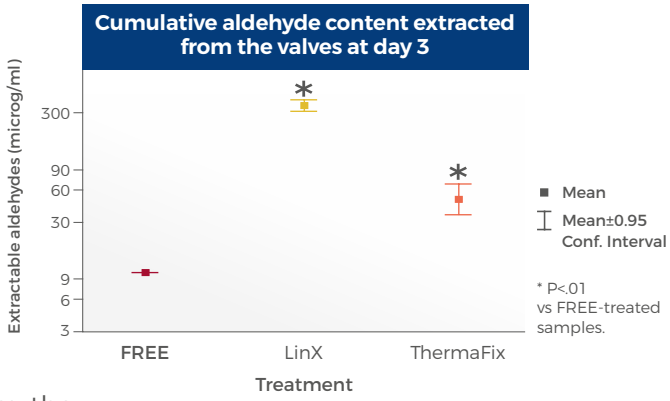
FREE outperforms other tissues, confirming a negligible aldehyde presence.

2. **Quantitative: biochemical assay**

This analysis enables to quantify the amount of aldehydes extracted from the valve samples. This amount is what could potentially be released by the valve after implantation.

FREE-treated samples display the lowest level of aldehydes extractable.

The quantity of extracted aldehydes from FREE is significantly lower than the one measured in ThermaFix and LinX after 3 days.



3. **Tissue toxicity level**

A cell adhesion and proliferation test on pericardial samples was performed in order to confirm the neutralization of aldehydes in FREE-treated valves. It measures tissue toxicity through the ability of cells to adhere and proliferate. In the presence of residual aldehydes, cells do not adhere and die.

FREE-treated tissue showed good cell viability and proliferation after 48 and 72 hours from cells seeding, while cells on GA treated samples were not able to adhere and proliferate.

Thanks to the combination of highly effective neutralization of aldehydes and a completely aldehyde-free storage, the FREE tissue treatment delivers a final product that has a very low level of aldehydes and is ready to use.

≃0 % aldehyde **toxicity**[2]

READY TO USE

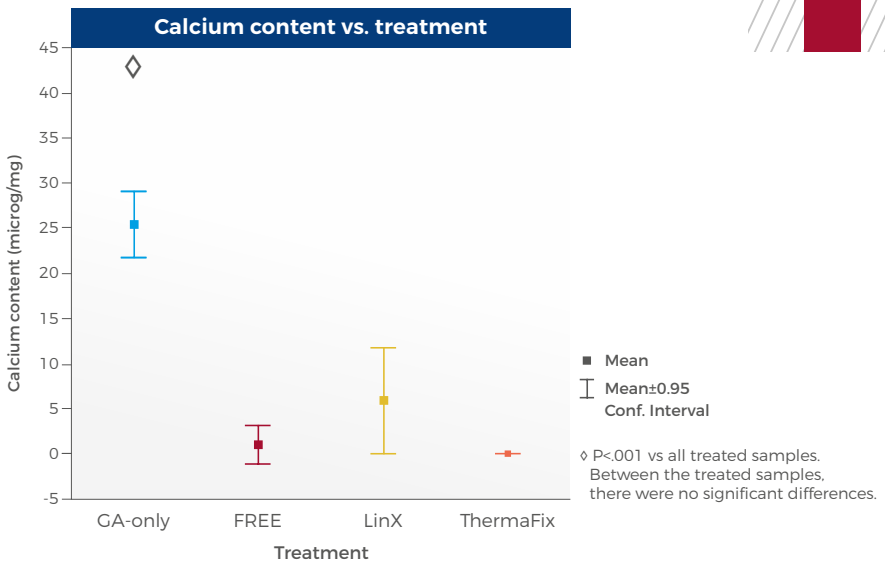
IN VIVO RESULTS

Rat Subcutaneous Implantations

The subcutaneous tissue implantation in rat model is the gold standard to assess tissue propensity to mineralize in vivo, as it resembles the dystrophic mineralization occurring in human patients years after implantation.

Extremely low calcium content was observed in FREE-treated tissue after implantation; similar to ThermaFix™ tissue and slightly lower than Linx™ tissue.

-99% calcification*

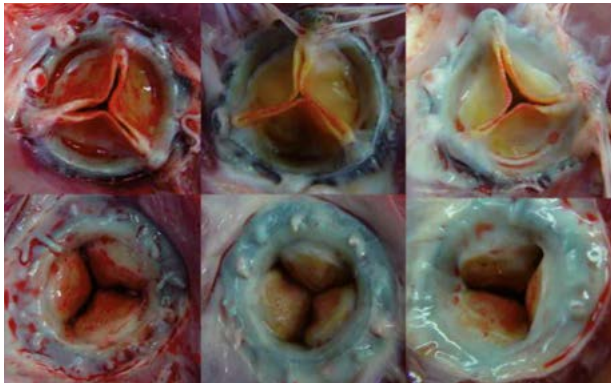


Calcium content within bovine pericardial tissues after 60 days subcutaneous implantation in juvenile rats.

Mitral Valve Implantations in Juvenile Sheep

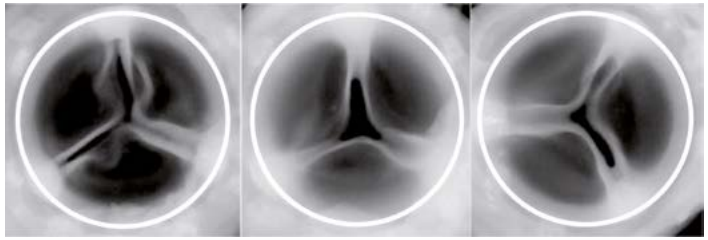
Valve replacement in juvenile sheep is the standard model to assess valve safety and performance, as it most closely resembles clinical conditions and represents an accelerated model for structural valve deterioration (high pressures, stress of the mitral position and accelerated calcium metabolism of growing animals).

"FREE treated valves showed no major abnormalities on both the inflow and outflow sides, with pliable leaflets and no visible signs of dystrophic calcification."



Outflow (upper panels) and inflow (lower panels) sides of mitral valve prostheses made of bovine pericardium subjected to the FREE treatment 20 weeks after implantation in juvenile sheep.

* vs control group



X-ray imaging of the explanted valves revealed no signs of dystrophic mineralization at 20 weeks after implantation.

The FREE tissue showed no signs of valve mineralization and degeneration, even in the challenging model of mitral valve implantation in juvenile sheep.

FREE is a next-generation tissue treatment that combines phospholipid reduction and aldehyde neutralization with aldehyde-free storage designed to improve durability.[1]

For the peace of mind of patients and surgeons.

Study limitation. The biomechanical tests of the FREE-treated tissue were compared with CORCYM tissue only; no comparisons to biomechanical properties of tissues from competitor valves were done. Only uniaxialtensile testing was performed; biaxial testing was not conducted. The sheep mitral implants served as a pilot study only. These first animals represent the proof-of-concept study performed before further in vivo implantations on a larger set of animals and including a control group.

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INTENDED USE/INDICATIONS

EUROPE: The Perceval/Perceval Plus prosthesis is intended to replace a damaged native aortic heart valve or a malfunctioning aortic prosthesis via open- heart surgery in adult patients: suffering from aortic valve stenosis or steno-insufficiency; with a previously implanted aortic valve prosthesis that is no longer functioning adequately and requires replacement.

US: The Perceval/Perceval Plus bioprosthesis is indicated for the replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves

CANADA: The Perceval/Perceval Plus bioprosthesis is intended for use in patients aged ≥ 65 years in which the aortic valve pathology is in an advanced stage to require the replacement of the native or malfunctioning previously implanted prosthesis.

AUSTRALIA: Perceval Plus bioprosthesis is indicated for the replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves. Perceval prosthesis is indicated for the replacement of a diseased native or a malfunctioning prosthetic aortic valve via open heart surgery. The prosthesis is indicated in patients who meet the following criteria: 1) subjects of age ≥ 65 years 2) subjects with aortic valve stenosis or steno-insufficiency.

KEY CONTRAINDICATIONS

Aneurysmal dilation or dissection of the ascending aortic wall; known hypersensitivity to nickel or cobalt alloys; ratio between the sinotubular junction and the annulus diameter greater than 1.3.

KEY WARNINGS

Do not under or oversize the prosthesis. This could result, in possible migration, excessive compression/ rupture of the aorta, suboptimal expansion or valve folding that may lead to fatal arrhythmia or hemorrhage, regurgitation or altered hemodynamics. Severe LVOT hypertrophy may prevent optimal expansion of the inflow portion of the stent.

TOP POTENTIAL SIDE EFFECTS

Potential adverse events associated with cardiac valve replacement with a bioprosthesis and the related surgical procedure include: bleeding, cardiac conduction disorders, endocarditis, heart failure, neurological events, non structural dysfunction, structural valve deterioration, thromboembolism.

MRI conditional

For professional use. Instructions for Use are available upon request through the manufacturer's website. Not approved in all geographies. Consult your labeling.

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