



WHITE PAPER

Uncross-linked Bovine Pericardium in Clinical Reconstruction

Biochemical Processing, Regenerative Scaffolding,
and Multi-Specialty Surgical Efficacy

Decellularized, Uncross-linked Bovine Pericardium in Clinical Reconstruction

1. Historical

The historical trajectory of decellularized, uncross-linked bovine pericardium (dBP) reflects a major shift in surgical philosophy—from the use of chemically fixed, permanent biological "plastics" toward bioactive scaffolds designed for constructive remodelling.^{1,10,30}

1.1 Early Origins and the Glutaraldehyde Era (1970s)

The clinical use of bovine pericardium began in the early 1970s, primarily within cardiovascular surgery. In 1971, Marian Ion Ionescu at the University of Leeds, UK) introduced the first bioprosthetic heart valve utilizing bovine pericardium preserved with glutaraldehyde (GA). Throughout the 1970s, GA cross-linked dBP became the gold standard for heart valves and vascular patches because the cross-linking process reduced immunogenicity and provided immediate structural durability. However, long-term follow-up quickly revealed significant drawbacks to GA fixation, including a high propensity for calcific degeneration and structural failure because the fixed tissue was biologically inert and could not be remodelled by host cells.^{3,10,27}

Historical Period		Key Development		Clinical Significance
● Early 1970s	→	First bioprosthetic valves (Ionescu) and vascular patches.	→	Established dBP as a viable surgical material.
● 1970s–1980s	→	Dominance of GA-fixation.	→	Provided immediate strength but led to late-stage calcification.
● Early 1980s	→	Introduction of Tutoplast technology.	→	Enabled sterile, acellular scaffolds that allow host integration.
● 1990s	→	Pivot in neurosurgery and abdominal repair.	→	Replaced cadaveric dura (prion risk) and synthetic mesh in infection.
● 2000s –Present	→	Advanced decellularization	→	Focus on alpha-Gal removal and bioactivation for tissue engineering.

The growing body of clinical and histomorphometric evidence has highlighted specific limitations of glutaraldehyde-fixed tissues, most notably their propensity for late-stage calcification, structural deterioration, and failure to support host cell infiltration. These challenges have catalyzed the development and widespread adoption of uncross-linked or minimally cross-linked bovine pericardium membranes, which are engineered to function as dynamic extracellular matrices (ECM) rather than static barriers.^{3-5,25,27}

2. Development of Tissue Decellularization and Sterilization Processes (1980s–1990s)

In response to the limitations of fixed tissues, researchers in the 1980s began developing alternative preservation methods. A pivotal milestone was the development of the Tutoplast technology approximately 40 years ago (early 1980s). This multi-step chemical process—combining osmotic shock, oxidative washes, and solvent dehydration—allowed for the creation of sterile, acellular matrices that preserved the natural three-dimensional collagen structure without the need for GA cross-linking.^{1,10,17,18}

As a consequence of these scientific developments, the 1990s marked a critical expansion for decellularized, uncross-linked medical devices, particularly in the following area:^{10,17,18}

- ➔ **Neurosurgery:** Following the abandonment of cadaveric human dura mater allografts in the 1990s due to the risk of iatrogenic Creutzfeldt-Jakob Disease (CJD) transmission, decellularized bovine pericardium emerged as a safe alternative for dural repair.^{11,41,42}
- ➔ **Abdominal Wall Repair:** The introduction of biological extracellular matrices (ECMs) in the 1990s initiated a new era in hernia repair, as these materials could be used in contaminated surgical fields where synthetic meshes were contraindicated.^{19,33}

2.1 The Tutoplast Tissue Sterilization Process

Tutoplast Processing Stage	Objective and Mechanism	Impact on Matrix Integrity
Osmotic shock	Lysis of cellular membranes through solvent shifts.	Initiates cell removal without disrupting fiber bundles.
Alkaline bath (NaOH)	Hydrolysis of residual proteins and neutralization of acidic residues.	Removes potential immunogens while maintaining type I collagen.
Ultrasonic acetone bath	Delipidization and removal of hydrophobic proteins.	Reduces calcification potential by eliminating lipid-rich sites.
Oxidative wash (H₂O₂)	Inactivation of viruses, bacteria, and prions.	Ensures biological safety and aids in tissue whitening.
Gamma Irradiation (17.8 kGy)	Terminal sterilization for clinical safety.	Achieves SAL 10 ⁻⁶ while preserving collagen triple helix.

The Tutoplast process is one of the most established methods for preparing uncross-linked, decellularized collagen tissues. It has been utilized for over three decades to produce dBP products such as Tutopatch, Tutodent, and Copios. The hallmark of this process is its ability to ensure sterility and non-immunogenicity without the introduction of exogenous cross-linking agents, thereby preserving the natural three-dimensional architecture of type I collagen fibers.^{17,18}

The Tutoplast sequence involves several sophisticated steps designed to target specific cellular and pathogenic components. The tissue undergoes an osmotic treatment to disrupt cell membranes, followed by an alkaline bath and oxidative treatments using agents such as hydrogen peroxide (H₂O₂) and sodium hydroxide (NaOH) to inactivate pathogens and remove non-collagenous proteins. A critical phase involves delipidization in an ultrasonic bath with an organic solvent, which extracts lipids and hydrophobic residues that are frequently implicated as nucleation sites for calcification. The final product is solvent-

dehydrated and terminally sterilized using low-dose gamma irradiation, typically calibrated to 17.8 kGy, ensuring a Sterility Assurance Level (SAL) of 10^{-6} while maintaining the multi-directional mechanical properties of the native pericardium.^{17,18,30}

Scanning electron microscopy (SEM) of Tutoplast-processed membranes reveals a porous, intertwined network of collagen fibers that is histologically similar to native human tissue. This architecture provides the necessary topographical cues for host fibroblast adhesion and migration, facilitating the transition from an implanted xenograft to integrated host tissue.^{17,18,21}

2.2 Enzymatic and Detergent-Based Decellularization Strategies

Beyond the Tutoplast methodology, research into tissue engineering has yielded various enzymatic and detergent-based decellularization protocols. These methods aim to optimize the balance between the removal of xenoantigens and the preservation of bioactive molecules such as elastin and glycosaminoglycans (GAGs), which are often lost during aggressive chemical cleaning. Common agents include sodium dodecyl sulphate (SDS), deoxycholic acid (DCA), and Triton X-100 (TX).^{7,13,20}

Decellularization Agent	Efficiency of DNA Removal	Preservation of Collagen and Elastin	Preservation of GAGs
SDS (Anionic)	High (>80% reduction)	Moderate (may cause swelling and denaturing)	Low (significant loss)
Triton X-100 (Non-ionic)	Moderate	High	Moderate
Trypsin (Enzymatic)	Moderate	Variable (temperature and concentration dependent)	Moderate
Hydrogen Peroxide (H₂O₂) (Oxidant)	Moderate	High (preserves stiffness)	Moderate

Quantitative analysis of different protocols demonstrates that while SDS is highly efficient at removing DNA and alpha-Gal antigens, it can lead to significant reductions in GAG content and a decrease in the overall collagen density by 'hollowing-out' the fibrils of the collagen matrix. SDS is also extremely difficult to remove by washing and any residual SDS can cause significant cytotoxicity. In contrast, non-ionic detergents like Triton X-100 are gentler on the extracellular matrix structure but may require combination with freeze-thaw cycles or enzymatic digestion (e.g., Trypsin-EDTA) to achieve equivalent levels of cell removal. A combined protocol utilizing freeze-thaw cycles, Triton X-100, and sodium deoxycholate (FTS) has been identified as providing optimal decellularization efficiency with high preservation of the ECM, making it a leading candidate for the production of heart tissue engineering scaffolds.^{13,20}

The physical and biological properties of the resulting scaffold are sensitive to these processing choices. For example, bovine pericardium scaffolds treated with

SDS exhibit increased elasticity but reduced tensile strength compared to those treated with HO, which maintains higher stiffness and tensile properties.²² The selection of a processing method must therefore be tailored to the mechanical demands of the specific clinical application.^{5,20,22}

2.3 Supercritical Carbon Dioxide (scCO₂)

Supercritical carbon dioxide (scCO₂) technology offers a "green" and highly efficient methodology for the terminal sterilization and decellularization of sensitive biomaterials. Its primary advantages—the complete absence of toxic residues, the preservation of the delicate extracellular matrix structure, and the significant reductions in processing time—address the most critical failings of traditional chemical methods. While the initial capital investment and technical complexities remain substantial hurdles, the long-term economic and environmental benefits make scCO₂ an attractive process option for the medical device industry.³⁰

Although scCO₂ is excellent at removing hydrophobic lipids and smaller cellular components, achieving the absolute removal of hydrophilic genetic material (DNA) from dense tissues like bone, tendon, or thick dermal layers can be challenging. Studies have shown that scCO₂ alone often fails to reach the gold-standard threshold of < 50ng DNA/mg tissue. This limitation has necessitated the development of "hybrid" decellularization methods. In these protocols, the tissue undergoes a brief exposure to a traditional detergent like SDS (e.g., for 8–48 hours) to facilitate cell lysis, followed by a scCO₂ wash cycle (e.g., 1–5 hours) to extract the debris and flush out the residual SDS detergent to ensure cell biocompatibility. These hybrid methods combine the effective DNA removal of SDS detergent with the cleaning and sterilizing power of scCO₂, achieving complete decellularization in a fraction of the traditional time.³⁰

However, another major risk in scCO₂ processing is the interaction between CO₂ and residual water within the tissue, which forms carbonic acid and locally depresses the pH. If the temperature is not strictly maintained below the tissue denaturation threshold or if the acidification is too severe, the collagen triple helix can collapse. This denaturation is often observed as a blurred band in SDS-PAGE analysis or a loss of the characteristic "crimp" in microscopic observations. While scCO₂ at 37° C is generally considered chemically compatible with collagen, liquid

CO₂ used at lower temperatures has been shown to cause significant denaturation, likely due to the higher solubility of CO₂ in water at lower temperatures, which intensifies pH reduction.³⁰

Although hydrophobic in polarity, scCO₂ is a highly effective solvent for water, which can lead to the rapid and unintentional dehydration of collagen membranes. Excessive water removal leads to "scaffold embrittlement," where the membrane becomes stiff and brittle, losing its original handling characteristics and mechanical compliance. To counteract this, advanced protocols utilize a "presaturation" technique where scCO₂ is pre-mixed with water before reaching the tissue. This method has been shown to preserve over 97% of the native moisture content in porcine tissues, thereby maintaining the structural and mechanical properties of the scaffold. However, implementing presaturation requires sophisticated equipment to ensure a uniform distribution of water within the supercritical phase, adding to the complexity of the manufacturing process.³⁰

Despite its clear economic and environmental advantages, the application of scCO₂ to collagen purification is accompanied by several technical drawbacks that must be carefully managed to ensure product safety and manufacturing viability and batch reproducibility.³⁰

3. Diversification and Modern Regenerative Medicine (2000s –Present)

During the last three decades, the use of dBP has diversified into advanced dental, urological, and orthopaedic applications. Modern processing focuses on the complete removal of xenoantigens, such as the alpha-Gal epitope, which was historically responsible for most, if not all, of the clinically relevant, immune-mediated rejection of implanted collagen medical devices.^{7,30}

Currently, dBP devices such as Tutopatch, Copios, and CardiaMend are recognized for their "exit strategy"—the ability to be systematically resorbed (typically within 12 to 20 weeks) and replaced by vascularized host tissue. While early failures of some decellularized patches highlighted the need for careful synchronization between scaffold resorption and host remodelling, the historical shift toward these uncross-linked matrices has largely redefined the standards for biocompatibility in reconstructive surgery and tissue regeneration.^{2,10,17,18,30,34}

3.1 Current Development

The clinical utility of dBP devices is predicated on its ability to provide immediate mechanical support while simultaneously serving as a scaffold for cellular repopulation, angiogenesis, and functional tissue

remodelling and regeneration. Unlike fixed tissues that remain neutralized, foreign bodies, these uncross-linked matrices undergo a controlled physiological degradation coordinated with the deposition of new host-derived collagen. This process of constructive remodelling is essential in diverse surgical specialties

ranging from cardiovascular and neurosurgical reconstruction to advanced periodontal regeneration and complex abdominal wall repair, perhaps especially in paediatric patients.^{1,10,30}

3.2 Commercial Decellularized Bovine Pericardium Products

This section examines the biochemical processing

methodologies, biomechanical profiles, clinical outcomes, and future bioactivation strategies that define the contemporary use of dBP in modern medicine. The following table shows the primary medical devices derived from dBP, highlighting their regulatory status, commercial origins, and technical details.^{16-18,29-32,34,44,45}

Product Name	Marketing Year	Company	Therapeutic Indication	Patent Technology Details & Non-
Veritas	2005	Synovis Life Technologies (Baxter) Collagen Matrix	Staple line reinforcement, hernia repair, pelvic floor reconstruction, breast reconstruction	crosslinked dBP; amine capping via propylene oxide. US Patent 7,166,282 and related processes. (c.f. Synovis Collagen Matrix) dBP: Non-crosslinked biological patch specifically cleared for pericardial closure applications. (c.f. Veritas)
Synovis Collagen Matrix	2013	Synovis Surgical Innovations (Baxter)	Reconstruction and repair of the pericardium	dBP: Tutoplast® Process (solvent dehydration, irradiation). US Patent 5,997,895.
Tutopatch	2000	RTI Surgical	Dura mater replacement, pericardial repair, thoracic wall replacement, breast reconstruction	dBP: Fenestrated version of Tutopatch; non-crosslinked acellular collagen matrix.
Tutomesh	2002	RTI Surgical	Abdominal wall defects, hernia repair, breast reconstruction	dBP: Processed via Tutoplast®. Non-crosslinked Type I & III collagen matrix.
CopiOs Pericardium Membrane	2008	Zimmer Biomet	Guided bone regeneration, Schneiderian membrane sealing, dental soft tissue grafting	dBP: Processed via Tutoplast®. Non-crosslinked Type I & III collagen matrix.
Lyoplant	1994	B. Braun	The replacement and extension of connective tissue structure in neurosurgery.	

4. Biochemical Processing and the Preservation of Scaffold Bioactivity

The efficacy of dBP as a regenerative scaffold is inextricably linked to the purity and structural integrity of its underlying extracellular matrix. The primary objective of processing is decellularization—the complete removal of cellular components, genetic material, and xenoantigens that could otherwise trigger hyperacute rejection or a chronic inflammatory response. For bovine-derived tissues, the elimination of the galactose- α -1,3-galactose (α -Gal) antigen is particularly critical, as humans possess pre-existing IgG antibodies against this particular epitope.^{7,13,21,30}

4.1 Biomechanical Performance and Physiological Integration

The primary advantage of dBP over traditional glutaraldehyde-fixed BP lies in its biomechanical compliance and its biocompatibility which enables it to integrate with the host's physiological environment. Glutaraldehyde fixation creates a mixture of temporary and permanent covalent lysine-derived bridges between collagen fibrils, which results in a material that is structurally rigid and highly resistant to enzymatic degradation. It will also form relatively stable cyclic acetals with collagen-linked glycosides, such as α -Gal, thus, albeit temporarily, masking its immunogenic effects. While this rigidity is beneficial for immediate mechanical stability, it prevents the tissue from responding to dynamic physiological loads and obstructs the normal cycle of tissue maintenance and repair, and also remodelling in paediatric patients.^{3-5,22,25,27}

4.2 Resistance to Calcification and the Role of Cross-linking

Calcific degeneration is the leading cause of clinical failure in bioprosthetic implants, particularly heart valves and vascular patches. The relationship between glutaraldehyde uptake and calcification is non-linear and governed by the availability of residual aldehyde groups and the absence of vital cellular regulation.^{3,23-27}

Quantitative studies in rat models have demonstrated that bovine pericardium with high glutaraldehyde uptake (indicating significant cross-linking) undergoes severe calcification, whereas uncross-linked or minimally cross-linked membranes show minimal mineral deposition. Specifically, tissue with limited cross-linking—characterized by a high residual lysine count—exhibited calcification levels as low as 12.8 micrograms of Ca^{2+} per milligram of tissue. In stark contrast, highly cross-linked tissues, which maintained 95% of their weight during enzymatic challenge, calcified at rates exceeding 93.5 micrograms/mg.^{3,25,27}

The mechanism of this disparity is rooted in both chemical and cellular factors. Glutaraldehyde-fixed tissue acts as a “biological desert,” where residual cellular debris and preserved phospholipids can provide a phosphate-rich environment that attracts calcium ions from the surrounding plasma.

Furthermore, the dense cross-linking prevents host cells from infiltrating the graft. Without a living population of fibroblasts or endothelial cells, the implant cannot regulate the local calcium environment or perform the active tissue remodelling necessary to prevent mineral nucleation. Uncross-linked membranes, by allowing rapid revascularization and repopulation, maintain a vital biological status that inherently resists the passive mineral deposition seen in fixed tissues.^{3,25,27}

4.3 Biomechanical Dynamics under Cyclic Loading

The mechanical durability of dBP has been a subject of rigorous testing, particularly in cardiovascular contexts where cyclic stress is constant. Biomechanical analysis demonstrates that unfixed or decellularized bovine pericardium undergoes minimal cyclic-dependent strain compared to glutaraldehyde-fixed counterparts. Fixed BP exhibits a marked increase in stiffness and a significant change in structure and mechanical function over time, a phenomenon that can lead to stress mismatch at the surgical interface.^{5,22}

Unfixed bovine pericardium has been shown to withstand cyclic deformations equivalent to at least six months of in vivo heart valve leaflet performance while maintaining its original mechanical integrity and fiber arrangement. This resilience is attributed to the preservation of the natural triple-stranded helical arrangement of collagen molecules, which allows the fibers to slide and realign under stress—a property that is lost when the fibres are covalently locked together by glutaraldehyde.²²

4.4 Cardiovascular Applications: Beyond Patch Angioplasty

In cardiovascular surgery, bovine pericardium has traditionally served as the material of choice for patch closure of longitudinal arteriotomies (patch angioplasty) to prevent the restenosis associated with primary closure. While glutaraldehyde-treated patches are still commonly used, there is a distinct clinical trend toward uncross-linked or minimally cross-linked biological matrices, especially in paediatric populations and complex adult reconstructions.^{2,10,30,31}

4.5 Carotid Endarterectomy and Vascular Reconstruction

The use of dBP in carotid endarterectomy (CEA) is supported by meta-analyses demonstrating reduced perioperative complications and lower rates of recurrent stenosis compared to primary closure or some synthetic materials. dBP patches offer several technical advantages in this setting, including superior handling, excellent suture retention, and a significant reduction in intraoperative suture line bleeding.^{10,31}

A major research focus in vascular surgery is the prevention of intimal hyperplasia, the primary cause of restenosis after patch angioplasty. Unlike synthetic patches made of Dacron or ePTFE, dBP provides a natural microenvironment that supports the migration and proliferation of host endothelial cells. This re-endothelialization is critical for establishing a non-thrombogenic surface and regulating the inflammatory signals that drive intimal hyperplasia. Furthermore, biological patches exhibit a higher resistance to infection than synthetic materials, making them safer for use in potentially contaminated surgical fields.^{10,14}

4.6 Paediatric Congenital Heart Defect Repair

Paediatric cardiac surgery presents a unique requirement for biomaterials: the ability to accommodate the growth of the patient. Permanent synthetic patches and heavily cross-linked biological tissues fail to grow, which can lead to subsequent stenoses or aneurysmal dilations as the child develops. dBP, which serves as a scaffold for constructive remodelling, offers the potential for the repair site to be gradually replaced by the child's own living tissue.^{10,30}

Clinical case studies have highlighted the successful use of uncross-linked matrices, such as the CardiaMend Pericardial and Epicardial Reconstruction

Matrix, in repairing simple and complex congenital anomalies including Ventricular Septal Defects (VSD) and Atrial Septal Defects (ASD). These matrices, often derived from fetal bovine dermis, are exceptionally rich in type III collagen—a protein essential for regenerative, scarless healing. Large animal models have demonstrated that these matrices can be completely remodelled into native-looking cardiac tissue within three months, showing neo-vascularization and no evidence of adhesion to the epicardium.^{28,34,47}

The choice between these products often involves a clinical judgment regarding the required duration of mechanical support. While glutaraldehyde-fixed patches provide immediate, high-strength permanent reinforcement, uncross-linked matrices are selected for their regenerative potential and long-term biological harmony.^{10,28,34}

4.7 Advanced Periodontal and Dental Regeneration

The dental specialty has perhaps more than any other field embraced the use of dBP as a bioabsorbable barrier membrane. In Guided Tissue Regeneration (GTR) and Guided Bone Regeneration (GBR), the membrane acts as a temporary wall, preventing the rapid ingrowth of gingival epithelium into a bony defect and allowing slower-growing osteogenic and periodontal ligament cells to populate the space.^{12,15,16,35,36,46}

4.7.1 Root Coverage and Gingival Thickness Augmentation

Periodontal plastic surgery frequently employs dBP (e.g., CopiOs) for the treatment of localized gingival recessions and root exposure, which are often associated with dentine hypersensitivity and aesthetic concerns. Clinical trials evaluating these membranes in Miller Class I and II recessions have shown remarkable results over a six-month follow-up period.^{12,15}

The most significant finding in these studies is the conversion of the gingival biotype. Before surgery, the majority of sites were classified as a “thin” biotype, which is more prone to recession and trauma. Following the implantation of the dBP matrix, 100% of the treated sites were assessed as having a “thick” biotype. This increase in gingival thickness is not merely a swelling effect but represents true soft tissue augmentation through the integration of the bovine matrix into the host's connective tissue.^{12,15,35}

4.7.2 Alveolar Ridge Augmentation and Site Preservation

Following tooth extraction, significant resorption of the alveolar ridge can occur, making subsequent dental implant placement challenging. Lateral ridge augmentation utilizing CopiOs membrane in combination with particulate mineralized cancellous bone has proven to be an effective strategy for restoring ridge dimensions.^{37,38}

In a multicentre prospective study involving 44 patients, 86.4% of participants were able to receive dental implants in ideal, restoratively driven positions six months after augmentation with CopiOs membrane. While approximately 50% of the horizontal volume of the graft was resorbed or displaced during healing, the clinical gain in ridge width averaged 2.61 mm. Histological analysis of cores taken from the augmented ridges revealed a vital bone volume of approximately 58%, with only 12% residual allograft particles and no foreign body inflammatory infiltrate. These outcomes confirm that dBP effectively shields the graft from epithelial invasion while permitting the revascularization and osteogenesis necessary for bone formation.^{37,38}

4.8 Neurosurgical Repair and Dural Substitution

The closure of the dura mater is a critical step in cranial and spinal surgery to prevent cerebrospinal fluid (CSF) leaks, pseudomeningocele formation, and the risk of meningitis. An ideal dural substitute must be watertight, biocompatible, non-adherent to the cerebral cortex, and strong enough to retain sutures.^{11,39-42}

Uncross-linked bovine pericardium (e.g., Tutopatch) has emerged as an excellent dural substitute, replacing the use of cadaveric human dura (dura mater allografts), which was abandoned in the 1990s due to the risk of prion transmission. Clinical outcomes using BP dural grafts have been reported as “good” or “excellent” in 94% to 100% of cases in various surgical series.^{11,17,18,39,41,42}

The clinical benefits in neurosurgery include:

- ➔ **Watertight Sealing:** The dense, collagenous nature of the pericardium allows for a secure, watertight closure using standard 4-0 silk or Prolene sutures, significantly reducing the incidence of post-operative CSF leaks.^{11,41,42}
- ➔ **Compliance and Handling:** The uncross-linked membrane is thin and pliable, allowing it to

conform to the complex contours of the brain and spinal cord without kinking or folding.^{11,41,42}

- ➔ **Low Antigenicity:** The removal of cellular components and the aseptic processing of the bovine tissue result in a graft with extremely low toxicity and immunogenicity, minimizing post-operative inflammation and cortical scarring.^{5,11,21,41,42}
- ➔ **Cost-Effectiveness:** BP is significantly less expensive than many synthetic non-biological grafts or autologous grafts that require a separate donor site incision, reducing overall surgical expense and operative time.^{11,41,42}

Comparative studies have shown that non-autologous grafts like bovine pericardium have complication rates (e.g., CSF leak, infection) similar to autologous grafts such as temporalis fascia or pericranium, while providing the advantage of immediate availability and standardized mechanical properties.⁴⁰⁻⁴²

4.9 Complex Abdominal Wall Repair and General Surgery

The management of complex ventral hernias and abdominal wall defects, particularly in the presence of contamination or infection, represents one of the most demanding applications for biological biomaterials. Synthetic polypropylene or polyester meshes, while effective in clean cases, are generally contraindicated in infected fields because their porous structure can harbour bacteria, leading to chronic mesh infection and the need for surgical removal.^{8,9,19,33}

4.9.1 Biological Reinforcement in Contaminated Fields

Acellular bovine pericardium (e.g., Veritas, Tutomesh) provides a safe and feasible alternative for abdominal wall reconstruction in high-risk scenarios, such as hernia relapse on an infected synthetic mesh or in the setting of diffuse peritonitis. These biological matrices are engineered to withstand enzymatic degradation while promoting rapid revascularization. This vascular influx is the key to their infection resistance, as it allows the host's immune cells and antibiotics to reach the heart of the graft.^{8,9,19,33}

In a retrospective review of 26 patients with complex hernias treated with acellular bovine pericardium, the recurrence rate was 19% with a mean follow-up of 22 months. Importantly, no fistulas developed in this series, despite 16 patients presenting with ongoing infection or gross contamination at the time

of repair. Another series involving 48 patients similarly concluded that acellular bovine pericardium is a safe option for managing complicated defects where prosthetic mesh is unsuitable, with a recurrence rate comparable to traditional mesh repair.^{19,33}

4.9.2 Adhesion Prevention and Host Integration

A significant complication of synthetic intra-abdominal meshes is the formation of dense adhesions to the underlying viscera, which can lead to bowel obstruction or enterocutaneous fistulas. Acellular bovine pericardium has been found to elicit a significantly lower inflammatory response compared

to polypropylene mesh. Histological analysis 40 days post-implantation shows that while polypropylene induces extensive granulation tissue and giant cell formation, bovine pericardium promotes high levels of host collagen deposition and smooth, constructive integration with the abdominal wall.^{19,43}

Experimental studies have shown that the dermal and pericardial matrices support fibroblastic infiltration and neovascularization without inducing a foreign body response, allowing them to eventually be replaced by vascularized host tissue. This “exit strategy”—where the biomaterial is eventually replaced by the host’s own tissue—minimizes the long-term risk of chronic inflammatory complications and mesh-related pain.^{19,43}

5.0 Safety, Recalls, and the MAUDE Database Experience

While uncross-linked bovine pericardium has an excellent overall safety profile, the clinical performance of these materials depends heavily on the specific processing technology and the quality of the raw material source. Regulatory bodies and clinical centres monitor these devices through tools like the FDA’s Manufacturer and User Facility Device Experience (MAUDE) database.^{17,18,45}

The rigorous testing required for FDA clearance (510k pathway) includes evaluations for biocompatibility, pyrogenicity, toxicity, and mechanical strength to ensure that these materials perform reliably across their indicated uses.⁴⁵

6. The Future of Bioactivation: Scaffolds as Therapy Delivery Systems

The current research frontier for uncross-linked bovine pericardium lies in moving beyond the “passive scaffold” model toward “active” or “smart” bio-matrices. By modifying the pericardium with pharmacological agents or biological signals, researchers aim to further accelerate remodelling and expand clinical indications. However, this pharmaceutical approach will probably not be feasible via the FDA 510k pathway.^{30,47}

6.1 Bioactive Modification with Hyaluronic Acid (HA)

A significant hurdle for decellularized scaffolds is the initial rate of cell adhesion and proliferation. Research has explored the bioactive potential of combining bovine pericardium membranes with low-molecular-weight hyaluronic acid (HA, 120 kDa). Physicochemical characterization using Fourier Transform Infrared Spectroscopy (FTIR) and X-ray Diffraction (XRD) confirms that HA modification increases the hydrophilicity of the membrane and improves its surface morphology.⁶

In vitro fibroblast cell viability analysis has shown that HA-modified membranes maintain high cytocompatibility, with mean cell viability reaching 85%. This modification is expected to enhance the membrane’s bioactivity, making it more effective for rapid tissue regeneration in both soft and hard tissue engineering applications.⁶

6.2 Stem Cell Seeding and Tissue Engineering

The next generation of biological substitutes involves seeding dBP with mesenchymal stem cells (MSCs)

to create “living” replacements. MSC-seeded BP scaffolds have demonstrated the potential for differentiation into mesothelial cells, which could provide a living, anti-adhesive surface for cardiac and abdominal repairs. Furthermore, perfusion-assisted bioreactors are being used to populate dBP with heart valve cells, creating bioprosthetic leaflets that exhibit functional traits typical of mature heart valves and show enhanced integration with the extracellular matrix.⁴⁷

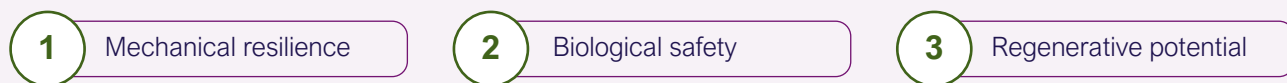
6.3 Hybrid and Non-Glutaraldehyde Cross-linking

To address the limitations of traditional glutaraldehyde, researchers are developing hybrid cross-linking

methods using non-toxic substitutes such as Neomycin Trisulfate (to stabilize GAGs), Polyethylene glycol diglycidylether (to stabilize collagen), and Tannic acid (to stabilize elastin). This “triple stabilization” approach (NPTD) has been shown to reduce calcification and inflammation while improving the thermodynamic stability and hemocompatibility of the tissue. Other novel treatments include riboflavin-UVA-cross-linking combined with low-energy electron beam irradiation (SULEEI), which has shown promise in reducing calcification propensity while maintaining biomechanical properties similar to standard patches.^{23,24,26,48}

7. Conclusions

The clinical application of dBP has transitioned from a niche surgical choice to a primary strategy in regenerative reconstruction. The synthesis of biochemical processing expertise and an improved understanding of host-graft interactions has resulted in a material that satisfies the three critical requirements of a modern surgical implant:^{1,10,30}



The move away from high-concentration glutaraldehyde fixation is supported by the quantitative evidence of severe calcification and biological inertness associated with fixed tissues. In contrast, uncross-linked membranes processed via optimized decellularization protocols serve as bioactive scaffolds that are systematically remodelled into vascularized host tissue. This property is particularly transformative in paediatric cardiac surgery, where growth potential is required, and in complex abdominal and dental repairs, where infection resistance and soft tissue augmentation are the primary goals.^{3-5,23-25,27}

Clinicians must, however, remain cognizant of the trade-offs between biological activity and immediate structural integrity. The rare but significant failure cases of some decellularized products emphasize that the window for remodelling must be synchronized with the mechanical demands of the environment. As research progresses into stem cell seeding, the role of decellularized bovine pericardium is expected to expand further, solidifying its place as a premier platform for tissue engineering and the advancement of patient outcomes in multi-specialty surgical practice.^{30,47}

References

- Gomes, M.C.N.S., Cruz, D.G. and Alberti, L.R., 2022. The importance of the use of bovine pericardium for surgical reconstructions: a systematic review. https://rmmg.org/expor tar-pdf/3911/en_e32206.pdf
- Goja, S., Sankhyan, L.K., Chowdhury, U.K., Pandey, N.N. and Arava, S., 2022. Echocardiographic and Computed-tomographic Evaluation of the Fate of Bovine Pericardial Patch as a Pericardial Substitute in Bental's Procedure: Twenty-year' Results. *J. Clinical Cardiology and Cardiovascular Interventions*, 5(1), pp.2641-0419. <https://auctoresonline.com/article/echocardiographic-and-computed-tomographic-evaluation-of-the-fate-of-bovine-pericardial-patch-as-a-pericardial-substitute-in-bentalls-procedure-twenty-year-results>
- Golomb, G., Schoen, F.J., Smith, M.S., Linden, J., Dixon, M. and Levy, R.J., 1987. The role of glutaraldehyde-induced cross-links in calcification of bovine pericardium used in cardiac valve bioprostheses. *The American journal of pathology*, 127(1), p.122. <https://pubmed.ncbi.nlm.nih.gov/articles/PMC1899585/>
- Umashankar, P.R., Arun, T. and Kumari, T.V., 2011. Short duration glutaraldehyde cross linking of decellularized bovine pericardium improves biological response. *Journal of biomedical materials research Part A*, 97(3), pp.311-320
- Hülsmann, J., Grün, K., El Amouri, S., Barth, M., Hornung, K., Holzfuß, C., Lichtenberg, A. and Akhyari, P., 2012. Transplantation material bovine pericardium: biomechanical and immunogenic characteristics after decellularization vs. glutaraldehyde-fixing. *Xenotransplantation*, 19(5), pp.286-297.
- Indrawati, D.W., Setiawatie, E.M., Rahayu, R.P., Manurung, R.B.S. and Aljunaid, M.A., 2026. Exploring the bioactive potential of bovine pericardium membrane combined with hyaluronic Acid: characterization and cellular viability analyses. *Biochemistry and Biophysics Reports*, 45, p.102490. - PMC, <https://pubmed.ncbi.nlm.nih.gov/articles/PMC12905706/>
- Zouhair, S., Dal Sasso, E., Tuladhar, S.R., Fidalgo, C., Vedovelli, L., Filippi, A., Borile, G., Bagno, A., Marchesan, M., De Rossi, G. and Gregori, D., 2020. A comprehensive comparison of bovine and porcine decellularized pericardia: new insights for surgical applications. *Biomolecules*, 10(3), p.371. <https://pubmed.ncbi.nlm.nih.gov/articles/PMC7175169/>
- Frascino, L.F., De Campos Severi, J.D., Funes Lorenzato, F.R. and Xavier Funes, H.L., 2021. REPAIR OF ABDOMINAL WALL DEFECTS WITH ACELLULAR BOVINE PERICARDIUM MATRIX A MULTICENTRE PROSPECTIVE STUDY. *medRxiv*, pp.2021-06. <https://www.medrxiv.org/content/10.1101/2021.06.15.21257792v1.full-text>
- Frascino, L.F., Lorenzato, F.R.F., Funes, H.L. and Severi, J.D.D.C., 2024. Abdominal wall repair with acellular bovine pericardial membranes-Part I-Clinical and radiological findings. *Revista Brasileira de Cirurgia Plástica*, 39, p.e0798. - Part I - Clinical and radiological findings. https://www.researchgate.net/publication/377906623_Abdominal_wall_repair_with_acellular_bovine_pericardial_membranes_-_Part_I_-_Clinical_and_radiological_findings
- Li, X., Guo, Y., Ziegler, K.R., Model, L.S., Eghbali, S.D., Brenes, R.A., Kim, S.T., Shu, C. and Dardik, A., 2011. Current usage and future directions for the bovine pericardial patch. *Annals of vascular surgery*, 25(4), pp.561-568. <https://pubmed.ncbi.nlm.nih.gov/articles/PMC3085588/>
- Filippi, R., Schwarz, M., Voth, D., Reisch, R., Grunert, P. and Perneczky, A., 2001. Bovine pericardium for duraplasty: clinical results in 32 patients. *Neurosurgical review*, 24(2), pp.103-107. https://www.researchgate.net/publication/11858387_Bovine_pericardium_for_duraplasty_Clinical_results_in_32_patients
- Schlee, M., Ghanaati, S., Willershausen, I., Stimmler, M., Sculean, A. and Sader, R.A., 2012. Bovine pericardium based non-cross linked collagen matrix for successful root coverage, a clinical study in human. *Head & face medicine*, 8(1), p.6. https://www.researchgate.net/publication/221888530_Bovine_pericardium_based_noncross_linked_collagen_matrix_for_successful_root_coverage_a_clinical_study_in_human
- Li, N., Li, Y., Gong, D., Xia, C., Liu, X. and Xu, Z., 2018. Efficient decellularization for bovine pericardium with extracellular matrix preservation and good biocompatibility. *Interactive cardiovascular and thoracic surgery*, 26(5), pp.768-776. <https://pubmed.ncbi.nlm.nih.gov/29340634/>
- Kimicata, M., Allbritton-King, J.D., Navarro, J., Santoro, M., Inoue, T., Hibino, N. and Fisher, J.P., 2020. Assessment of decellularized pericardial extracellular matrix and poly (propylene fumarate) biohybrid for small-diameter vascular graft applications. *Acta biomaterialia*, 110, pp.68-81. <https://pubmed.ncbi.nlm.nih.gov/articles/PMC7294167/>
- Schlee, M., Ghanaati, S., Willershausen, I., Stimmler, M., Sculean, A. and Sader, R.A., 2012. Bovine pericardium based non-cross linked collagen matrix for successful root coverage, a clinical study in human. *Head & face medicine*, 8(1), p.6. <https://pubmed.ncbi.nlm.nih.gov/articles/PMC3311137/>
- Collagen Dental Membrane – Conformable IIBP 510(k) Summary of Safety and Effectiveness - [accessdata.fda.gov](https://accessdata.fda.gov/cdrh_docs/pdf14/K142496.pdf), https://www.accessdata.fda.gov/cdrh_docs/pdf14/K142496.pdf
- Tutopatch RTI biologics - [accessdata.fda.gov](https://accessdata.fda.gov/cdrh_docs/pdf/k991296.pdf), https://www.accessdata.fda.gov/cdrh_docs/pdf/k991296.pdf

18. Coloplast-IFU-Tutoplast-Pericardium.pdf, <https://iu.coloplast.us/wp-content/uploads/2021/09/Coloplast-IFU-Tutoplast-Pericardium.pdf>
19. D'Ambra, L., Berti, S., Feleppa, C., Magistrelli, P., Bonfante, P. and Falco, E., 2012. Use of bovine pericardium graft for abdominal wall reconstruction in contaminated fields. *World journal of gastrointestinal surgery*, 4(7), p.171., <https://pmc.ncbi.nlm.nih.gov/articles/PMC3420984/>
20. Adiputra, K.A.A., Soebroto, H. and Puruhito, I., 2024. Comparative Analysis of Decellularization Methods on Bovine Pericardium Scaffolds for Cardiac Tissue Engineering. *Journal of Angiotherapy*, 8(8), pp.1-7. https://publishing.emanresearch.org/CurrentIssuePDF/EmanPublisher_1_5590angiotherapy-889833.pdf
21. Sokol, A., Grekov, D., Yemets, G., Galkin, O., Shchotkina, N., Rudenko, N. and Yemets, I., 2020. Biocompatibility analysis of the decellularized bovine pericardium. *Cell Organ Transpl*, 8(2), pp.193-197., <https://transplantation.org/2020-8-2-en/article-02/>
22. Oswal, D., Korossis, S., Mirsadraee, S., Wilcox, H., Watterson, K., Fisher, J. and Ingham, E., 2007. Biomechanical characterization of decellularized and cross-linked bovine pericardium. *Journal of Heart Valve Disease*, 16(2), p.165. - ResearchGate, https://www.researchgate.net/profile/Kevin-Watterson/publication/6347853_Biomechanical_characterization_of_decellularized_and_cross-linked_bovine_pericardium/links/00b7d5165696a213a0000000/Biomechanical-characterization-of-decellularized-and-cross-linked-bovine-pericardium.pdf
23. Jiang, Z., Wu, Z., Deng, D., Li, J., Qi, X., Song, M., Liu, Y., Wu, Q., Xie, X., Chen, Z. and Tang, Z., 2022. Improved cytocompatibility and reduced calcification of glutaraldehyde-crosslinked bovine pericardium by modification with glutathione. *Frontiers in Bioengineering and Biotechnology*, 10, p.844010. <https://www.frontiersin.org/journals/bioengineering-and-biotechnology/articles/10.3389/fbioe.2022.844010/full>
24. Liu, Y., Wu, Z., Chen, C., Lu, T., Song, M., Qi, X., Jiang, Z., Liu, S. and Tang, Z., 2022. The hybrid crosslinking method improved the stability and anti-calcification properties of the bioprosthetic heart valves. *Frontiers in Bioengineering and Biotechnology*, 10, p.1008664. - Frontiers, <https://www.frontiersin.org/journals/bioengineering-and-biotechnology/articles/10.3389/fbioe.2022.1008664/full>
25. Abolhoda, A., Yu, S., Oyarzun, J.R., McCormick, J.R., Bogden, J.D. and Gabbay, S., 1996. Calcification of bovine pericardium: glutaraldehyde versus No-React biomodification. *The Annals of thoracic surgery*, 62(1), pp.169-174 <https://pubmed.ncbi.nlm.nih.gov/8678638/>
26. Liu, Y., Chen, C., Lu, T., Liu, S., Wu, Z. and Tang, Z., 2023. Free-aldehyde neutralized and oligohyaluronan loaded bovine pericardium with improved anti-calcification and endothelialization for bioprosthetic heart valves. *Frontiers in Bioengineering and Biotechnology*, 11, p.1138972 <https://www.frontiersin.org/journals/bioengineering-and-biotechnology/articles/10.3389/fbioe.2023.1138972/full>
27. Jorge-Herrero, E., Fonseca, C., Barge, A.P., Turnay, J., Olmo, N., Fernández, P., Lizarbe, M.A. and Garcia Paez, J.M., 2010. Biocompatibility and calcification of bovine pericardium employed for the construction of cardiac bioprotheses treated with different chemical crosslink methods. *Artificial Organs*, 34(5), pp.E168-E176 <https://pubmed.ncbi.nlm.nih.gov/20633147/>
28. Bhende, V.V., Sharma, T.S., Krishnakumar, M., Ramaswamy, A.S., Bilgi, K., Pathan, S.R. and Ramaswamy, A.S., 2024. Beyond synthetics: promising outcomes with the Invengenx® bovine pericardial patch for ventricular septal defect repair in a young pediatric population. *Cureus*, 16(3). <https://pdfs.semanticscholar.org/e07b/b76e3bd19a6304fba6869f84980ab8e8c581.pdf>
29. Bovine Pericardial Patch | Bovine Pericardial Tissue Patch, <https://tisgenx.com/>
30. Shariat Rad, P., Khazaei, M., Ghanbari, E., Rashidi, M. and Rezakhani, L., 2025. Recent advances in pericardium extracellular matrix for tissue regeneration, along with a short insight into artificial intelligence. *Frontiers in Medical Technology*, 7, p.1503153. <https://pmc.ncbi.nlm.nih.gov/articles/PMC12400526/>
31. Bovine Pericardial Patch | Edwards Lifesciences, <https://www.edwards.com/healthcare-professionals/products-services/surgical-heart/bovine-pericardial-patch>
32. Bovine Pericardium Patches - FOC Medical, <https://focmedical.com/en/bovine-pericardium-patches/>
33. Limpert, J.N., Desai, A.R., Kumpf, A.L., Fallucco, M.A. and Aridge, D.L., 2009. Repair of abdominal wall defects with bovine pericardium. *The American journal of surgery*, 198(5), pp.e60-e65. <https://pubmed.ncbi.nlm.nih.gov/19811771/>
34. Helios Cardio announces US FDA 510(k) clearance for a new ..., <https://www.helioscardio.com/news/helios-cardio-announces-us-fda-510k-clearance-for-a-new-pericardial-and-epicardial-reconstruction-matrix>
35. Dasuki, N.D.N.M., Taib, H., Berahim, Z. and Hassan, A., 2025. Bovine Pericardium Membrane as a Barrier Material for Periodontal Tissue Regeneration: A Retrospective Study. *Journal of Health Science and Medical Research*, 43(5), p.20251179. - ResearchGate, <https://www.jhsmr.org/index.php/jhsmr/article/view/1179>
36. Guided Tissue Regeneration | Surgical Treatment | BV PeriodonticsBV Perio, <https://www.bvperio.com/services/guided-tissue-regeneration/>
37. Sterio, T.W., Katancik, J.A., Blanchard, S.B., Xenoudi, P. and Mealey, B.L., 2013. A prospective, multicenter study of bovine pericardium membrane with cancellous particulate allograft for localized alveolar ridge

- augmentation. *International Journal of Periodontics & Restorative Dentistry*, 33(4). https://www.researchgate.net/publication/244991869_A_Pro prospective_Multicenter_Study_of_Bovine_Pericardium_Membrane_with_Cancellous_Part iculate_Allograft_for_Localized_Alveolar_Ridge_Augmentation
38. Study Details | NCT00889265 | CopiOs® Pericardium Membrane for Localized Alveolar Ridge Augmentation | ClinicalTrials.gov, <https://clinicaltrials.gov/study/NCT00889265>
 39. Bovine Pericardium in Neurosurgery: Dural Substitutes Explained, <https://bovinepericardium.com/bovine-pericardium-in-neurosurgery-dural-substitutes-explained/>
 40. Splavski, B. and Frol, S., 2025. Selecting Substitutes for Cranial Dural Repair and Preventing Intracranial Iatrogenic Amyloid Transmission. *Cureus*, 17(6). - Semantic Scholar, <https://pdfs.semanticscholar.org/63d7/2f1410fcd6cc79b282b85affff4cfd6a723d.pdf>
 41. Baharuddin, A., Go, B.T., Firdaus, M.N.A.R. and Abdullah, J., 2002. Bovine pericardium for dural graft: clinical results in 22 patients. *Clinical neurology and neurosurgery*, 104(4), pp.342-344. <https://pubmed.ncbi.nlm.nih.gov/12140102/>
 42. Anson, J.A. and Marchand, E.P., 1996. Bovine pericardium for dural grafts: clinical results in 35 patients. *Neurosurgery*, 39(4), pp.764-768. <https://pubmed.ncbi.nlm.nih.gov/8880771/>
 43. Bakri, M., Lovato, F.C., Diosti, G.D.M., Salles, Y.L.S.D.G., Moreira, P.H.B., Collaço, L.M., Czezczko, N.G., Malafaia, O. and Kubrusly, L.F., 2021. Comparative analysis of tissular response after abdominal wall repair using polypropylene mesh and bovine pericardium mesh. *ABCD. Arquivos Brasileiros de Cirurgia Digestiva* (São Paulo), 34, p.e1527 <https://pmc.ncbi.nlm.nih.gov/articles/PMC8735132/>
 44. Invengenx Bovine Pericardial Tissue Patch: Widest variety of approved sizes on the market, https://www.dastavardesina.com/wp-content/uploads/2022/12/7.-Tisgenx-Brochure_compressed.pdf
 45. Premarket Notification 510(k) | FDA - Food and Drug Administration, <https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-notification-510k>
 46. Ordonez-Chavez, G.D.C., Rodríguez-Fuentes, N., Peñaloza-Cuevas, R., Cervantes-Uc, J.M., Alcántara-Quintana, L.E., Maya-García, I.A., Herrera-Valencia, V.A. and Mendiburu-Zavala, C.E., 2023. In vitro evaluation of crosslinked bovine pericardium as potential scaffold for the oral cavity. *Bio-Medical Materials and Engineering*, 34(6), pp.561-575., <https://pmc.ncbi.nlm.nih.gov/articles/PMC10657658/>
 47. Soebroto, H., Mahyudin, F., Mastutik, G., Nugraha, A.F., Rahman, A., Utama, R.G., Dwikatmono Johan, A.R., Hariftyani, A.S. and Albab, C.F., 2024. Bovine Pericardium Scaffold as a Critical Tool for Cardiac Surgery with Mesenchymal Stem Cell Seeding: A Narrative Review. *Malaysian Journal of Medicine & Health Sciences*, 20(4). - Scholar UNAIR, <https://scholar.unair.ac.id/en/publications/bovine-pericardium-scaffold-as-a-critical-tool-for-cardiac-surger/>
 48. In vivo application of a glutaraldehyde-free, UVA/riboflavin cross-linked bovine pericardium confirms suitability for cardiovascular substitutes - Fraunhofer-Publica, <https://publica.fraunhofer.de/entities/publication/cfc03431-696a-4694-9a36-e12f9f103734>