

REVIEW ARTICLE

Bovine Pericardium Scaffold as a Critical Tool for Cardiac Surgery with Mesenchymal Stem Cell Seeding : A Narrative Review

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ABSTRACT

This review explores the significance of pericardial dissection in cardiac surgery for managing congenital heart disease (CHD). The procedure often results in intrapericardial adhesion formation, impacting outcomes and increasing hospitalization costs. The focus is on the bovine pericardium (BP) scaffold and its compatibility with mesenchymal stem cells (MSCs) seeding. Various pericardial substitutes have been utilized to achieve complete closure without inducing rapid cardiac constriction. Successful substitutes must prevent adhesions between the chest wall/lung and pericardium, minimizing the risk of injury during re-sternotomy. The review emphasizes the promising application of BP scaffolds, particularly when seeded with MSCs, facilitating differentiation into mesothelial cells. Different methodologies are discussed for optimal MSCs seeding in BP scaffolds, suggesting a positive outlook for expanding the use of bovine pericardium in cardiac surgery. The review highlights the extensive use of bovine pericardium as a xenograft in vascular applications, supported by theoretical evidence, with potential for further enhancement through MSC seeding, indicating promising prospects for tissue engineering and regenerative medicine advancements. *Malaysian Journal of Medicine and Health Sciences* (2024) 20(4): 354-361. doi:10.47836/mjmhs20.4.43

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INTRODUCTION

Cardiac surgery is a frequently performed medical intervention. Within the field of congenital cardiac surgery, a significant proportion of operations recorded in the Society of Thoracic Surgery (STS) database involved either gradual or repeated procedures for up to 67% of cases. The remaining operations were classified as single-stage surgeries (1). In order to access the heart during surgical procedures involving the cardiac region, it is necessary to make an incision in the pericardium. The dissection of the pericardial segment is a common

procedure utilized in the creation of autologous patches or grafts for the management of congenital heart disease (CHD). However, this procedure is associated with an increased likelihood of intrapericardial adhesion formation, which can lead to unfavorable outcomes and higher hospitalization costs. The closure of the pericardium has the potential to maintain cardiac integrity and reduce the incidence of cardiac adhesions to the thoracic cavity.

Numerous attempts have been conducted to achieve closure, predominantly or exclusively, through the utilization of autologous, synthetic, and biosynthetic substances. Pericardial scaffolds refer to both synthetic and biosynthetic materials that are utilized for the purpose of pericardial closure. The examination of various biological scaffolds has included the bovine

pericardium (2). The frequently employed pericardial substitute is the Extended Polytetrafluoroethylene membrane, commonly known as “Gore-Tex”. Nevertheless, the utilization of “Gore-Tex” within the pericardial cavity is considered a foreign substance, which may trigger an inflammatory response from the epicardium. This response could potentially obscure the anatomical structure and result in adverse effects. The membrane has the potential to undergo shrinkage over time, especially during the developmental stages of pediatric patients. This may result in the onset of delayed constrictive pericarditis as the patient reaches maturity, as the membrane may not be able to expand in accordance with the individual’s growth. This poses a risk of restrictive pericarditis, which may impede the proper functioning of the heart (3).

Extensive research is currently being conducted on tissue engineering that involves the utilization of decellularized pericardium implanted with stem cells. This statement is grounded on the premise that stem cells possess a significant quantity of cells and the ability to proliferate, thereby presenting the possibility of cultivation. Stem cells can be obtained from various sources, including bone marrow, peripheral blood, and adipose tissue. Among the three sources, the adipose-derived mesenchymal stem cell (ADMSC) is characterized by its high cell count, superior cell proliferation, and straightforward tissue extraction method (4). The utilization of bovine pericardium that has been seeded with mesenchymal stem cells (MSCs) is anticipated to promote the proliferation and specialization of MSCs into mesothelial progenitor cells, which subsequently undergo complete differentiation into mesothelial cells (5). The aim of this study is to investigate the potential of bovine pericardium as a scaffold material for vascular applications, particularly in combination with mesenchymal stem cell (MSC) seeding, aiming to contribute to advancements in tissue engineering and regenerative medicine.

SUBSTITUTION OF PERICARDIUM: A HISTORY

The search for xenografts as heart surgery material substitutions started as early as 1977, where Ionescu et al replaced heart valves with xenografts in the form of pericardium stabilized with glutaraldehyde (6). According to their statement, the utilization of xenografts yielded greater profitability in comparison to the currently available prosthetic devices. In 1988, Heydorn et al conducted a survey among 2,344 members of the thoracic surgeon community to explore their experience with pericardial substitutes. The study involved the administration of a questionnaire (7).

Heydorn et al., 1988, stated that from a study they conducted to obtain at least 4000 living patients using pericardial replacement, most of whom used silicone rubber and xenografts. The operating rate is relatively

small at 1%, although there are reports of adhesions, perioperative fevers - pericarditis, graft infection and infection (7).

Various synthetic, biological, and autologous materials have been employed to address congenital cardiac anomalies in neonates and pediatric populations. (Table I). Bovine pericardium, an extracellular matrix biomaterial of xenogeneic origin, has found extensive application in the field of cardiovascular medicine. The use of bovine pericardium has been noted in addressing atrial septal defects, ventricular septal defects, and the reconstruction of the right ventricular outflow tract (8).

Table I. Biologics used as cardiac patch. (8)

Material	Method	Characteristics
Polytetrafluoroethylene (PTFE)	Synthetic	Encapsulation, calcification
Porcine intestinal sub-mucosa (Surgisis)	Decellularization	Remodels, enzymatic degradation
Bovine (Peri-guard)	Glutaraldehyde	Durable, calcification
Porcine dermis (Pelvicol)	Glutaraldehyde	Durable, calcification, encapsulation
Autologous pericardium	Intact / glutaraldehyde	Retraction, thickening, calcification

Multiple forms of pericardial substitutes have been employed previously to achieve complete closure of the pericardium while avoiding the onset of rapid cardiac constriction. According to their established standards, the pericardial substitutes must fulfill certain requirements. These include preventing adhesions between the chest wall/lung and pericardium, which in turn reduces the risk of injury to the anterior cardiac structures during re sternotomy and increases safety. Additionally, the substitutes should cause minimal adhesions between the pericardium and epicardium, not provoke a significant epicardial reaction, be relatively inert to avoid tissue reaction, and not increase the patient’s susceptibility to infection. Different materials have been utilised for this objective with varying levels of achievement (9).

AUTOLOGOUS PERICARDIUM

There are multiple choices in closing pericardium defects using autologous pericardium if primary closure is not feasible. “Tension free” technique, initiated by Merav et al. in 1979, involved creating lateral pericardial-relaxing incision. Although there is limited research on the application of this technique through randomized control trials, a serial case report described that the application of this technique did not result in any adverse effects on haemodynamic, LV dimension, ejection fraction, and wall thickness parameters (9). Other techniques reported are rotational flap and pericardial meshing (10,11).

In cases where native pericardium tissue is not

adequate for primary closure, some surgeons reported approximated surgery between pericardium with pericardial fat pad (12). Numerous case reports demonstrate the usage of fascia lata, thymus flap, and pedicle flap sourced from centrum tendineum diaphragm. Nevertheless, the existing case reports lack sufficient long-term follow-up and RCT (9,13,14). The application of autologous materials is restricted due to the limited capacity to employ tissue from a specific site in a patient for the purpose of repairing another. There are certain factors that need to be considered, such as the likelihood of donor site morbidity and the limited ability to replicate the original tissue's structure and functionality (15).

SYNTHETIC PERICARDIUM

The employment of synthetic materials can lead to the attainment of comprehensive pericardial closure. Multiple prosthetic materials are available as potential alternatives, such as Marlex polypropylene monofilamented fiber mesh, Polytetrafluoroethylene (PTFE), and Expanded-polytetrafluoroethylene (e-PTFE). Marlex mesh has been previously utilized; however, it has demonstrated the possibility of constrictive pericarditis as a complication (16). PTFE and e-PTFE are the synthetic materials that have been extensively studied and are considered the primary options for pericardial closure. Moreover, the utilization of PTFE has demonstrated advantageous outcomes in safeguarding the surfaces of ventricular-assist devices during bridge-to-transplant procedures. Both human and animal studies have reported certain drawbacks associated with the use of PTFE and e-PTFE as pericardial substitutes. Both PTFE and e-PTFE are considered permanent foreign bodies and have the potential to elicit an inflammatory response when utilized as pericardial substitutes (9,17).

The epicardial reaction that is typically observed may be exacerbated by PTFE, leading to the formation of a dense, fibrous, and often hemorrhagic layer that can obscure the epicardial anatomy (9). The microhistological analysis revealed that PTFE elicited significant foreign body reactions. It was reported that e-PTFE resulted in more severe adhesions to the heart and pleura and a more prominent inflammatory reaction when compared to a biosynthetic material (17). There was not an adequate amount of research that directly compares the utilization of synthetic materials with other materials for pericardial closure. Several studies indicated that the application of biological-based extracellular matrix in pericardial closure led to a decrease in postoperative complications, without concomitant augmentation of the risk of adverse effects in pericardial closure. These adverse effects included postoperative bleeding, postoperative myocardial infarction, tamponade, or post pericardiotomy syndrome (9,18). Potentially due to these factors, the overall use of synthetic materials was comparatively lower than that of biological materials.

These biological materials employed were xenogeneic materials. The clinical application of these materials is associated with certain disadvantages. Nevertheless, various processing methods and techniques have been investigated to mitigate these disadvantages and adverse reactions (15).

XENOGENEIC SUBSTITUTION: WHY SHOULD IT BE BOVINE PERICARDIUM?

The utilization of xenogeneic tissues as scaffolds for the purpose of tissue engineering has been observed across various tissue types. It is impeded by the immune response and graft rejection that are elicited by the presence of antigens. Consequently, it is imperative to eliminate the antigenic constituents from the tissues while maintaining the desirable structure, composition, and functionality of the initial tissue. Table II demonstrated the known and possible benefit of Bovine Pericardium as Scaffolds (15).

Table II. The known and possible benefits of bovine pericardium as scaffolds

Known benefit	Possible benefit
Reliable consistency	Anticalcification
Ease of handling	Reduced restenosis
Durability	Reduced infections
Strength	Support cellular ingrowth
Biocompatibility	
Lack of suture line bleeding	
Off-the-shelf availability	
Immediate insonation	

BP exhibits a consistent level of reliability in terms of its precise manufacturing and processing, which ensures a thickness of 0.5 mm. This feature contributes to the suture's dependable retention and optimal surgical handling characteristics. Moreover, bovine pericardium is obtainable in various sizes and shapes, can be preserved, and can be customized to meet specific design requirements. One of the primary advantages of BP pertains to its accessibility and affordability. The readily accessible availability of fixed tissue makes it an appealing option. Nevertheless, bovine pericardium exhibits a low incidence of infection and possesses notable strength (19,20). According to Li et al. (2011)(20) and Obermiller et al. (2004)(21), the fixation of BP can be achieved through the use of glutaraldehyde, which results in an enhancement of the material's strength and stability. Furthermore, the acellular composition of BP is characterized by a high concentration of collagen, which facilitates the establishment of microenvironments conducive to host cell proliferation and migration, as well as the acceleration of tissue regeneration and endothelialisation (22).

A comparative analysis between BP and alternative materials as potential substitutes for pericardial closure remains elusive. Nevertheless, BP has been employed as an alternative substance for pericardial closure. A study has demonstrated that the utilization of BP derived material for pericardial closure exhibited favorable outcomes in safeguarding the heart during a redo sternotomy procedure, while also exhibiting positive remodeling into functional, non-fibrotic connective tissue with no adverse inflammatory reaction (23).

In addition, there exist several studies that conduct a comparative analysis of the utilization of bovine pericardium material in contrast to alternative materials in various domains. According to Olsen's (2016), study on the utilization of BP in carotid surgery, it was found that BP patch closure exhibited superior performance in comparison to dacron and direct suture in carotid endarterectomy. The BP patch has demonstrated a lower incidence of bleeding complications and restenosis in comparison to alternative methods and materials utilized. Moreover, surgeons tend to favor the use of bovine pericardium patch over other methods due to its superior handling characteristics (24). Texakalidis et al. described that bovine pericardium patches in endarterectomy showed no significant differences compared to synthetic patch in terms of perioperative stroke, TIA, neck hematoma, and death (25). Nevertheless, non-randomized study for BP usage for carotid endarterectomy demonstrated that BP had a lower restenosis rate than autologous vein (26).

PRODUCTION PROCESS

Dalglish et al. conducted a study that demonstrated an effective method of decellularization while preserving the extracellular tissue matrix. The extracellular matrix network's structure, composition, and function create a favorable milieu for cell adhesion, migration, differentiation, and proliferation, especially in the context of xenogeneic scaffolds (27).

The methodology employed in this study involved initial tissue collection, followed by storage at a temperature of -80 °C. Subsequently, a decellularization process was carried out, and protein residue extraction was performed. The ensuing steps included a series of examinations, such as cytotoxicity, histology, electrophoresis, western blot, quantitative biochemistry, calorimetry, and tensile strength assessments. Finally, the scaffold stem cells were implanted and evaluated (27).

OTHER ALTERNATIVES

A randomized controlled trial research was carried out to assess the effectiveness of Bovine pericardial grafts in comparison to synthetic grafts for repairing pericardial defects (28). On the other side, a retrospective study was conducted to evaluate the incidence of atrial fibrillation

post-coronary artery bypass grafting through an analysis of the utilization of extracellular matrix derived from porcine sources. The utilization of extracellular matrix derived from porcine in pericardium reconstruction was observed to decrease the occurrence of postoperative AF (28). The utilization of an autologous pericardium graft substitute has the capability to hinder the adhesion of the pericardium to the chest wall or lungs. This can provide protection to the anterior side of the heart during resternotomy procedures. Additionally, the use of this substitute may minimize adhesion between the pericardium and epicardium, thereby preventing significant epicardial reaction. Moreover, it can prevent any reaction between the heart and surrounding tissues (28).

Boyd et al also reviewed a number of materials possessing certain benefits, including PTFE, glutaraldehyde-treated xenograft, and bioresorbable polymer film (9). Furthermore, PTFE has been extensively studied as a material for pericardial closure. Certain studies have shown that PTFE exhibits non-adhesive properties, and a randomized controlled trial has suggested that it does not increase the likelihood of pericardial tamponade and infection (29). According to previous studies, PTFE has been found to be beneficial in safeguarding ventricular-assist devices during the bridge to transplant procedure. The efficacy of PTFE in the closure of pericardial defects remains a topic of discussion, as it has been associated with a potentially significant adverse effect (30).

The study conducted on humans demonstrated that PTFE induces an epicardial reaction resulting in the formation of a dense, fibrous, and hemorrhagic layer that occludes the epicardial anatomy (31). The literature indicated that PTFE elicited a notable foreign body reaction and heightens the occurrence of tamponade and injury during resternotomy in pediatric cardiac surgery when compared to alternative grafts, as determined through microhistopathological analysis (9,13,17,32).

Glutaraldehyde-treated xenograft is quite popular in its early invention. Over time, it has been demonstrated that the administration of this substance in both bovine and equine species elicits a significant epicardial reaction, leading to calcification and an antigen-antibody response. This is the reason why its usage was discontinued (33).

Khorramirouz et al utilized porcine as the primary material and revealed the existence of diverse CD3 inflammatory cells in decellularized porcine pericardium that was subcutaneously implanted in rats. An additional investigation documented a persistent inflammatory reaction in a porcine prosthesis that had been removed and was deteriorating, accompanied by notable harm to the aortic wall of the porcine specimen (34). Moreover, Nair et al. treated porcine aortic valves and exhibited the presence of inflammatory cells,

which potentially leads to contributing to structural dysfunction. The study observed the infiltration and degradation of implant-collagen by macrophages in explanted bovine pericardial valves, resulting in cellular infiltrates and collagen disruption. The proposal was put forth that the observed variations could potentially be accounted for by the cross-reactivity of alloantibodies, which lead to the presence of common carbohydrate antigens in both human and animal subjects (35). There exist several carbohydrate antigens that are shared between humans and pigs, and these antigens persist in bioprostheses following reticulation. This phenomenon has the potential to elicit an immune response in the recipient (35).

The application of equine pericardium as a patch material in congenital heart surgery is considered to be a safe approach for reconstruction purposes. In certain scenarios such as arch reconstruction or valve reconstruction, the utilization of a pliable patch or a complex shape may be more desirable than bovine pericardium. No indications of thrombosis, infection, calcification, or degeneration were observed. The extracellular matrix was conserved. The observation of a monolayer of endothelial cells on the inner surface of the patch and the presence of neovascularization on the outer surface was noted. The efficacy of EP has been demonstrated in diverse surgical locations. EP is utilized as a dural substitute in medical procedures. Its properties include transparency, impermeability to cerebrospinal fluid, non-adherence to the cortex, and promotion of dura regeneration. Bovine pericardium exhibits a higher susceptibility to infection and lower physical durability in comparison to its counterpart, thereby rendering the latter a more favorable option. Finally, it was discovered that the equine pericardial patched group exhibited fewer adhesions in comparison to the pericardium left open group (36). However, equine pericardium is still limited in availability and expensive.

BOVINE PERICARDIUM SCAFFOLDS THAT ARE SEEDED WITH MSCS

Presently, there is ongoing thorough investigation into tissue engineering techniques utilizing decellularized pericardium infused with stem cells. This exploration is based on the understanding that stem cells contain ample cells and possess the capacity for multiplication, thus offering potential for cultivation. Stem cells are accessible from diverse origins such as bone marrow, peripheral blood, and adipose tissue. Among these sources, adipose-derived mesenchymal stem cells (ADMSCs) stand out for their abundant cell count, excellent cell proliferation capabilities, and the ease of tissue extraction (4). The expectation is that using bovine pericardium combined with mesenchymal stem cells (MSCs) will encourage the growth and specialization of MSCs into mesothelial progenitor cells. These progenitor cells are then predicted to undergo full differentiation

into mesothelial cells (5).

ADVERSE EFFECTS AND DISADVANTAGES OF BOVINE PERICARDIUM UTILIZATION AS SCAFFOLD

The utilization of bovine pericardium as a substitute graft material is associated with certain limitations and challenges. The primary issue associated with the utilization of bovine pericardium as a xenogeneic graft pertains to the existence of antigens that elicit an immune response, ultimately leading to the rejection of the graft (15). Consequently, research endeavors have been undertaken to target the reduction or elimination of either the immune response or the antigens inherent in xenogeneic tissues for their potential application in human subjects. Graft fixation utilizing glutaraldehyde is a technique that has been postulated to ameliorate the majority of the immune response to connective tissue xenografts. The aforementioned procedure involves the irreversible cross-linking of graft matrix proteins (37).

The use of glutaraldehyde fixation encountered challenges related to the potential toxicity of GA, which was commonly employed in pericardium treatment. The apprehensions regarding residual GA release were centered on genetic toxicity risks rather than overt cytotoxicity, as it was likely to enter the systemic circulation (38). According to the July 2017 Toxicological Profile for Glutaraldehyde by ATSDR, it has been reported that the No Observed Adverse Effects Level (NOAEL) for chronic ingestion exposure to GA in rats is 4 mg/kg/day. This level was significantly greater than the anticipated levels that potentially be discharged from biological valves. Furthermore, report described that following intravenous administration of GA, over 70% of the substance is promptly eliminated through expired CO₂, while the remaining majority is excreted through urine or feces (39).

Decellularization is a technique employed to eliminate antigens from xenogeneic tissue. This process involves the use of chemical reagents to treat raw xenogeneic tissue, such as bovine pericardium. The chemical reagents used in the process of removing antigens from tissues can lead to a reduction in tissue strength by not only eliminating the antigens but also causing harm to the extracellular matrix of the materials (15). Furthermore, a noteworthy constraint association with bovine pericardium material pertains to calcification was found in a study (40).

According to research findings, there are various issues associated with the utilization of bovine pericardium as an alternative graft. The primary constraints encompass the calcification and degeneration of the graft materials (8). Moreover, the utilization of bovine pericardium as a substitute graft is associated with analogous drawbacks as other graft materials. These include the gradual loss of mechanical strength, the incapacity to adapt

to the patient's heart growth, and limited potential for regeneration or remodelling. The employment of these materials has been linked to the risk of infection and aneurysm, in addition to the cytotoxic impacts of different cross-linking agents (41). Currently, there exists a dearth of long-term follow-up studies on the utilization of bovine pericardium as a pericardial patch in patients. Nevertheless, it can be inferred from other investigations on its application in different contexts that bovine pericardium presents certain drawbacks and limitations that may be comparable or identical when employed as a pericardial patch for pericardial closure. However, research has demonstrated the benefits of bovine pericardium as a graft material, with some individuals preferring it over alternative methods or materials (24,25,41,42).

CONCLUSION

This review underscores the significant utilization of bovine pericardium as a xenograft, primarily in vascular applications, supported by theoretical evidence. Furthermore, the existing literature suggests promising prospects for further exploiting bovine pericardium scaffolds, particularly in conjunction with mesenchymal stem cell (MSC) seeding. This highlights the potential for advancements in tissue engineering and regenerative medicine, where bovine pericardium could serve as a valuable scaffold material. Future research in this field could focus on optimizing the integration of MSCs with bovine pericardium scaffolds to enhance tissue regeneration outcomes. Additionally, investigating the long-term durability and immunological response to these constructs would be valuable for clinical translation. Exploring alternative methods for scaffold modification or combination with other biomaterials could further broaden the applicability and effectiveness of bovine pericardium in regenerative medicine. The limitation of this review is the relatively limited number of studies that have been dedicated to investigating the efficacy of bovine pericardium scaffold augmented with stem cells for pericardium closure. The author states that there was no use of AI software or websites in the process of compiling this paper.

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