A state of the “heart”: application of bioengineered materials for cardiac surgery

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Abstract

Introduction. Cardiovascular diseases have become the leading mortality cause, requiring a novel technologies and techniques for the treatment. Cardiovascular biomaterials play a vital role as the potentially eligible alternative modality for an operation, covering the gap between facilities and patients in need of medical devices and procedures.

Purpose. The aim of this essay is to explore and analyze the currently used biomaterials for cardiac surgery as tools to repair or replace the damaged tissues. This study seeks to obtain data which will help to address research gaps and to stimuli the manufacturing process.

Description of the state of knowledge. We conduct the systematic literature review, based on the information found in PubMed, Research Gate and Google Scholar databases using the eligible parameters. Obtained data in form of descriptive information were analyzed.
Summary. This study has identified a wide area of cardiovascular biomaterials use in the modern clinical and scientific practice. The most obvious finding to emerge from this study is that decellularization of xenogenous heart valves is a crucial feature to obtain the optimal matrix for a tissue-engineered valve substitute. This information can be used to develop targeted interventions aimed at cardiac surgery.

Key words: cardiovascular disease; cardiovascular biomaterials; decellularization; xenogenous valves

Introduction

Bioengineering is an important component of the medical science, playing a key role in the scientific tremendous growth. In the new global health paradigm, cardiovascular diseases (CVD) have become the leading mortality cause, taking an estimated 17.9 million lives every year [1]. Kevin Mc Namara et al. highlight that combined ischemic heart disease and all forms of stroke were the attributed causes of death for an estimated 13 million people globally in 2015, a quarter of the global total (increased from just one in five deaths 20 years earlier) [2]. Patient’s management could be basically divided into two main approaches: conservative (pharmacological) and operative (surgical). More than 50% of patients with heart disease do not respond to current pharmacological therapies, requiring new solutions for their surgical treatment [3]. Despite existent demand for procedural improvement, several limitations associated with current treatment modalities contain a rapid development of the whole area.

Description of the state of knowledge

It is surprising, over 300,000 heart valve replacements and over 570,000 arterial bypasses are performed worldwide annually. Therefore, to cover the gap between facilities and patients in need of medical devices and procedures, numerous approaches in multiple branches of the biomedical sciences presented with a challenge to develop well-recognized material for cardiovascular repair [4]. Evidence suggests that cardiovascular biomaterials (CB) are among the most important categories to stimuli the investments in this field [5].

Saravana Kumar Jaganathan et al. draw our attention to the market analysis the CB to be predominant category of the biomaterials market in 2014, with a worth of about $20.7 billion [6].

Simultaneously, a considerable amount of literature has been published on CB defining and practical usage [2, 5, 7]. These studies propose several interpretations for
biomaterial, throughout this paper we will refer to the Biomaterials Consensus Committee meeting at the National Institutes of Health (NIH) definition “any substance (other than a drug) or combination of substances synthetic or natural in origin, which can be used for any period of time, as a whole or part of a system which treats, augments, or replaces tissue, organ, or function of the body” [7]. We need to admit, that engineered cardiac tissue constructs are potentially eligible to offer an alternative modality in the treatment process.

Studies over the past decades have provided important information on surgical tools to repair or replace the damaged tissues, for instance with bypass grafts, transplants etc. Nevertheless, sources for human donor tissues are extremely limited. Drawing upon strands of research into bioengineered materials, this study attempts to observe alternative tools for expanding patient care options. For today, blood compatibility is one of the major criteria which limit the use of biomaterials for cardiovascular application. In this review article we classify the CB into three major classes, namely, metals, polymers, and biological materials. The table below illustrates some of the main types of each class. On the other hand, described biomaterials fall into two big groups: synthetic (polymers and metals) and natural.

<table>
<thead>
<tr>
<th>Biological materials</th>
<th>Polymers</th>
<th>Metals and alloys</th>
</tr>
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<tbody>
<tr>
<td>Homografts</td>
<td>Polyamides</td>
<td>Stainless steel</td>
</tr>
<tr>
<td>Porcine materials</td>
<td>Polyolefin</td>
<td>Cobalt alloy</td>
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<tr>
<td>Bovine materials</td>
<td>Polyesters</td>
<td>Titanium alloy</td>
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<tr>
<td></td>
<td>Polymethylene</td>
<td>Chromium alloy</td>
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As Matthew W. Curtis points out, natural biomaterials are derived from native tissues from autogenic, allogenic or xenogeneic (animal: bovine or porcine) sources [8]. These materials are preferable due to the biocompatibility and biodegradation rates, minimizing the immune response to prevent biomaterial encapsulation.
Recent trends in bioengineering have led to a proliferation of studies that review key characteristics of biomaterial implants. This paper gives a brief overview of the recent development, taking into account safety, efficacy and effectiveness of multiple biomaterials, manufacturing approaches and features of use in cardiac surgery.

There are several possible indicators of materials, which should be covered before implementing in the clinical practice: (1) selection of the best-suited material for devices and application, (2) environmental impact, (3) bioavailability, (4) degradation etc. It is now well established from a variety of studies that several advantages and disadvantages, set out in Figure 1, could affect the benefit-risk ratio for each type of CB.

![Figure 1. Different types of biomaterial’s strong and weak sides](image)

Nonetheless, aforementioned materials are widely used in a huge area of cardiac devices manufacturing. As an example, metal alloys are preferably used for stents producing. The most desirable features of all stents which could be achieved by using metals are (1) absence of thrombogenesis for occlusion of the artery prevention; (2) resistancy to blood pressure changes; (3) flexibility and (4) ease of implantation [9]. Differently, in artificial heart valves (mechanical and biological constructions) all three types of biomaterials could be used depending on the goals and clinical endpoints.

Alas, cost-effectiveness, numerous uncomfortabilities related to the additional therapy and risk of reoperation after enforcement of existing heart valve prosthesis remains unsolved
and speculative. Antimineralization strategy is one of the most frequently stated problems in bioengineered materials for cardiac surgery manufacturing process.

**Xenografts in the cardiac surgery: past, present and future**

With the ongoing advances in cardiac xenotransplantats, an initial discussion regarding the potential clinical applications had begun several years ago. Hence, regenerative medicine promises immunologically compatible tissues produced from progenitor cells.

Going through the history, the first successful xenograft replacement of the aortic valve in a human was performed in September 1965 by Carpentier and his team in Paris [10]. After that, a new era of cardiac surgery was launched, despite achieved poor primary outcomes: only 60% of the valves were functioning well at 6 months and only 45% at 1 year. It took years to observe the possible pathogenic mechanisms and to invent feasible approaches for to reduce valves antigenicity as no ideal heart valve substitute combining optimal haemodynamics and lifelong durability without the need for anticoagulation therapy was available.

Finally, the valves were placed in a glutaraldehyde-buffered solution, through the antigenic components (especially the structural glycoproteins) could not be totally eliminated. Mario Lopez-Moya et al. mention that the main issue of this method is the lack of the bioactive properties of a heart valve and the appearance of a progressive process of calcification leading to structural valve deterioration and loss of function over time [11].

Currently, xenograft implantation is the standard therapy for heart valve replacement in the elderly, when valve repair does not offer superior long-term benefits or is technically simply not feasible.

However, the numerous approaches in multiple branches of the biomedical sciences presented with a challenge to develop well-recognized material for cardiovascular repair. This field is consequently becoming an important frontman for Translational Medicine. Decellularization of tissues (especially pericardium) has been proposed as a prospect method to diminish antigenicity, thus to enhance tissue compatibility, remodeling and long-term durability [12]. While a variety of definitions of the term decellularization of tissues and organs from human or animal donors have been suggested, this paper will use the definition first used by Estela de Oliveira Lima et al. (2019) who saw it as the process for ensuring immunologic safety and the preservation of basic structural and functional components of the extracellular matrix, such as proteins, collagen and glycosaminoglycans (GAGs). A proper complete decellularization with preservation of the tissue architecture is trying to be achieved by physical, chemical and enzymatic agents using [13].
Although, for successful xenogeny tissues decellularization covariates affect should be mentioned, including tissue cellularity (eg. liver vs cartilage), density (eg. heart valves vs adipose tissue), lipid content (eg. brain vs urinary bladder), and thickness (eg. dermis vs pericardium). Ideally, the decellularization should minimally affect both the extracellular matrix architecture and the mechanical properties of a tissue, which would be used as a graft.

Numerous procedures of decellularization has been described [12, 13] for being performed through chemical, physical, or combinative methods. The primary endpoint in these methods was cell removing assessment and mechanical properties. Table 2 summarizes the most common techniques used for pericardium decellularization.

The study presented by Wollmann et al. promotes the approach of human pericardium decellularization using a reduced quantity of detergent for application as a cardiovascular patch [14].

The use of decellularized tissues in cardiac surgery is already a well-established practice, however, the prospect of employing a decellularized pericardial patch, whose structural components are preserved and the antigenic molecules properly eliminated, is consequently of great interest for clinical application [15].

<table>
<thead>
<tr>
<th>Agents and techniques</th>
<th>Mechanism</th>
<th>Significant effects</th>
<th>Example of method</th>
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<tbody>
<tr>
<td>Sodium dodecyl sulfate (SDS)</td>
<td>Ionic</td>
<td>Cytotoxicity has been previously described Microstructure altering</td>
<td>10 mM Tris-HCl and protease inhibitors + 0.1% SDS + 50 U/mL DNase and 1 U/mL RNase Hypotonic/hypertonic solutions + 1% SDS</td>
</tr>
<tr>
<td>Triton X-100</td>
<td>Nonionic (Commonly used with ammonium Hydroxide)</td>
<td>Less damaging to structure of tissue than ionic surfactants</td>
<td>0.1% SDS + Triton X-100 + 0.1 mg/mL DNase</td>
</tr>
<tr>
<td>Ammonium Hydroxide</td>
<td>Breaks cell-matrix adhesions</td>
<td></td>
<td>Decellularization according to van Steenberghe et al., 2017 Acetone + Ethanol + 1 N NaOH + 7% NaCl + H2 O2</td>
</tr>
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These characteristics have the potential to enhance the signaling in the tissue for the recruitment and adhesion of cell apparatus and to maintain ideal mechanical characteristics, in addition to reducing the immunogenicity of the graft.

All this would increase the graft durability, support tissue regeneration leading to the quality of life of the patient improvement.

Interestingly, a numerous significant effect regarding safety and efficacy were achieved in in vivo experiments with subcutaneous implantation of decellularized pericardium into animal models. Lowering of immunogenicity, reducing of cytotoxicity and graft integration improvement were observed in comparison with the fresh/frozen or glutaraldehyde-fixed implanted tissue [16].

Differently, ex vivo analyses revealed low immunological response, enhanced angiogenesis, and cardiomyocyte differentiation [17].

Finally, using of decellularized pericardial patches, tested on animal models showed enhanced graft integration, low immunogenicity, and recellularization of scaffolds [18].

For today, the main issue is to achieve an effective cell removing, maintenance the extracellular matrix properties and mechanical integrity of decellularized bovine pericardium.

All the above-mentioned studies proved that biomaterials and protocols of their manufacturing are important, especially considering that cardiovascular disease is the driver of the main causes of death worldwide. Animal decellularized pericardial patches are widely used in adult and pediatric cardiac surgery and their adequate preparation could lead to biocompatibility and similarity to the natural tissues and as a consequence, new alternatives are emerging in the quest for an ideal cardiac biomaterial.

As a final comment we can say that the tissue decellularization protocols resulted in a complete cell removal, the preservation of the structure and rupture features (ultimate tensile properties) are coveted to be reached. Taking into account the broad spectrum of biological functions of micro and macroelements, we hypothesized that the alteration of the free glycosaminoglycans content in the pericardium-derived tissues is going to affect the bioactivity of the whole biomaterial. Thus, matrix degradation and replacement with de novo tissue could be potentially anticipated.

**Conclusions**

1. Cardiovascular biomaterials are among the most important categories to cover the gap between requirement and facilities in manufacturing for surgical procedures.
2. Decellularization method of xenogenous heart valves is a crucial feature to obtain the optimal matrix for a tissue-engineered valve substitute.

3. Further research is needed to establish the role of the novel xenografts in the cardiac surgery and to determine the optimal manufacturing protocols.

**Abbreviations**

- **CVD** – cardiovascular disease
- **CB** - cardiovascular biomaterials
- **NIH** - National Institutes of Health
- **GAG** - glycosaminoglycan

**References**


