Different type of matrix for cardiac implants: biomedical and bioengineering aspects

Shchotkina N.^{1,2,3}, Sokol A.¹, Dolinchuk L.², Skorohod I.³, Filipov R.², Shepeleva O.², Rudenko N.¹, Yemets I.¹

¹Ukrainian Children's Cardiac Center, Kyiv, Ukraine

²Igor Sikorsky Kyiv Polytechnic Institute, National Technical University of Ukraine, Kyiv, Ukraine

³Xpand LLC, Kyiv, Ukraine

Corresponding author's e-mail: cardiotissue@gmail.com

ABSTRACT

The rapid growth of cardiovascular morbidity and high mortality rates of patients with congenital heart disease requiring surgery have led to the search for new modern approaches to the treatment of these groups of patients. The main trends today include the use of cardiac implants of synthetic and biological origin. Of particular interest are scaffolds based on the decellularized extracellular matrix, which in its functional and structural characteristics is close to the native pericardium. In contrast to synthetic analogues, such grafts can fully replace tissue or organ defects, and then integrate and function properly.

This review presents the characteristics of different types of matrices used in cardiac surgery. The advantages and disadvantages of commercially available cardiac bioimplants currently used in the world are analyzed.

KEY WORDS: tissue engineering; cardiac bioimplant; extracellular matrix

Modern regenerative medicine successfully combines data from basic research and clinical practice, which provides great potential for therapeutic use. It is based on the restoration or replacement of tissues and organs that have a structural or functional deficiency, due to synthetic, biological and extracellular matrices [1]. Synthetic scaffolds provide the ability to modify and control the structural properties, but do not guarantee the same functionality as native tissue [2]. The advantage of using biomaterials in tissue engineering is due to their ability to be resorbed in the body with subsequent replacement by recipient's tissues. However, scaffolds based on natural extracellular matrix (ECM), reproducing the microarchitectonics of native tissue, are of increasing interest [3].

The **PURPOSE** of this review was to analyze modern approaches and trends in obtaining and application of different types of matrix scaffolds for cardiac implants, including biomedical and bioengineering aspects.

CLASSIFICATION AND CHARACTERISTIC OF DIFFERENT TYPES OF MATRIX SCAFFOLDS FOR CARDIAC IMPLANTS

One of the most difficult problems of modern tissue engineering is the choice of a scaffold for the engraftment of cells *in vitro* and *in vivo*, which is an important aspect in the implant transplantation into the human body. The main functions of the matrix are the providing of intercellular connections, control of tissue structure and regulation of cell phenotype [4]. Matrices made of biomaterials regulate cell density and production of

biologically active factors; determine three-dimensional structure of tissue and formation of new tissue [5, 6].

All the variety of matrices can be divided into three major groups:

1. Synthetic polymers.
2. Natural.
3. Extracellular matrix.

The main advantages of the first two groups are their natural origin and easier integration into the recipient's tissue. However, unlike synthetic polymers, it is almost impossible to control the microstructure of such substances. At the same time, natural biomaterials provide the same matrix architecture as the native tissue.

In cardiac surgery, synthetic polymers approved by the Food and Drug Administration (FDA) are used to create resorbable sutures [7]. Synthetic materials are mostly thermoplastic and can take any shape, which is important in the production of cell matrices with a certain pore diameter.

One of the known natural biomaterials for creating cellular scaffolds is collagen. The plasticity, low toxicity and antigenicity of the biomaterial and at the same time its high mechanical strength provide advantages for the widespread use of collagen in surgery [6].

Polysaccharide of plant origin, such as an extract from seaweed – alginate – is used to create jelly-like matrices with a high content of calcium ions [5, 8, 9]. Alginate has found application for the treatment of open wounds. However, the structural and functional properties of alginate are

limited by the length of the polysaccharide chains, which limits its widespread use [5].

Extracellular pericardial matrix is created by removing cells and their components from the native pericardial tissue using chemical, physical and biochemical methods [3, 10]. In terms of its biomechanical properties, the extracellular matrix differs little from the native pericardial tissue and is, therefore, suitable for the use in the replacement of heart valves and congenital heart defects [11, 12].

Most of the currently known bioimplants used in tissue engineering are resorbable and replaced by recipient's tissues. The material must meet the following requirements: the absence of toxic products, it should not change the pH of the tissue or inhibit the growth and differentiation of cells. Non-resorbable materials are practically not used today (except for bone prostheses, although the use of metal implants is being reduced due to their ability to corrode in aggressive tissue environments), as they limit regenerative potential and can cause excessive connective tissue growth, and sometimes provoke an immune response to foreign bodies [10-13].

From the perspective of biomechanics, the functional materials for implantation in the body should be similar to tissues, i.e. be characterized by elasticity and have a stress-strain curve close to tissues and specific loading-unloading hysteresis loop [11].

SYNTHETIC MATRICES

Synthetic polymers due to its properties (light, flexible, elastic, strong) are well suitable for the application in cardiac surgery. Today, polyethylene, polypropylene, silicone, polytetrafluoroethylene (Teflon®), polyethylene terephthalate (Dacron®), polymethyl methacrylate, polyurethane, some types of resins, etc. are used to create heart valves and blood vessels. However, in the long term after implantation there is a degradation of polymer compounds, which determines the main disadvantage of this group of substances. In an aggressive tissue environment, implants are attacked by the cells of the immune system that have a lot of oxidizing and hydrolyzing substances. Also, the presence of oxidizing free radicals, such as peroxides, lipids, lipoproteins, etc., adversely affects the structure of synthetic polymers, while reducing their strength. The degradation of the prosthesis is accompanied by monomers cleavage from the long chain. Theoretically, these monomers can enter blood, lymph and cause toxic effects, changes in tissue pH. Also, the lack of biocompatible and biological signals in these polymers is of serious concern [14]. Synthetic scaffolds lack the spatial organization that can be observed in natural extracellular matrices. However, their great advantage is that they can be easily modified, change a wide range of mechanical and chemical properties, including the degradation rate.

For the correction of some congenital heart defects in children and the replacement of the pulmonary valve, which is used for aortic valve prosthesis, prostheses made of porous polytetrafluoroethylene composite are widely used. They are biologically and chemically inert, resistant to aggressive body fluids and bacterial agents. It is important to note that polytetrafluoroethylene can be used to build arterial shunts in newborns with complex cyanotic heart disease, for the palliative reconstruction of the interrupted aortic arch, the construction of an extra-anatomic aortic bypass graft and total cavopulmonary connection. It is also suitable for the septal defects closure, the plastic reconstruction of the right and left ventricular outflow tracts, as well as the correction of aortic coarctation and the plastic repair of stenosis in the pulmonary artery and its branches. Polytetrafluoroethylene patches can be used for the plastic reconstruction of atrioventricular valves [15-18].

Porous polytetrafluoroethylene has been successfully tested for the manufacture of artificial prostheses for cardiac surgery in the clinical practice of the State "Scientific and Practical Medical Center for Pediatric Cardiology and Cardiac Surgery of the Ministry of Health of Ukraine". In comparison with prototypes, this synthetic polymer has the following advantages: the high level of biocompatibility; no cytotoxic effects; necessary biomechanical properties; low microbial adhesion; the low rate of postoperative complications.

The closest analogue of this polymer is polyethylene terephthalate (trade names Dacron®, Gore-Tex Surgical Membrane, Mylar). This is a thermoplastic used to create artificial prostheses with high mechanical performance. However, its use has a number of disadvantages, i.e. cytotoxicity. Also, compared to other synthetic substances, polyethylene terephthalate was associated with a higher risk of stroke, transient ischemic attack and carotid artery thrombosis in the postoperative period [19].

NATURAL MATRICES

Collagen. Type I collagen is most often used as a scaffold in tissue engineering, because it is the major protein of the extracellular matrix of many native tissues and provides most of the mechanical and tensile strength. In addition, collagen has low antigenicity, weak immunogenicity and is biodegradable [7]. The use of collagen of animal origin raises concerns about the possible transmission of infectious agents such as prions. An innovative promising alternative strategy is the synthesis of supramolecules based on peptides that imitate the structure and function of collagen [20].

In cardiac surgery, the lyophilized collagen delivery system of gentamicin Collatamp® G (EUSA Pharma, UK) is used in the prevention and treatment of postoperative complications [21]. The implant is based on bovine collagen, which is rapidly degradable and is an effective for local delivery of antibiotics. The advantage is that such implants are degraded by collagenases and do not require surgical removal. At the same time, they provide a high dose of antibiotic in the damaged area, thereby accelerating wound healing [21].

Fibrin. Fibrin gels have controlled characteristics of biodegradability and polymerization. An additional advantage is the fact that they are obtained from the patient's blood allowing to obtain an autologous matrix, which does not emit toxic products or cause inflammatory or immune reactions. In addition, fibrin interacts with tissue and may promote cell proliferation and migration [22]. Elastin-like recombinant fibrin hydrogels were synthesized for the manufacture of heart valves by a seamless method in a modular form with the required geometry of heart valves. This approach will also allow you to create multilayer structures [23, 24].

Hydrogels. Hydrogels are three-dimensional scaffolds made of highly hydrophilic polymers, which allows them to contain a certain amount of water. Depending on the topology, structure and chemical composition of polymer scaffolds, the mechanical properties of such hydrogels range from brittle with low fracture energy (10-100 J/m²) to extremely rigid with fracture energy (~100-10000 J/m²) [25].

Hydrogels based on hyaluronic acid are increasingly used to create tissue-engineered matrices of heart valves, because hyaluronic acid is a unique type of glycosaminoglycans that exists in free form without a covalently bound protein. Hyaluronic acid plays an important role in biological processes, such as the construction of tissue structures, cell migration and differentiation. Such hydrogels significantly increase the production of the extracellular matrix by the inner cells of the valve, and the products of degradation of the hydrogel increase the proliferation of the intercellular matrix of the valve [26]. Elastin synthesis is also induced when cells are seeded on such a hydrogel; as a result, elastin scaffold is similar to the matrix of a native aortic valve [27].

The components of the collagen-chondroitin sulfate hydrogel type I were also studied [28]. When seeded on chondroitin sulfate hydrogel, the porosity of the matrix increases, biological activity of cells and matrix remodeling improve. Increased gel engraftment by endothelial cells and increased extracellular matrix production, including fibronectin, laminin, collagen and elastin, have also been demonstrated. Thus, many hydrogel systems used in cardiovascular surgery act as biocompatible scaffolds to support cells [29, 30].

Silk fibroin. Scaffolds based on fibrillar protein fibroin derived from *Bombyx mori* are increasingly used for tissue engineering of vascular endothelium [31]. The material has unique biophysical and biochemical properties that determine its reliability, flexibility, biocompatibility, ability to biodegrade [32]. To create implants, the technique of electrospinning

PRODUCT NAME, MANUFACTURER/ DEVELOPER	TYPE OF XENOGENEIC TISSUE	PROCESSING METHOD	REFERENCE
Bovine Pericardium Patch (Braile Biomedica, São José do Rio Preto, Brazil)	Bovine pericardium	Glutaraldehyde	[43]
Edwards Bovine Pericardial (Edwards Lifesciences, Irvine, CA, USA)	Bovine pericardium	GA-cross-linking, patented anti-calcification treatment	[44]
PhotoFix (CryoLife, Kennesaw, GA, USA)	Bovine pericardium	Decellularization and photooxidation	[45]
SURGIFOC (FOC Medical, Buenos Aires, Argentina)	Pig pericardium / Bovine pericardium	GA-cross-linking	[46]
CardioCel (Admedus, Malaga, Western Australia)	Bovine pericardium	GA-cross-linking, decellularization and processing by a patented technique	[47]
Matrix Patch (Auto Tissue Berlin, Germany)	Horse pericardium	Decellularization	[29]
No-React (BioIntegral Surgical Mississauga, Ontario, Canada)	Pig pericardium	Heparin treatment	[48]
Peri-Guard (Baxter International Inc. Deerfield, Illinois, USA)	Bovine pericardium	GA-cross-linking	[49]
Tiflex (Xpand LLC, Ukraine)	Bovine pericardium	Decellularization with 0.1 % sodium dodecyl sulfate + cross-linking	[11]

Table 1. Commercially available acellular pericardial scaffolds from xenogeneic tissues.

is used, which allows the production of nano/microfibers of silk fibroin in large number with accurate imitation of the extracellular matrix of the required tissue [33, 34]. The advantages of the electrospinning technique are the creation of a porous surface that ensures the penetration of oxygen molecules, and the increase of cells adhesion to the implant by increasing the surface area of the matrix. Cells can easily adhere to such structures, multiply and form monolayers of cells with preserved phenotypic characteristics.

Thus, biological/natural matrices have advantages over synthetic scaffolds, because they are capable of intermolecular signaling, promote cell proliferation, differentiation and functioning. However, it is very difficult to control the mechanical properties and the rate of biodegradation of such implants. Natural materials can also provoke an undesirable immune response.

EXTRACELLULAR MATRIX

Biomaterials used in tissue engineering and regenerative medicine try to reproduce the multifactorial aspects of the extracellular matrix (ECM) function. However, synthetic materials and matrices formed from biological materials, such as collagen, fibrin or hyaluronic acid, cannot achieve molecular and spatial organization of native tissue. This promoted the use of natural ECM as a source of scaffold.

In order to obtain biomaterial that is structurally and functionally close to tissues or organs and at the same time is immunologically safe, a technology of decellularization of tissues and organs from humans and animals for clinical application of ECM has been proposed. This technology uses physical, chemical and/or biochemical methods to remove cellular antigens from native tissue or organ of xenogeneic or allogeneic origin. This process is aimed at ensuring immunological safety and preserving the architecture of the matrix, which includes protein, collagen and glycosamines. The final product is a three-dimensional ECM scaffold, which is similar to the native tissue [3]. To date, some organs and tissues have been successfully decellularized, including heart valves, myocardium, pericardium, blood vessels, lungs, pancreas, kidneys, liver, mammary gland, and nerves [10]. Decellularized xenogeneic scaffolds have been successfully used in the clinic for tissue engineering and regenerative medicine [35].

One of the most common materials for xenoplasty is the decellularized bovine pericardium, which is widely used in cardiac surgery to re-

place heart valves and treat congenital heart defects [11]. The structure of xenogeneic tissues is rich in elastic and collagen fibers, which gives the pericardium increased resistance to mechanical load. The formation of a straight suture line in cardiovascular surgery is also an important advantage of using a decellularized bovine pericardium [36, 37]. To reduce the immune response and graft rejection, the pericardium is fixed in glutaraldehyde. However, its incomplete removal can lead to cytotoxicity and late calcification of the implant *in vivo* [38]. That led to the search and development of new methods for the production of safe heart implants. One of the most common techniques is to treat the tissue with ionic detergents such as sodium dodecyl sulfate. However, its use in high concentrations can lead to structural disorders of ECM and have a cytotoxic effect on human cells [39]. At the same time, there are convincing data on the safety of sodium dodecyl sulfate in low concentrations (0.1 %).

Table 1 presents commercially available decellularized scaffolds for cardiac surgery, manufactured by various methods. Such type of product is mostly represented in Europe and America. Manufacturers prefer the use of xenogeneic tissues based on the pericardium of pigs, cattle and horses. A cardiac implant made from bovine pericardium has a number of technical advantages such as easy application, necessary biomechanical properties, biocompatibility, less bleeding from the sutures and the possibility of immediate arterial duplex ultrasound at the angioplasty site [40]. The extracellular matrix of the bovine pericardium is cell-free and contains pure collagen. Thus, it can provide natural transport of micro-nutrients and proliferation of recipient cells, accelerating endothelialization and tissue regeneration [41]. Comparison of bovine pericardium with other materials, such as polytetrafluoroethylene, to close ventricular septal defects, did not show significant differences in results [42]. However, surgeons prefer bovine pericardium because of its elasticity and lower risk of postoperative endocarditis. Some manufacturers claim that their implants have anti-calcification technology that can significantly reduce calcification and support endothelialization [44, 49].

The testing of a unique method of bovine pericardium decellularization was started in the State "Scientific and Practical Medical Center of Pediatric Cardiology and Cardiac Surgery" of the Ministry of Health of Ukraine. It has already successfully passed the stage of preclinical study, which in the long run allows the certification of domestically produced cardiac implants [50, 51].

CONCLUSION

According to the analytical review, it was determined that today a large number of biocompatible materials are used to create cardiac implants, but none of them is ideal. Therefore, the search for new materials for cardiovascular tissue plastics is relevant at the current stage of tissue engineering development. Three groups of matrices (synthetic, natural, extracellular matrix), which are currently used to create cardiac implants, have been identified. The main advantages of matrices of biological origin are the providing of molecular intercellular signaling, improved cell proliferation and differentiation in the post-transplant period, which promotes the biointegration of the implant. Synthetic matrices are at the same time standardized with certain mechanical properties and the rate of biodegradation, which contributes to the controlled management of postoperative treatment. An important disadvantage of natural implants is the possibility of developing an immune response to their components. An increasing preference is given to natural matrices, in particular extracellular matrix based on bovine pericardium, which has advantages over synthetic analogues. The ECM of xenogeneic tissues is the most promising in use for cardiac implants due to its high biocompatibility and integration into the recipient's body.

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Різні типи матриксів для кардіоімплантів: біомедичні та біоінженерні аспекти

Щоткіна Н. В.^{1,2,3}, Сокол А. А.¹, Долінчук Л. В.², Скороход І. М.³, Філіпов Р. Ю.²,
Шепелева О. В.², Руденко Н. М.¹, Ємець І. М.¹

¹Науково-практичний медичний центр дитячої кардіології та кардіохірургії МОЗ України, Київ, Україна

²Національний технічний університет України «Київський політехнічний інститут імені Ігоря Сікорського», Київ, Україна

³ТОВ «Ікспанд», Київ, Україна

РЕЗЮМЕ

Стрімкий ріст захворюваності серцево-судинної системи та високі показники смертності пацієнтів із вродженими вадами серця, що потребують хірургічного втручання, обумовили пошук нових сучасних підходів до лікування цих груп пацієнтів. До основних тенденцій сьогодення можна віднести застосування кардіоімплантів синтетичного та біологічного походження. Окремий інтерес викликають трансплантати виготовлені на основі очищеного від клітин та їх компонентів позаклітинного матриксу, що за своїми функціональними та структурними характеристиками близький до нативного перикарду. На противагу синтетичних аналогів, такі конструкції можуть повноцінно замінити дефектну частину тканини чи органу, після чого інтегруватися і повноцінно функціонувати.

В даному огляді представлено характеристики різних видів матриксів, що застосовуються в кардіотрансплантології. Проаналізовано переваги та недоліки комерційних біоімплантів, що на сьогодні використовуються в світі.

КЛЮЧОВІ СЛОВА: тканинна інженерія; серцевий біоімплант; екстрацелюлярний матрикс