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Tissue-engineered vascular grafts for congenital cardiac disease: Clinical experience and current status

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ABSTRACT

Congenital heart disease is a leading cause of death in the newborn period, and man-made grafts currently used for reconstruction are associated with multiple complications. Tissue engineering can provide an alternative source of vascular tissue in congenital cardiac surgery. Clinical trials have been successful overall, but the most frequent complication is graft stenosis. Recent studies in animal models have indicated the important role of the recipient's immune response in neotissue formation, and that modulating the immune response can reduce the incidence of stenosis.

Key words: Tissue engineering, Tissue-engineered vascular graft, Congenital cardiac disease, Surgery, Fontan, Bone marrow-derived mononuclear cells.

Introduction

Congenital cardiac anomalies are the most common birth defect, affecting nearly 1% of all live births [1]. Of these patients, one-quarter have severe disease and will ultimately require major reconstructive surgery during their lifetimes [2]. Although significant improvements have been made in the management of congenital heart defects in recent decades, they remain a leading cause of death in the newborn period [3]. A substantial portion of the morbidity and mortality of pediatric cardiac surgery arises from the synthetic conduits and patches frequently used to repair congenital defects. These man-made grafts, which are constructed of materials such as polytetrafluoroethylene (PTFE or Gore-Tex®), are susceptible to thromboembolism, stenosis, ectopic calcification, and infection [4,5]. They also lack growth potential, contributing to one of their greatest sources of morbidity in the pediatric population: somatic overgrowth, or the process by which patients outgrow their grafts. Allografts, xenografts, and autologous tissues such as pericardium and saphenous vein have been used as alternatives, but all are associated with similar complications to varying degrees, and none have growth potential. Graft failure rates have been reported to be 70–100% at 10 years [5,6]. Patients therefore require serial reoperations to replace their failed grafts, each of which is associated with its own morbidity and mortality.

Vascular tissue engineering provides a potential solution to this problem. Rather than using a synthetic material, a biodegradable scaffold is implanted and degrades over time, replaced with autologous vascular tissue that can repair,

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remodel, and even grow with the patient [7]. Because the neovessel is composed entirely of autologous tissue, it is theoretically not plagued by the complications associated with synthetic materials. Classically, cells from the recipient are seeded onto the graft prior to implantation. In addition to the scaffold itself, these seeded cells play a crucial role in the process of neotissue formation. In this review, we present the current status of tissue-engineered vascular grafts (TEVGs) for use in congenital cardiac surgery and our experience implanting TEVGs seeded with bone marrow-derived mononuclear cells.

Congenital heart disease and the demand for tissue

Approximately 25% of patients with congenital heart disease have critical defects, which are a subset that require surgical or transcatheter intervention before 1 year of age [2]. The traditional paradigm for these patients was early palliation followed by definitive correction later in life. With advancements in surgical technique and perioperative critical care, however, that strategy has shifted to one of early repair, even in small infants [8]. In several critical congenital heart defects, transcatheter interventions are an emerging option, providing an alternative to open surgery and its associated complications.

Critical congenital heart defects have traditionally been divided into cyanotic and noncyanotic lesions, but with the aforementioned advancements in surgical care, some have advocated for a classification into (1) defects which should be repaired, (2) those which must be palliated, and (3) a final group in which either option is acceptable [8]. A list of critical congenital heart defects, their pathophysiology, and surgical options is summarized in Table 1. The most common critical congenital heart defects are ventricular and atrial septal defects, which are two of a limited number of defects which may be monitored in certain patients [1]. Most other critical defects require repair or palliation irrespective of any other criteria [8].

As indicated in Table 1, critical congenital heart defects are characterized by an absence or malformation of normal cardiac tissue during development. Many surgical reconstructions therefore require a supplemental source of tissue. Ventricular septal defects and large atrial septal defects are closed with patches. Long aortic coarctations require patch aortoplasties or interposition grafts. Aortic stenosis can be managed by the Ross procedure, which uses the native pulmonary valve to replace the stenotic aortic valve, with the right ventricular outflow tract then reconstructed with a valved conduit [8]. In contrast to coronary artery bypass and arteriovenous grafts for dialysis access, which are common uses of tubular grafts in adult cardiovascular surgery, most grafts in congenital heart disease are implanted entirely or partially in the lower-pressure venous circulation. In addition, the target graft diameter is larger than in the comparatively narrow coronary circulation.

This contrast is apparent in the Fontan procedure, in which a 2-cm diameter graft is implanted in a low-pressure system to palliate single-ventricle anomalies. It routes vena caval blood directly to the pulmonary circulation, with the single functional ventricle then pumping oxygenated blood systemically [9]. In the original description by Fontan in 1971, the venous blood was directed to the pulmonary circulation via an anastomosis between the right atrium and the right pulmonary artery [9]. Over the following decades, the procedure was altered in several ways. In the modified Fontan procedure, an interatrial lateral tunnel directs the blood to the superior vena cava. The superior vena cava is ligated, with the superior end sutured to the upper right pulmonary artery and the inferior portion to the underside of the right pulmonary artery [8]. Venous blood then flows passively and laminarly to the pulmonary circulation.

A further modification is the extracardiac Fontan, in which a prosthetic graft is used to connect the inferior vena cava to the pulmonary artery (Fig. 1). By utilizing an extracardiac conduit, this procedure does not alter the native atrial geometry, and it maximizes laminar flow [8]. Compared to other variations of the Fontan, the extracardiac approach has a lower incidence of arrhythmias, cavopulmonary pathway obstructions, re-interventions, and late deaths [4]. However, the implantation of prosthetic grafts without growth potential means surgeons must wait for patients to grow to a size where graft implantation is possible, at which time they frequently implant oversized grafts to account for future additional patient growth.

Prosthetic grafts have thus been used in the Fontan procedure with acceptable outcomes, but there remains room for improvement. The grafts are implanted in a high-flow system, which theoretically reduces the risk of thrombosis, and are subjected to low pressures, which decrease the chance of aneurysmal dilation. For these reasons, the Fontan procedure represents an ideal starting point for the investigation of TEVGs. Nevertheless, single-ventricle anomalies are rare relative to other types of critical congenital heart defects [1]. In the long term, tissue engineering has the potential to be applied to all situations in which prosthetic grafts are used in congenital cardiac surgery, including synthetic patches and heart valves. However, patches are frequently exposed to high arterial pressures, and functional heart valve leaflets are more complex to create than tubular blood vessels. As a result, the TEVG field is closer to clinical application than tissue-engineered patches and valves. This review will therefore focus primarily on the use of TEVGs for critical congenital heart defects.

Tissue-engineered vascular graft scaffolds as structures for neotissue formation

Principles of vascular tissue engineering

Vascular tissue engineering is governed by the tissue engineering triad, which consists of three essential pillars: (1) the scaffold, which ultimately degrades and is replaced by extracellular matrix, (2) cells (either seeded *in vitro* or mobilized *in vivo*), and (3) signals (humoral and mechanical) [10]. The three factors are interdependent and are all required for the formation of organized vascular tissue. Various combinations of the components have been intermixed throughout