Cardiovascular Engineering and Technology, Vol. 10, No. 2, June 2019 *(© 2019)* pp. 205–215
https://doi.org/10.1007/s13239-019-00406-5

Current Challenges and Emergent Technologies for Manufacturing Artificial Right Ventricle to Pulmonary Artery (RV-PA) Cardiac Conduits

Iman Manavitehrani,[1,2] Pegah Ebrahimi,[3] Irene Yang,[4] Sean Daly,[3] Aaron Schindeler,[2,3,4] Akshat Saxena,[1,2] David G. Little,[2,4] David F. Fletcher,[3] Fariba Dehghani,[3] and David S. Winlaw[1,2]

[1]The Heart Centre for Children, The Children's Hospital at Westmead, Westmead, NSW 2145, Australia; [2]Sydney Medical School, The University of Sydney, Sydney, NSW 2006, Australia; [3]School of Chemical and Biomolecular Engineering, The University of Sydney, Sydney, NSW 2006, Australia; and [4]Orthopaedic Research & Biotechnology Unit, The Children's Hospital at Westmead, Westmead, NSW 2145, Australia

(Received 30 May 2018; accepted 5 February 2019; published online 14 February 2019)

Associate Editors Frank Gijsen and Ajit P. Yoganathan oversaw the review of this article.

Abstract—Despite advances in modern surgery, congenital heart disease remains a medical challenge and major cause of infant mortality. Valved conduits are routinely used to surgically correct blood flow in hearts with congenital malformations by connecting the right ventricle to the pulmonary artery (RV-PA). This review explores the current range of RV-PA conduits and describes their strengths and disadvantages. Homografts and xenografts are currently the primary treatment modalities, however both graft types have limited biocompatibility and durability, and present a disease transmission risk. Structural deterioration of a replaced valve can lead to pulmonary valve stenosis and/or regurgitation. Moreover, as current RV-PA conduits are of a fixed size, multiple subsequent operations are required to upsize a valved conduit over a patient's lifetime. We assess emerging biomaterials and tissue engineering techniques with a view to replicating the features of native tissues, including matching the durability and elasticity required for normal fluid flow dynamics. The benefits and limitations of incorporating cellular elements within the biomaterial are also discussed. Present review demonstrates that an alignment of medical and engineering disciplines will be ultimately required to produce a biocompatible and high-functioning artificial conduit.

Keywords—Congenital heart disease, Valvular implant, RV-PA conduit, Tissue engineering.

ABBREVIATIONS

BJV	Bovine jugular vein
CHD	Congenital heart disease
ECM	Extra cellular matrix
PCL	Poly(ε-caprolactone)
PHB	Poly(hydroxybutyrate) or poly(hydroxybutyric acid)
PHBV	Poly(3-hydroxybutyrate-co-3-hydroxyvalerate)
PLA	Poly(lactic acid)
PLGA	Poly(lactic-co-glycolic acid)
PPC	Poly(propylene carbonate)
PPF	Poly(propylene fumarate)
RV-PA	Right ventricle to pulmonary artery
TE	Tissue engineering

Address correspondence to Iman Manavitehrani, Sydney Medical School, The University of Sydney, Sydney, NSW 2006, Australia. Electronic mail: i.manavitehrani@sydney.edu.au

CHALLENGES IN THE MANAGEMENT OF STRUCTURAL CARDIAC DEFECTS

Congenital heart disease (CHD) remains an important health issue; even with treatment success in children these conditions can have lifelong impact. The incidence of CHD is estimated at 6–13 per 1000 live births, with 1.76 in 1000 requiring hospitalization.[2,36] CHD is associated with significant mortality and morbidity [84] and effective treatments remain an area of active study. Significant resources are invested in delivering timely care and improving patient outcomes. There are persistent long-term physical, economic, and psychological impacts on children and their families.[27]

At least a third of patients born with CHD will require a significant procedure to address their disease. For more severe malformations, several open-heart operations or percutaneous cardiac catheter-based

interventions can be required. A common and high impact procedure requires the introduction of a right ventricle to the pulmonary artery valved conduit (RV-PA), to substitute for a pathway that is either absent or of insufficient size. Cadaveric human tissue (human pulmonary valve allograft, also known as a 'homograft') has frequently been used, with the first homograft RV-PA conduit described in 1966.[59] Today, the most common indications for use of RV-PA conduits include truncus arteriosus, pulmonary atresia, some forms of transposition of the great arteries with a ventricular septal defect, and pulmonary stenosis (Fig. 1). An RV-PA conduit is also required for the Ross operation for aortic valve disease, where the native pulmonary valve is moved to the aortic position and a RV-PA conduit is used to replace the resulting deficit.

Homografts continue to be the mainstay of RV-PA connection, but their supply is limited, particularly in smaller sizes suitable for infant procedures. Xenografts (animal products usually from cows or pigs) and hybrid xeno-synthetic grafts are available as alternatives to homografts. All current RV-PA connections have shortcomings as a result of progressive structural valve deterioration, loss of effective valve function, narrowing of the tube over time, and lack of capacity for growth.[17] These problems require replacement of the valved conduit—with most types lasting only 5–15 years depending on the age of insertion [41] and host response to the foreign material. Such interventions require repeat open heart surgery and percutaneous placement of xenograft valves *via* the femoral vein are available for larger children and adults (> 35 kg).[43]

With the inherent limitations of current implants, substantive effort is being dedicated to producing improved valved conduits. Ideally, such a conduit could be made from biomaterials with superior biomechanical and biocompatible properties, and may also be bioengineered with a capacity for post-implantation tissue integration and growth.[2] In this review, we discuss current and future perspectives on RV-PA conduits as applied to infants and children and highlighting the emergent role of tissue engineering.

CURRENT APPROACHES FOR RV TO PA CONDUIT CONSTRUCTION

RV-PA conduits have been widely used to surgically palliate children suffering from various forms of CHDs. The conduit selection between the available options, such as bovine jugular vein (BJV) graft, homograft or synthetic implants, presents a major challenge in the treatment of the patients. In addition, the material and mechanical properties of the native PA can guide us to understand implant failure and to design a durable alternative.

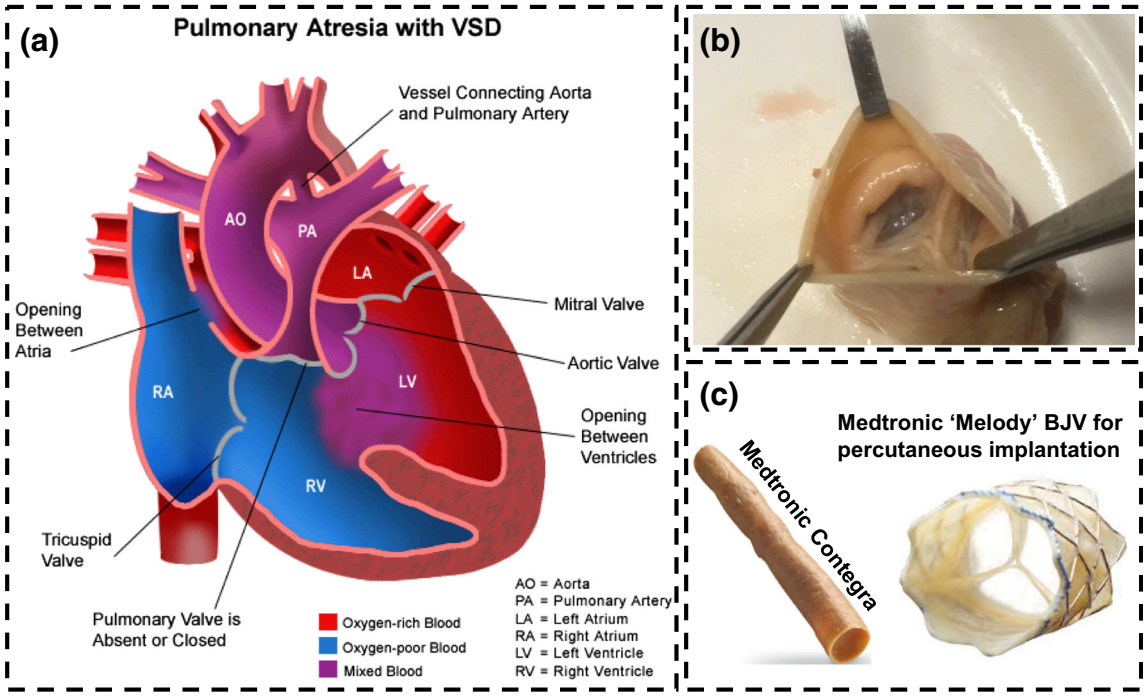

FIGURE 1. (a) Schematic of pulmonary atresia with ventricular septal defect. Reused from Lucile Salter Packard Children's Hospital Web Site, Stanford Children's health for nonprofit research purposes only.[23] RV-PA conduit options (b) homograft and (c) xenograft.

Material Properties of the Native Pulmonary Artery

The pulmonary artery (PA) is reinforced by cytoskeletal proteins, such as collagen and elastin, that are laid down in a directional manner. This ensures that the native PA exhibits complex anisotropic mechanical behavior.[18] For example, artery walls show nonlinear elastic properties under stress and hysteretic behaviors under cyclic loading and unloading.[52] Critically, none of the currently available RV-PA conduits possess material characteristics identical to those of native tissue, particularly anisotropic behavior.

The material properties of the pulmonary artery distal to a RV-PA homograft in a patient who had developed severe regurgitation were compared with those of a healthy individual.[3] The *in vivo* pressure-diameter data was fitted to a nonlinear material model to study stress, strain, and compliance, indicated by the slope of the pressure-diameter curve of the PA wall. For patients receiving RV-PA homograft, the distal left pulmonary artery diameter was increased due to higher pressure and there was a decrease in mechanical compliance. There was also a significant increase in strain (elongation) values at constant force. These biomechanical differences may arise due to the shift in material properties between the PA walls and the homograft conduit; this variation may cause reactive changes at the interface between the two surfaces which is evident in histology, and can be attributed to differences in collagen deposition and elastin fragmentation.[85] Such changes in cytoskeletal protein levels can enhance stiffness, lead to changes in the PA, and eventually result in implant failure. Therefore, understanding the material properties of the native PA provides critical cues to design an ideal implant and prevent the conduit failure.

Strength and Weaknesses of Homograft and Xenograft RV-PA Conduits

While homograft conduits were introduced in the 1960s, widespread adoption was limited by a lack of effective methods for sterilization and preservation.[59] The early methods for processing homograft led to premature calcification and progressive stenosis. The contemporary approach to storage, cryopreservation, delays the onset of these problems, however they still occur in the medium to long term.[50] Cryopreservation comparatively improves the durability of the homograft and allows for long term storage. Structural changes in the graft can be compounded by 'thaw' injury,[45] however warm ischemic conditions prior to procurement of the donor valve can ameliorate this problem.[12]

The bovine jugular vein (BJV) graft was introduced as an alternative option in 1999 and contained a trileaflet venous valve.[24] The flexibility of the leaflets could be preserved using glutaraldehyde solution under vacuum.[29] Off-the-shelf availability in a range of sizes has made these conduits popular with some surgeons. The BJV maintains good valve competence. It is likely related to the more extended area of leaflet apposition and reduced susceptibility to deformation by surrounding structures, including the right ventricle, aorta, and chest wall. The BJV has been associated with distal anastomotic stenosis and a higher rate of endocarditis when compared with homografts.[7,10,11,41,57,63] Porcine stented valves with Dacron tube, so called Hancock conduits, may also be utilized.[4] The same practice is used in adult cardiac surgery. However, in the pediatric setting, pseudointima formation and calcification, as well as inferior tissue handling properties at surgery make the Hancock conduit a less common choice in RV-PA construction.

Current homograft and xenograft conduits lack any capacity for additional growth. As a child grows, the fixed size of the conduit means there is a progressive size mismatch between the patient and the conduit that necessitates future replacement surgery. Typically, conduit replacement is required around 4–5 years after initial placement in an infant or young child.[41] Critically, studies reporting time to replacement often combine patient groups that have starkly different anatomical characteristics, confounding the analysis. For example, RV-PA conduit placement in pulmonary atresia involves a non-orthotopic and convoluted pathway for blood flow—out of the anterior right ventricle, over the surface of the heart, and then posteriorly to the pulmonary arteries. Conversely, RV-PA conduit placement for the Ross pulmonary autograft procedure involves essentially orthotopic placement of the implant. This could be expected to have less turbulence and energy loss than the pulmonary atresia patient and such factors are likely to influence conduit durability.

Multiple medical issues can contribute to conduit failure in addition to somatic outgrowth. These include stenosis of the distal anastomosis, compression by the sternum, aneurysm formation at the site of proximal anastomosis augmentation, and valvular stenosis.[86] Some of these factors reflect the surgical work required to customize the donor valve to the host as well as donor specific and non-specific immune responses. In one study, cases of both homograft and xenograft were shown to trigger the recipient's immune response resulting in calcification with thick intima or pannus

formation and/or stenosis with deterioration of valve function.[64]

CONDUIT TISSUE ENGINEERING

Evolving improvements to tissue engineering (TE) technology will be critical for the next generation of synthetic RV-PA conduits and their capacity to surpass currently used homografts and xenografts. Clinically applicable technologies need to provide a long-term functional replacement and, in the case of the heart, need to be operative immediately from the time of implantation. While other tissues can be allowed time post-TE to gradually regain function, heart function can only be disrupted for short durations. Moreover, TE implants need to be biocompatible while also minimizing the formation of thrombus, stenosis, calcification, and aneurysm, and preventing problems with patency or rupture of vascular pathways.

Traditional Scaffold-Based Implants

The first category of tissue engineering construct consists of a 3D porous biodegradable scaffold that can be seeded with cells prior to implantation into the patient.[13] Traditionally such scaffolds can be made bioactive using growth factors, peptides, or proteins prior to any cell seeding.[22] One notable limitation to come out of clinical studies is that such implants often lack a capacity to control the differentiation and function of seeded cells to recreate features of the native tissue adequately.[51]

The selection of an artificial conduit biomaterial also needs to consider the mechanical properties of the native pulmonary artery and its hemodynamics. The tensile strength of human pulmonary artery demonstrated values of 0.95 ± 0.37 MPa.[21] The elongation at break, which defines as strain at maximal load, is reported at 1.61 ± 0.52 mm/mm, and the Young's modulus is 1.69 ± 0.87 MPa.[21] Any proposed biomaterial to be used as a RV-PA conduit would ideally mimic these biomechanical behaviors to avoid any clinical complications.

Natural Versus Synthetic Biomaterials

Biodegradable polyesters such as poly(lactic acid) (PLA) were first used as potential candidates for cardiac TE in early preclinical studies. However, the stiffness and rigidity of these polymers were non-ideal for mimicking the properties of PA.[77] Significant post-implantation issues ranging from increased scar tissue formation to non-ideal bioabsorption rates decreased the interest on biodegradable polyesters.

Natural polymers are inherently degradable by enzymes and are thus well suited to biological applications,[48,82] but have not found utility in cardiac TE. Natural polymers such as collagen, silk protein, and gelatin have high biocompatibility and cell affinity.[42] These polymers have been used as the basis for skin TE applications and include a range of commercial collagen-based scaffolds. However, they have been eschewed for conduit design due to risk of a substantial immunogenic response, disease transmission, and deterioration of biomechanical properties over time.[48,82]

In contrast, synthetic biomaterials have tailorable property profiles. They are frequently bio-inert and structurally simpler than natural polymers. Consequently, the performance of these synthetic materials are easier to predict and optimize for the replacement of pulmonary artery.[48] Despite these benefits, synthetic materials often are poorly biocompatible, can produce non biocompatible degradation products, and lose their mechanical properties during degradation.[28] These complications need to be addressed before clinical studies of TE-based scaffold for RV-PA conduit replacement can take place.

To overcome the drawbacks of both synthetic and natural polymers, composite materials have been developed to use in TE. For example, Pok *et al.* developed a chitosan, gelatin hydrogel and poly(ε-caprolactone) (PCL) multi-layered scaffold for use as a biodegradable patch for use in surgical reconstruction of congenital heart defects.[55] While promising, this approach has not been translated for clinical use. This method showed some insufficiency in mechanical stiffness and cell invasion when the patch applied in a full thickness right ventricle defect. The same research group presented a multilayered engineered patch that shows higher right ventricular ejection fractions compared to commercially available fixed bovine pericardium at 8 weeks post-surgery.[56] In efforts to enhance synthetic scaffolds, cell affinity and biocompatibility, scaffolds of biodegradable polyesters such as PCL were modified by the naturally-occurring polymer, chitosan. This led to an enhancement in scaffold biocompatibility and *in vitro* cell proliferation.[40]

Recent Efforts to Develop Biomaterials for Cardiac TE

The search for an ideal scaffold and manufacturing method for conduit TE remains an area of continued effort and innovation.[88] Advancements in electrospinning, 3D printing, and bioprinting have led to the creation of more complicated designs able to mimic the anisotropy of the cardiovascular tissues.

Electrospinning has captured significant attention as a potential manufacturing modality. One of the most

promising recent composite scaffolds to date is an electrospun PGA mesh reinforced with poly(lactate-co-caprolactone) (P(LA-CL). This has been successfully employed in preclinical and clinical trials.[9,19,38,39,49,58,65–69,78] In the human trials, patients survived with no catastrophic failures or complications related to the bioresorbable implant. There were some instances where stenosis developed, which could be related to acidic degradation byproducts (lactic acid) leading to localized cell necrosis and immune cell invasion.[33–35] To overcome the problems of lactic acid byproducts, numerous alternative polymers have been employed. Bockeria *et al*. utilized electrospun chain-extended polycaprolactone with 2-ureido-4[1H]-pyrimidinone,[6] as this material degrades to products with less acidity than PLA/PGA. A supramolecular elastomer based on bis-urea-modified polycarbonate with non-acidic byproducts has also been proposed for *in situ* heart valve TE.[31]

Alternative electrospun nanofibrous grafts have been made from composite materials such as polyethylene glycol dimethacrylate, PLA, PCL, and polyvinyl alcohol have been developed to replicate the structure and mechanical properties of native valve leaflets.[20,61] These implants were reported to mimic the stiffness and anisotropy of native cardiac tissue were resistant to thrombus formation, elastic, and aided neovascularization. Despite the continued efforts in electrospun scaffolds, electrospinning is time consuming and inefficient for the production of the large constructs. Furthermore, this method remains limited in its capacity to efficiently produce implants with complex 3D geometries based on a patient's anatomy.

The Xeltis implant is the most developed electropsun pulmonary valved conduit made from arrays of synthetic polymers.[5] The polymeric blocks are based on 2-ureido-4[1H]-pyrimidinone with tunable mechanical properties and biodegradation. The tube wall is based on polycaprolactone while the leaflets are fabricated from polycarbonates. This technology found success in preclinical studies where the Xeltis valved conduit showed favorable and durable hemodynamic performance (up to two years after implantation), without conduit narrowing/obstruction or severe regurgitation.[74]

Stereolithographic 3D printing and extrusion-based 3D printing both have been used to fabricate scaffolds on the scale of heart valves. Biomaterials such as silicone aortic valve and PGA valve scaffold have been tested for heart valve tissue engineering.[62,72] To mimic the mechanical and biological properties of the valve leaflets, 3D printing of hydrogels such as photocrosslinkable hyaluronan, and gelatin have been employed.[71,90] However, 3D printing geometrically complex constructs with the similar biological behavior to the native tissue remains a considerable challenge with many materials.

Bioprinting is a final method being actively developed for TE applications. Trileaflet valve conduits based on methacrylated hyaluronic acid and methacrylated gelatin have been successfully implanted in mouse models and shown high cell viability and remodeling potential.[15,16,87] Their mechanical properties were comparable to the internal wall of the pulmonary artery.

Incorporating Cells Within an Artificial Scaffold

In the cardiac tissue engineering, the availability of functional cells and careful selection of the cell type for either *in vitro* or *in vivo* repair of the native tissue is essential. Cells can recover the normal vessel wall and valve tissue functions such as resistance to thrombus formation, inhibition of neo-intimal proliferation and transduction of physiological growth signals by creation of extracellular matrix and endothelial lining.[25] In this context, cardiomyocytes are responsible for electrical conduction and generation of contractile force; however, fibroblasts, stromal cells, and endothelial cells all play important roles in matrix deposition, vascularization, and paracrine signaling.[53] For instance, fibroblasts engage ECM proteins and promotes cardiomyocyte maturation while the endothelial cells encourage the survival and *in vivo* integration of those cells.[26,76] The majority of current cell seeding approaches focus on a single cell type.

The behavior of cells in an implant also depend on cell-scaffold interactions. Cell migration into the scaffold as well as subsequent cell proliferation and differentiation influenced by both scaffold macroarchitecture (porosity) and microarchitecture (pore size and interconnectivity).[47,32] For example, in a scaffold manufactured from polyethylene terephthalate fibers, it was reported that enhanced cell proliferation rate was achieved in higher porosity structure, while microarchitecture affected cell attachment and morphology.[79]

Despite the substantive efforts spend on developing cell-seeded grafts, the relative importance of incorporating cells inside a TE structure has yet to be resolved.[53] This is made more complex by the variety of cell types and pre-culture treatments that can be applied prior to implantation. An alternative approach for the next generation of TE solutions is to eliminate the use of scaffolds and focus on scaffold-free cell

delivery. This has the potential to ablate undesirable interactions between cells and biomaterials.

Scaffold-Free Constructs for Conduit Tissue Engineering

In this emergent approach, materials known as bioinks are used to mimic the natural ECM environment and support the adhesion, proliferation, and differentiation of living cells.[80] These implants feature a range of advantages including biomimicry, autonomous self-assembly, and construct miniaturization.[46] Cells play an essential role to remodel the tissue function by producing tissue-specific ECM proteins. The ECM-rich cell monolayer can then be extracted and assembled to form the shape of the desired tissue.[46]

3D printing was introduced into the tissue engineering field through the use of biodegradable polymers for building complex composite scaffolds. Due to the inherently complex nature of biological constructs, there is a need to engineer tissue constructs that match the corresponding structural, mechanical and biological complexities. 3D bioprinting is a technique that enables the deposition of various bioinks through different printing mechanisms in predefined patterns, while preserving cell viability and functionality.[15] The technology facilitates personalized patient-specific treatments *via* a capacity to fabricate 3D structures using patients' medical images, such as CT-scans and MRI.[15]

Bioinks can be defined as a 3D printable, pre-gel or liquid solutions that contain cells.[75] They are chosen to mimic an extracellular matrix environment to support cell adhesion, proliferation, and differentiation. Mostly, bioinks are derived from natural polymers such as gelatins, collagen, fibrin, alginates, chitosan, agarose and hyaluronic acids, as their processability under mild conditions is required to maintain and preserve living cells.[95] Synthetic polymers, such as Pluronic and PEG have demonstrated suitability as bioinks with an ability to maintain and promote cell viability.[95] Gelatin, pluronic, and PEG polymers are typically utilized as bioinks either alone or in combination with other hydrogels as of their shear-thinning properties.[95] Through extrusion, the advantageous shear-thinning properties allow polymers to behave like a liquid under the high shear stress imposed by the extruder, and quickly recover back to their gel state once printed.

3D printing provides a promising platform for the development of cardiovascular tissue engineering. Biomaterials are required to withstand the high shear stresses displayed by the continuous contraction and relaxation of the heart.[30] Accordingly, the biomaterials need to demonstrate consistent mechanical properties which is not affected by the blood flow during the development of the tissue engineered construct.[30]

THE ROLE OF COMPUTATIONAL MODELLING IN IMPLANT DESIGN AND ASSESSMENT

Computational Fluid Dynamics (CFD) can be utilized to optimize the geometrical design as well as the tissue engineered material of RV-PA conduit. CFD can be used to calculate the fluid flow forces affecting an implant, the response of different materials to those forces, and predict risks of implant failure. CFD can be used in combination with increasingly sensitive and accessible medical imaging techniques, to create a toolbox for evaluating hemodynamic parameters in a personalized manner.[14] Features such as wall shear stress (WSS), flow distribution, and pressure gradients can be described by CFD.

CFD is a method of simulating fluid passing through or around an object by replacing the partial differential equations with algebraic equations that can be solved numerically using digital computers. There are several open-source and commercially-available CFD software packages that facilitate the completion of these calculations, with easy to use interfaces that are compatible with various types of medical imaging data.[54,83,94] Users can generate their desired hemodynamic data resulting from the governing mathematical equations. The created models can be used to analyze a patient-specific geometry when it is desirable to focus on a clinical question for a specific patient, or for a group of patients with similar pathology.[60]

Other mathematical methods such as the finite volume method has been used more often than CFD to predict the flow dynamics in RV-PA conduits used for different patient morphologies and separate clinical contexts. Results of such simulations have shown a good agreement with the observed clinical data, supporting the practicality of these methods in surgical planning.[8]

Although the number of studies that have used CFD to investigate RVOT flow dynamics are limited, many lessons can be learned from studies that have employed CFD to evaluate and optimize the geometrical design of systemic-to-pulmonary shunts, TCPC, and Fontan geometries. This is due to the fact that the performance metrics, such as energy efficiency and stress distribution, and the mechanisms that affect the durability of the implant, such as platelet activation and thrombosis, are similar in all these cases. The schematic in Fig. 2 illustrates RV-PA and extracardiac Fontan conduits in their sites of clinical application.

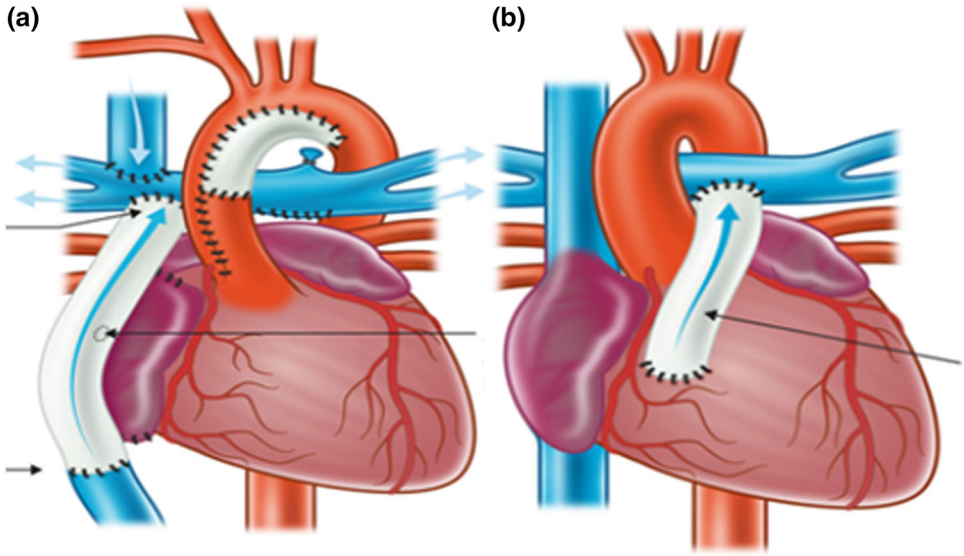

FIGURE 2. Schematic of extracardiac Fontan (a) and RV-PA repair (b). Reused from The Royal Children's Hospital Melbourne website.

The use of abovementioned tools has proliferated in cardiovascular medicine over the last decade. CFD can provide a means for evaluating and optimizing a grafts' geometrical design. Soerensen *et al.* introduced a hemodynamically-optimized total cavopulmonary connection with bifurcated caval veins using equal-sized connections to both PAs (Y-shaped graft).[73] It was shown using CFD with simplified geometric models that the new design with curved junctions leads to more streamlined flow paths and lower fluid mechanical power losses compared with 1D idealized model.[93] However, the clinical implications, feasibility of procedure in a young child, risk of thrombosis and growth were not investigated.

Another study[37] proposed a Y-graft with more clinical considerations allowing it to be used in procedure without cavopulmonary bypass, be custom manufactured, and be modified patient-specifically. The study adopts a patient-specific model and improves the accuracy of hemodynamic evaluation of the graft by incorporating greater level of pulmonary branching, and the effects of respiration and cardiac contraction, as well as including resistance, impedance and lumped model boundary conditions. The study took advantage of the computational tools to compare pressures, energy efficiencies, flow distributions and wall shear stress (WSS) of the Y-graft, T-junction, and offset model. It demonstrated lower Fontan pressures, increased efficiency, and improved inferior vena cava (IVC) flow distribution in the proposed Y-graft design. The use of a rigid wall in the simulations and lack of patient-specific data for validation are some limitations of this study.

Despite the many studies focusing on an energy loss in Fontan hemodynamics, Yang *et al.* focused on hepatic flow distribution (HFD) in shape optimization of the Y-grafts.[91] The impact of the pulmonary flow split, IVC/SVC (superior vena cava) flow ratio, and SVC flaring were examined for multiple designs. A flared SVC design was preferred over unequal-sized branches due to energy loss in the latter case. The optimized designs improved HFD by 79% and 94% in two patient-specific models studied. However, prediction of thrombotic risks demand incorporation of a fluid structure interaction to account for wall deformations and to evaluate the WSS more accurately. In a later study,[92] they validated the abovementioned predictions by comparing simulation-derived HFD with *in vivo* lung perfusion data of the patients undergoing the procedure. The authors attributed the occurrence of thrombosis in one patient to low WSS and flow stasis and highlighted the effects of patient-specific factors on the performance of Y-grafts. However, thrombosis is a multifactorial problem. Also, effects of a deformable wall and suture lines involved in the grafting process were not investigated in the WSS calculations.[81]

In a recent study, a new approach was developed that integrated image data acquisition, simulation-based design, and validation of simulation results through *in vitro* testing. This was used to optimize patient-specific graft designs before manufacturing based on a balanced HFD and minimal energy loss.[70] Utilization of electro-spun tissue-engineered vascular grafts in this study increased the degrees of freedom for graft design. The WSS profile and its effect on thrombosis, along with long-term durability of the

TABLE 1. Employment of CFD in geometrical design optimization of the grafts.

System modelled by CFD	Medical imaging	Patient-specific model	Validation	Optimization goals	References
Total cavopulmonary connection	✗	✗	✗	Less energy loss Less helical PA flow	73
Y-shaped Fontan graft	✔	✔	✗	lower Fontan pressures More efficiency Better flow distribution	37
Y-graft	✔	✔	✔ (In a later study)	HFD Lower energy loss	91
Fontan graft	✔	✔	✔	HFD Lower energy loss	70

graft are yet to be investigated. A comparison of these studies is shown in Table 1.

Many studies on prosthetic heart valves have employed CFD to evaluate and optimize their design, yielding the optimal hemodynamic and lowest achievable risk of design-related thrombosis.[44] The "Device Thrombogenicity Emulator (DTE)" has been proposed as a method that integrates numerical and experimental approaches to evaluate the design of prosthetic valves to achieve a better thrombo-resistance performance.[89] In the experimental phase, platelets are exposed to rapidly changing dynamic shear stress loading waveforms extracted from detailed numerical simulations. The extreme flow conditions are imposed and the resultant platelet activity, which is indicative of blood clotting and thrombosis, is then measured. Similar approaches can be adopted to achieve lower risks of thrombosis in conduit geometries.

From another perspective, simulation can be employed to achieve TE design optimization by predicting the structural mechanics and fluid flow associated with *in vitro* perfusion systems.[1] In preparing pre-vascularized three-dimensional cardiac bio-substitutes, CFD analysis of a modular chamber bioreactor with a porous scaffold was used to evaluate the perfusion and oxygenation of a millimeter-sized scaffold.[54] Variation of scaffold oxygenation as a function of bioreactor flow rate was confirmed. Another study underlined the importance of control of mechanical conditioning, especially WSS, in the development of functional Small-Caliber Tissue-Engineered blood vessels.[83] They utilized a fluid–structure interaction (FSI) approach to develop a scaffold-specific model for viscoelastic tubular scaffolds to evaluate *a priori* WSS and deformations to guarantee the desired stress distribution. The resulting mechanical conditioning was satisfactory, and the method was less time consuming and costly compared with the trial-and-error process used in vascular tissue engineering to control mechanical stresses on scaffold/vessel wall in perfusion bioreactors. Another study on perfusion bioreactors used micro–computed tomography images of complex 3D scaffolds and fluid dynamics to evaluate the velocity field and the WSS distribution through the scaffold.[94] The knowledge of WSS distribution guides the design and optimization of the scaffold geometry.

In summary, CFD is a practical tool for predicting the hemodynamics of graft substitute designs, and subsequent optimization steps. It also provides a tool for optimizing the process for synthesizing tissue engineered material of RV-PA conduit by predicting the required mechanical properties for the implant. The integration of computational modelling with medical imaging equipment has the potential to facilitate patient-specific implant designs. Nevertheless, for CFD results to be reliable, it is necessary to utilize realistic boundary conditions and to validate the findings using concrete models. Although the majority of these studies have focused on creation of venous pathways for Fontan completion, the approaches are highly relevant to creation of an ideal RV-PA pathway.

CONCLUSION

Homografts and xenografts as well as the currently available biomaterials for construction of artificial RV-PA conduits have significant limitations. These include a lack of durability, poor biocompatibility, risk of disease transmission (homograft/xenograft), and perhaps most importantly a lack of growth capability. TE is an emerging technology with the potential to create high-functioning implants able to provide structural and mechanical support. Ideally, implants will be generated possessing a capability for growth proportional to host somatic growth, obviating the need for the further operations. Significant research challenges remain in terms of designing and manufacturing durable conduits incorporating tubes and valves, all while considering the specialized and highly variable cardiac anatomy of individuals with CHD. We note that computational modelling of flow and structures will

continue to have an important role in optimizing the design and generation of patient-specific ducts.

CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

REFERENCES

[1]Akintewe, O. O., *et al*. Design approaches to myocardial and vascular tissue engineering. *Annu. Rev. Biomed. Eng*. 19(1):389–414, 2017.

[2]Avolio, E., M. Caputo, and P. Madeddu. Stem cell therapy and tissue engineering for correction of congenital heart disease. *Front. Cell Dev. Biol*. 3:39, 2015.

[3]Banerjee, R., *et al*. Comparison of pulmonary arterial wall properties between a congenital heart disease patient and a normal subject using in vivo pressure–diameter measurements: A feasibility study. *Prog. Pediatr. Cardiol*. 41:97–102, 2016.

[4]Belli, E., *et al*. The performance of Hancock porcine-valved Dacron conduit for right ventricular outflow tract reconstruction. *Ann. Thorac. Surg*. 89(1):152–158, 2010.

[5]Bennink, G., *et al*. A novel restorative pulmonary valved conduit in a chronic sheep model: mid-term hemodynamic function and histologic assessment. *J. Thorac. Cardiovasc. Surg*. 155(6):2591–2601, 2018.

[6]Bockeria, L. A., *et al*. Total cavopulmonary connection with a new bioabsorbable vascular graft: First clinical experience. *J. Thorac. Cardiovasc. Surg*. 153(6):1542–1550, 2017.

[7]Boethig, D., *et al*. Mid term course after pediatric right ventricular outflow tract reconstruction: a comparison of homografts, porcine xenografts and Contegras. *Eur. J. Cardiothorac. Surg*. 27(1):58–66, 2005.

[8]Bove, E. L., *et al*. Use of mathematic modeling to compare and predict hemodynamic effects of the modified Blalock–Taussig and right ventricle–pulmonary artery shunts for hypoplastic left heart syndrome. *J. Thorac. Cardiovasc. Surg*. 136(2):312–320.e2, 2008.

[9]Brennan, M. P., *et al*. Tissue engineered vascular grafts demonstrate evidence of growth and development when implanted in a juvenile animal model. *Ann. Surg*. 248(3):370–377, 2008.

[10]Brown, J. W., *et al*. Valved bovine jugular vein conduits for right ventricular outflow tract reconstruction in children: an attractive alternative to pulmonary homograft. *Ann. Thorac. Surg*. 82(3):909–916, 2006.

[11]Christenson, J. T., *et al*. Homografts and xenografts for right ventricular outflow tract reconstruction: long-term results. *Ann. Thorac. Surg*. 90(4):1287–1293, 2010.

[12]Crescenzo, D. G., *et al*. Human cryopreserved homografts: electron microscopic analysis of cellular injury. *Ann. Thorac. Surg*. 55(1):25–31, 1993.

[13]Dhandayuthapani, B., *et al*. Polymeric scaffolds in tissue engineering application: a review. *International Journal of Polymer Science*, 2011.

[14]Doost, S. N., *et al*. Heart blood flow simulation: a perspective review. *BioMed. Eng. OnLine* 15(1):101, 2016.

[15]Duan, B. State-of-the-art review of 3D bioprinting for cardiovascular tissue engineering. *Ann. Biomed. Eng*. 45(1):195–209, 2016.

[16]Duan, B., *et al*. Three-dimensional printed trileaflet valve conduits using biological hydrogels and human valve interstitial cells. *Acta Biomater*. 10(5):1836–1846, 2014.

[17]Dunne, B., *et al*. The freestyle valve as a right ventricle to pulmonary artery conduit. A systematic review and meta-analysis. *Heart Lung Vessels* 7(4):304–310, 2015.

[18]Fung, Y., K. Fronek, and P. Patitucci. Pseudoelasticity of arteries and the choice of its mathematical expression. *Am. J. Physiol. Heart Circ. Physiol*. 237(5):H620–H631, 1979.

[19]Hibino, N., *et al*. Late-term results of tissue-engineered vascular grafts in humans. *J. Thorac. Cardiovasc. Surg*. 139(2):431–436.e2, 2010.

[20]Hinderer, S., *et al*. Engineering of a bio-functionalized hybrid off-the-shelf heart valve. *Biomaterials* 35(7):2130–2139, 2014.

[21]Hoerstrup, S. P., *et al*. Living, autologous pulmonary artery conduits tissue engineered from human umbilical cord cells. *Ann. Thorac. Surg*. 74(1):46–52, 2002.

[22]Horch, R. E. Future perspectives in tissue engineering:'Tissue Engineering'review series. *J. Cell. Mol. Med*. 10(1):4–6, 2006.

[23]Hospital, L.S.P.C.s. *Pulmonary Atresia (PA)*. http://www.stanfordchildrens.org/en/topic/default?id=pulmonary-atresia-pa-90-P01809. Accessed Mar 13 2018.

[24]Iyer, K. S. The Contegra bovine jugular valved conduit: Living up to expectations? *Ann. Pediatr. Cardiol*. 5(1):34–35, 2012.

[25]Jackman, C. P., *et al*. Human cardiac tissue engineering: from pluripotent stem cells to heart repair. *Curr. Opin. Chem. Eng*. 7:57–64, 2015.

[26]Jung, J. P., *et al*. An integrated statistical model for enhanced murine cardiomyocyte differentiation via optimized engagement of 3D extracellular matrices. *Sci. Rep*. 5:18705, 2015.

[27]Kasparian, N. A., D. S. Winlaw, and G. F. Sholler. "Congenital heart health": how psychological care can make a difference. *Med. J. Aust*. 205(3):104–107, 2016.

[28]Kim, J. E., S. H. Kim, and Y. Jung. Current status of three-dimensional printing inks for soft tissue regeneration. *Tissue Eng. Regen. Med*. 13(6):636–646, 2016.

[29]Kirklin, J. W., *et al*. Intermediate-term fate of cryopreserved allograft and xenograft valved conduits. *Ann. Thorac. Surg*. 44(6):598–606, 1987.

[30]Klouda, L., *et al*. Effect of biomimetic conditions on mechanical and structural integrity of PGA/P4HB and electrospun PCL scaffolds. *J. Mater. Sci*. 19(3):1137–1144, 2008.

[31]Kluin, J., *et al*. In situ heart valve tissue engineering using a bioresorbable elastomeric implant–From material design to 12 months follow-up in sheep. *Biomaterials* 125:101–117, 2017.

[32]Loh, Q. L., and C. Choong. Three-dimensional scaffolds for tissue engineering applications: role of porosity and pore size. *Tissue Eng. B* 19(6):485–502, 2013.

[33]Manavitehrani, I., *et al*. Reinforced poly (propylene carbonate) composite with enhanced and tunable characteristics, an alternative for poly (lactic acid). *ACS Appl. Mater. Interfaces* 7(40):22421–22430, 2015.
[34]Manavitehrani, I., *et al*. Biomedical applications of biodegradable polyesters. *Polymers* 8(1):20, 2016.
[35]Manavitehrani, I., *et al*. Fabrication of a biodegradable implant with tunable characteristics for bone implant applications. *Biomacromolecules* 18(6):1736–1746, 2017.
[36]Marelli, A.J., *et al*., Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. *Circulation,* CIRCULATIONAHA-113.008396, 2014.
[37]Marsden, A. L., *et al*. Evaluation of a novel Y-shaped extracardiac Fontan baffle using computational fluid dynamics. *J. Thorac. Cardiovasc. Surg*. 137(2):394–403, 2009.
[38]Matsumura, G., *et al*. First evidence that bone marrow cells contribute to the construction of tissue-engineered vascular autografts in vivo. *Circulation* 108(14):1729–1734, 2003.
[39]Matsumura, G., *et al*. Successful application of tissue engineered vascular autografts: clinical experience. *Biomaterials* 24(13):2303–2308, 2003.
[40]Mei, N., *et al*. Biocompatibility of poly(ε-caprolactone) scaffold modified by Chitosan—the fibroblasts proliferation in vitro. *J. Biomater. Appl*. 19(4):323–339, 2005.
[41]Mery, C. M., *et al*. Risk factors for development of endocarditis and reintervention in patients undergoing right ventricle to pulmonary artery valved conduit placement. *J Thorac Cardiovasc Surg* 151(2):432–441.e2, 2016.
[42]Mi, H.-Y., *et al*. Approaches to fabricating multiple-layered vascular scaffolds using hybrid electrospinning and thermally induced phase separation methods. *Ind. Eng. Chem. Res*. 55(4):882–892, 2016.
[43]Morray, B. H., *et al*. Multicenter experience evaluating transcatheter pulmonary valve replacement in bovine jugular vein (Contegra) right ventricle to pulmonary artery conduits. *Circulation* 10(6):e004914, 2017.
[44]Morris, P. D., *et al*. Computational fluid dynamics modelling in cardiovascular medicine. *Heart* 102(1):18–28, 2016.
[45]Müller-Schweinitzer, E. Cryopreservation of vascular tissues. *Organogenesis* 5(3):97–104, 2009.
[46]Murphy, S. V., and A. Atala. 3D bioprinting of tissues and organs. *Nat. Biotechnol*. 32(8):773–785, 2014.
[47]Murphy, C.M., *et al*. Cell-scaffold interactions in the bone tissue engineering triad. 2013.
[48]Nair, L. S., and C. T. Laurencin. Biodegradable polymers as biomaterials. *Progress in Polymer Science (Oxford)* 32:762–798, 2007.
[49]Naito, Y., *et al*. Successful clinical application of tissue-engineered graft for extracardiac Fontan operation. *J. Thorac. Cardiovasc. Surg*. 125(2):419–420, 2003.
[50]Niemantsverdriet, M., *et al*. Determinants of right ventricular outflow tract conduit longevity: a multinational analysis. *Congenital Heart Disease* 3(3):176–184, 2008.
[51]Norotte, C., *et al*. Scaffold-free vascular tissue engineering using bioprinting. *Biomaterials* 30(30):5910–5917, 2009.
[52]Ogden, R. W. Nonlinear elasticity, anisotropy, material stability and residual stresses in soft tissue. Biomechanics of Soft Tissue in Cardiovascular Systems, New York: Springer, 2003, pp. 65–108.
[53]Ogle, B. M., *et al*. Distilling complexity to advance cardiac tissue engineering. *Sci. Transl. Med*. 8(342):342ps13, 2016.
[54]Pagliari, S., *et al*. A multistep procedure to prepare prevascularized cardiac tissue constructs using adult stem sells, dynamic cell cultures, and porous scaffolds. *Front. Physiol*. 5:210, 2014.
[55]Pok, S., *et al*. A multilayered scaffold of a chitosan and gelatin hydrogel supported by a PCL core for cardiac tissue engineering. *Acta Biomater*. 9(3):5630–5642, 2013.
[56]Pok, S., *et al*. Full-thickness heart repair with an engineered multilayered myocardial patch in rat model. *Adv. Healthc. Mater*. 6(5):1600549, 2017.
[57]Rastan, A. J., *et al*. Bovine jugular vein conduit for right ventricular outflow tract reconstruction: evaluation of risk factors for mid-term outcome. *Ann. Thorac. Surg*. 82(4):1308–1315, 2006.
[58]Roh, J. D., *et al*. Tissue-engineered vascular grafts transform into mature blood vessels via an inflammation-mediated process of vascular remodeling. *Proc. Natl. Acad. Sci. USA* 107(10):4669–4674, 2010.
[59]Ross, D., and J. Somerville. Correction of pulmonary atresia with a homograft aortic valve. *Lancet* 288(7479):1446–1447, 1966.
[60]Samyn, M. M., and J. F. LaDisa. Novel applications of cardiovascular magnetic resonance imaging-based computational fluid dynamics modeling in pediatric cardiovascular and congenital heart disease. In: Assessment of cellular and organ function and dysfunction using direct and derived MRI methodologies, edited by C. Constantinides. Rijeka: InTech, 2016.
[61]Sankaran, K. K., U. M. Krishnan, and S. Sethuraman. Axially aligned 3D nanofibrous grafts of PLA–PCL for small diameter cardiovascular applications. *J. Biomater. Sci. Polym. Ed*. 25(16):1791–1812, 2014.
[62]Schaefermeier, P., *et al*. Design and fabrication of three-dimensional scaffolds for tissue engineering of human heart valves. *Eur. Surg. Res*. 42(1):49–53, 2009.
[63]Sekarski, N., *et al*. Right ventricular outflow tract reconstruction with the bovine jugular vein graft: 5 years' experience with 133 patients. *Ann. Thorac. Surg*. 84(2):599–605, 2007.
[64]Shinkawa, T., *et al*. Outcome of right ventricle to pulmonary artery conduit for biventricular repair. *Ann. Thorac. Surg*. 99(4):1357–1366, 2015.
[65]Shinoka, T. What is the best material for extracardiac Fontan operation? *J. Thorac. Cardiovasc. Surg*. 153(6):1551–1552, 2017.
[66]Shin'oka, T., Y. Imai, and Y. Ikada. Transplantation of a tissue-engineered pulmonary artery. *N. Engl. J. Med*. 344(7):532–533, 2001.
[67]Shinoka, T., *et al*. Tissue engineering heart valves: Valve leaflet replacement study in a lamb model. *Ann. Thorac. Surg*. 60:S513–S516, 1995.
[68]Shinoka, T., *et al*. Creation of viable pulmonary artery autografts through tissue engineering. *J. Thorac. Cardiovasc. Surg*. 115(3):536–546, 1998.
[69]Shinoka, T., *et al*. Midterm clinical result of tissue-engineered vascular autografts seeded with autologous bone marrow cells. *J. Thorac. Cardiovasc. Surg*. 129(6):1330–1338, 2005.
[70]Siallagan, D., *et al*. Virtual surgical planning, flow simulation, and 3-dimensional electrospinning of patient-specific grafts to optimize Fontan hemodynamics. *J. Thorac. Cardiovasc. Surg*. 155(4):1734–1742, 2018.
[71]Skardal, A., *et al*. Photocrosslinkable hyaluronan-gelatin hydrogels for two-step bioprinting. *Tissue Eng. Part A* 16(8):2675–2685, 2010.
[72]Sodian, R., *et al*. Application of stereolithography for scaffold fabrication for tissue engineered heart valves. *ASAIO J*. 48(1):12–16, 2002.

[73]Soerensen, D. D., *et al*. Introduction of a new optimized total cavopulmonary connection. *Ann. Thorac. Surg*. 83(6):2182–2190, 2007.
[74]Soliman, O. I. I., *et al*. Midterm performance of a novel restorative pulmonary valved conduit: preclinical results. *EuroIntervention* 13(12):e1418–e1427, 2017.
[75]Stanton, M. M., J. Samitier, and S. Sanchez. Bioprinting of 3D hydrogels. *Lab on a Chip* 15(15):3111–3115, 2015.
[76]Stevens, K. R., *et al*. Physiological function and transplantation of scaffold-free and vascularized human cardiac muscle tissue. *Proc. Natl. Acad. Sci*. 106(39):16568–16573, 2009.
[77]Stock, U. A., *et al*. Tissue-engineered valved conduits in the pulmonary circulation. *J. Thorac Cardiovasc. Surg*. 119(4):732–740, 2000.
[78]Sugiura, T., *et al*. Novel bioresorbable vascular graft with sponge-type scaffold as a small-diameter arterial graft. *Ann. Thorac. Surg*. 102(3):720–727, 2016.
[79]Takahashi, Y., and Y. Tabata. Effect of the fiber diameter and porosity of non-woven PET fabrics on the osteogenic differentiation of mesenchymal stem cells. *J. Biomater. Sci. Polym. Ed*. 15(1):41–57, 2004.
[80]Tan, Y., *et al*. 3D printing facilitated scaffold-free tissue unit fabrication. *Biofabrication* 6(2):024111, 2014.
[81]Tang, E., and A. P. Yoganathan. Optimizing hepatic flow distribution with the Fontan Y-graft: lessons from computational simulations. *J. Thorac. Cardiovasc. Surg*. 149(1):255–256, 2014.
[82]Tang, X., *et al*. Chapter 21—polymeric biomaterials in tissue engineering and regenerative medicine A2—Kumbar, Sangamesh G. In: Natural and Synthetic Biomedical Polymers, edited by C. T. Laurencin, and M. Deng. Oxford: Elsevier, 2014, pp. 351–371.
[83]Tresoldi, C., *et al*. Estimation of the physiological mechanical conditioning in vascular tissue engineering by a predictive fluid-structure interaction approach. *Comput. Methods Biomech. Biomed. Eng*. 20(10):1077–1088, 2017.
[84]Triedman, J. K., and J. W. Newburger. Trends in congenital heart disease. *Next Decade* 133(25):2716–2733, 2016.
[85]Wang, Z., *et al*. Effects of collagen deposition on passive and active mechanical properties of large pulmonary arteries in hypoxic pulmonary hypertension. *Biomech Model. Mechanobiol*. 12(6):1115–1125, 2013.
[86]Wells, W. J., *et al*. Homograft conduit failure in infants is not due to somatic outgrowth. *J. Thorac. Cardiovasc. Surg*. 124(1):88–96, 2002.
[87]Wise, S. G., *et al*. A multilayered synthetic human elastin/polycaprolactone hybrid vascular graft with tailored mechanical properties. *Acta Biomater*. 7(1):295–303, 2011.
[88]Wissing, T. B., *et al*. Biomaterial-driven in situ cardiovascular tissue engineering—a multi-disciplinary perspective. *NPJ Regen. Med*. 2(1):18, 2017.
[89]Xenos, M., *et al*. Device thrombogenicity emulator (DTE)—design optimization methodology for cardiovascular devices: a study in two bileaflet MHV designs. *J. Biomech*. 43(12):2400–2409, 2010.
[90]Xu, C., *et al*. Scaffold-free inkjet printing of three-dimensional zigzag cellular tubes. *Biotechnol. Bioeng*. 109(12):3152–3160, 2012.
[91]Yang, W., *et al*. Optimization of a Y-graft design for improved hepatic flow distribution in the Fontan circulation. *J. Biomech. Eng*. 135(1):011002-011002-12, 2012.
[92]Yang, W., *et al*. Flow simulations and validation for the first cohort of patients undergoing the Y-graft Fontan procedure. *J. Thorac. Cardiovasc. Surg*. 149(1):247–255, 2015.
[93]Zelicourt, D. D. A mechanical fluid assessment of anatomical models of the total cavopulmonary connection (TCPC) (MS thesis). Atlanta: Ga Inst Technol, 2004.
[94]Zermatten, E., *et al*. Micro-computed tomography based computational fluid dynamics for the determination of shear stresses in scaffolds within a perfusion bioreactor. *Ann. Biomed. Eng*. 42(5):1085–1094, 2014.
[95]Zhang, Y. S., *et al*. 3D bioprinting for tissue and organ fabrication. *Ann. Biomed. Eng*. 45(1):148–163, 2017.