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Review

Cardiovascular tissue engineering: From basic science to clinical application

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ABSTRACT

Valvular heart disease is an increasing population health problem and, especially in the elderly, a significant cause of morbidity and mortality. The current treatment options, such as mechanical and bioprosthetic heart valve replacements, have significant restrictions and limitations. Considering the increased life expectancy of our aging population, there is an urgent need for novel heart valve concepts that remain functional throughout life to prevent the need for reoperation.

Heart valve tissue engineering aims to overcome these constraints by creating regenerative, self-repairing valve substitutes with life-long durability. In this review, we give an overview of advances in the development of tissue engineered heart valves, and describe the steps required to design and validate a novel valve prosthesis before reaching first-in-men clinical trials. In-silico and in-vitro models are proposed as tools for the assessment of valve design, functionality and compatibility, while in-vivo preclinical models are required to confirm the remodeling and growth potential of the tissue engineered heart valves. An overview of the tissue engineered heart valve studies that have reached clinical translation is also presented. Final remarks highlight the possibilities as well as the obstacles to overcome in translating heart valve prostheses into clinical application.

1. Introduction

The leading cause of death worldwide today is cardiovascular disease (CVD). Coronary heart disease, stroke and heart failure are the main contributors to CVD morbidity and mortality in industrialized nations. The prevalence of heart disease in adults rises steeply with progressing age with nearly 70% of people over the age of 60 affected by at least one form of CVD and > 80% of people 80 years or older (Benjamin et al., 2017; Townsend et al., 2016). Heart disease due to rheumatic fever still plays an important role in developing countries and continues to have a relatively high prevalence in elderly patients (Marijon et al., 2012; Iung & Vahanian, 2011).

While not the most prevalent form of cardiovascular disease, valvular heart disease (VHD) represents a fast-growing public health problem (Supino et al., 2006). The risk of developing valve dysfunction – characterized by stenosis and/or regurgitation due to degenerative changes and calcification – increases drastically with age. In fact, > 13% of people 75 years of age or older show moderate to severe valvular dysfunction, compared to 0.7% in younger patients (≤ 45 year olds) (Nkomo et al., 2006; Iung et al., 2003; d'Arcy et al., 2011). Given the worldwide increasing life expectancy, the significance of VHD as a socioeconomic burden is set to rise notably over the coming years (Supino et al., 2006) underlining the importance of gaining deeper insights into these conditions and their treatment.

1.1. VHD treatment challenges

Medical treatment for VHD is currently symptomatic at best and the lack of understanding regarding the pathophysiology and progression of VHD have prevented advances in medical therapy (Maganti et al., 2010). Valve repair has extensively evolved in the past years and is considered a promising option for young patients with aortic regurgitation (Komiya, 2015). Valve replacement remains the therapy of choice for severe valvular dysfunction and globally over 300,000 interventions are performed each year (Kheradvar et al., 2015) using mechanical or bioprosthetic valves. Due to comorbidities, many elderly patients are, however, not suitable candidates for highly invasive open-heart surgery. In addition, the non-physiological hemodynamics of mechanical heart valves make lifelong anticoagulation therapy a necessity, putting the patients at increased risk of bleeding and thromboembolic events (Kvidal et al., 2000). Advances in transcatheter valve replacement (TVR) have opened up therapeutic possibilities for high-

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risk patients or patients ineligible for open-heart surgery. The significantly less-invasive TVR approach has, in the meantime, been extended to intermediate risk patients with outcomes non-inferior – and in some cases superior – to surgical intervention (Thourani et al., 2016; Piazza et al., 2013; Tarantini et al., 2017; Barker & Reardon, 2017). However, long-term follow-up studies are still required.

One of the reasons why there is hesitation to employ the TVR technique in younger patients (< 65 years) is the fact that currently the only clinically relevant valve prosthesis compatible with TVR is a bioprosthesis based on xenogenic glutaraldehyde-fixed materials (porcine- or bovine-derived). These valves are being applied in elderly and high-risk patients. They are, however, prone to immune-driven calcification and degradation leading to structural failure after 10 to 20 years. This degenerative process is even more pronounced in younger patients, causing the potential need for multiple re-interventions (Weber et al., 2012; Emmert & Hoerstrup, 2017). A crimpable, durable prosthetic valve with reduced immunogenicity would therefore be of central importance in successfully translating the TVR approach also to younger patients. Treating valve dysfunction in children and teenagers is even more complex due to continued somatic growth, exposing these patients to a series of reoperations to adapt for changes in heart size. Thus, a prosthetic valve which, in addition to the above properties, has the ability to remodel and grow would be required to enable the very young to fully benefit from TVR.

In summary, there is an evident and pressing need for novel valve prostheses whose characteristics resemble more closely those of native heart valves. The ideal prosthesis exhibits excellent hemodynamics and hemocompatibility, has the capacity for remodeling and growth, possesses little or no immunogenicity and is thereby resistant to degradation and calcification. The ideal valve would also be suitable for all patient cohorts allowing for the minimally-invasive TVR procedure to substitute open-heart surgery for valve replacement.

Cardiovascular tissue engineering (TE) aims to overcome the limitations of current valve prostheses by creating living heart valves with excellent hemodynamics that have the ability to remodel and grow once implanted.

2. Heart valve tissue engineering

2.1. In-vitro TEHV

The classic TEHV consists of a biodegradable porous scaffold – either of biologic or synthetic origin – onto which previously harvested and in-vitro expanded autologous cells are seeded. The scaffold-cell construct is then usually cultured in a bioreactor to enable extracellular matrix (ECM) deposition prior to implantation (Langer & Vacanti, 1993). The scaffold material itself plays a crucial role for the geometry of the valve prosthesis as well as for cell proliferation and organization, and for the final mechanical properties of the construct. Several materials have been investigated to this end and have been extensively reviewed elsewhere (Jana et al., 2014; Bouten et al., 2011). Briefly, natural and synthetic biodegradable polymers provide an attractive scaffold solution due to their unlimited availability, their tunable mechanical properties and geometries, and their inherent lack of xenogenic disease transmission. Cell adhesion, tissue organization, resorption and inflammatory response to degradation products are, however, parameters that are more difficult to control in this setting. Both synthetic and natural polymer-based scaffolds, or combinations thereof, have yielded functional TEHVs when seeded with autologous cells and cultured in vitro (Schmidt et al., 2007; Weber et al., 2011; Hoerstrup et al., 2002; Shinoka et al., 1998; Gottlieb et al., 2010).

Decellularized heart valves of either homogenic or xenogenic origin are an alternative biological scaffold solution. They serve as geometrically and hemodynamically optimal biological substrates that may positively influence cell differentiation and remodeling when seeded with autologous cells (T Kasimir et al., 2003; VeDepo et al., 2017). However, the negative effect of cryopreservation on the harvested valves, the effects of decellularization on the scaffold (microstructural changes, altered protein composition), the limited supply of human tissue, the residual immunogenicity of animal tissue and the limited cellular infiltration impose non-negligible restrictions on this TE approach (VeDepo et al., 2017).

In addition to the scaffold material, the success or failure of an in-vitro TEHV depends on the cell source used for the approach. The latter plays a fundamental role in the early functionality of a TEHV by being responsible for ECM production and organization. To prevent an immunogenic response, autologous and accessible cells sources are required for (pre)clinical application. However, autologous primary cells harvested from patients affected by VHD may be unsuitable for the approach, because of limited proliferation and ECM production potential (Jana et al., 2016). Various other cell sources (e.g.: mesenchymal stem cells, endothelial progenitor cells, and fibroblasts) have been investigated and used for seeding heart valve scaffolds, as reviewed elsewhere (Jana et al., 2016).

The requirement for (autologous) cell isolation, cell expansion and scaffold seeding and culturing obviously adds to the complexity of the conventional TE approach and makes it a time- and labor-intense procedure leading to the question whether the seeding and culturing step is really a necessity. The rapid evolution of TE has led research to focus on an alternative pathway aiming to reduce cost and circumvent the logistical hurdles of the classic in-vitro approach (Emmert et al., 2017). In the so-called in-situ TE approach a cell-free construct is directly implanted and the ensuing cell infiltration and host response are modulated to yield a functional, regenerative valve.

2.2. In-situ TEHVs – guided tissue regeneration

In 1969 Sparks investigated the idea of using the body as a bioreactor by exploiting the foreign body reaction to create vascular grafts (Sparks, 1969). Evolving from this notion, the in-situ TE strategy aims at exploiting the body's natural regenerative capacity by directly implanting acellular biodegradable scaffolds amenable to host cell recruitment, migration and remodeling. Thereby, the need for harvesting autologous cells as well as the scaffold seeding and in-vitro culturing steps are eliminated. The objective is to obtain a native-like living valve in-situ by guiding and modulating the host's response to the implanted scaffold (Bouten et al., 2011).

Obviously, the scaffold material again plays a crucial role in this context. It must provide an optimal environment for cell adhesion and growth and sustain the required mechanical properties during neotissue formation (Bouten et al., 2011; Wissing et al., 2017). Currently, both biological and polymer solutions, as well as hybrid systems, are being investigated and preclinical (Table 1) and first clinical data (Table 2) are emerging underlining the current interest in this technique (Motta et al., 2018).

2.2.1. Homo- and xenograft-based heart valves

The decellularization of xenogenic or allogenic valves aims to provide a scaffold consisting of extracellular matrix (ECM) with decreased immunogenicity while maintaining its structural and cell-mediating properties. Initially, preclinical studies using decellularized valves showed promising results (Zafar et al., 2015; Iop et al., 2014) but clinical trials using xenografts have led to dramatic outcomes due to residual immunogenicity of the graft and graft failure due to degradation (Simon et al., 2003; Rüffer et al., 2010; Voges et al., 2013).

Clinical studies involving decellularized homografts have shown low immunoreactivity (Hawkins et al., 2003) and good functionality in both pulmonary and aortic position (Sarikouch et al., 2016a; Brown et al., 2011; da Costa et al., 2010; Zehr et al., 2005). However, contrary results regarding cell infiltration (Konertz et al., 2011; Sayk et al., 2005; Dohmen et al., 2007) and questions regarding long-term durability (Helder et al., 2016a) call for further investigation. Also, donor shortage

Table 1
preclinical evaluation of TEHVs functionality and remodeling in the sheep model.

TEHV material	Approach	Procedure	End-point	Major results	Year/Ref.
Aortic valve replacement					
UPy-polyester-urethanes	Polymer-based in-situ TE	TVR	Acute	Good hemodynamic performance and competence upon implantation	2017 (Miyazaki et al., 2017)
Decell. TEM based on fibrin	ECM-based in-situ TE	Surgical	6 months	Functionality, matrix remodeling, and recellularization	2015 (Syedain et al., 2015)
Decell. porcine valve	Xenomaterial-based in-situ TE	Surgical	4 months	Smooth and pliable leaflets, full cellularization	2012 (Dohmen et al., 2012)
PGA-P4HB with autologous cells	Polymer-based with pre-seeding in-vitro TE	TVR	Acute - 2 weeks	Technical feasibility of minimally invasive aortic replacement with TEHV; adequate leaflet mobility and coaptation, early cellular infiltration	2011–2014 (Weber et al., 2011; Emmert et al., 2014; Emmert et al., 2012)
Pulmonary valve replacement					
Bisurea-polycarbonate	Polymer-based in-situ TE	Surgical and TVR	12 months	Sustained functionality, remodeling with de-novo collagen and elastin synthesis, partial scaffold reabsorption	2017 (Kluin et al., 2017)
Upy-polyester-urethanes	Polymer-based in-situ TE	TVR	24 months	Good hemodynamic performance, de-novo collagen and elastin synthesis, partial scaffold reabsorption	2017 (Serruys et al., 2017)
P4HB-gelatin	Polymer-based in-situ TE	TVR	Acute	Good hemodynamic performance and competence upon implantation	2017 (Capulli et al., 2017)
Decell. TEM based on fibrin	ECM-based in-situ TE	Surgical	5 months	Good functionality up to 8 weeks, followed by increased regurgitation; host cell infiltration, collagend and elastin deposition, leaflet shortening,	2017 (Reimer et al., 2017)
Decell. porcine aortic valve	Xenomaterial-based in-situ TE	Surgical	5 months	Feasibility of the trans-species implantation with recellularization and sufficient hemodynamic function	2017 (Hennessy et al., 2017)
Decell-FD ovine pulmonary valve	Xenomaterial-based in-situ TE	Surgical	6 months	Good functionality and host cell repopulation; freeze-drying as a promising method to extend the shelf-life of valvular grafts	2017 (Goecke et al., 2018)
Bio-conditioned decell. Ovine pulmonary valve	Xenomaterial-based in-situ TE	Surgical	6 months	Bio-conditioned valves were similar to native valves, with no signs of thickening, good endothelialisation and host cell repopulation	2016 (Quinn et al., 2016)
Decell. TEM based on PGA-P4HB	ECM-based in-situ TE	TVR	6 months	Good early functionality, with minor regurgitation starting at 8 weeks and progressing to moderate at 24 weeks, significant host cell repopulation and matrix remodeling	2014 (Driessen-Mol et al., 2014)
Autologous TEM based on PGA-P4HB	in-vitro TEHV	Surgical and TVR	6 months	Successful implantation with both method, crimping does not affect remodeling or functionality, cell infiltration and remodeling with de-novo collagen expression, leaflet thickening	2010 (Schmidt et al., 2010; Dijkman et al., 2012b)
Autologous TEM based on PGA-P4HB	in-vitro TEHV	Surgical	5 months	Good functionality, de-novo collagen synthesis, biochemical and mechanical properties comparable to native	2000 (Hoerstrup et al., 2000)
Decell. porcine aortic valves	Xenomaterial-based in-situ TE	Surgical	5 months	Good functionality, lack of calcification, repopulation of the leaflet, suggesting that decellularization can stabilize xenogenic valves	1999 (O'Brien et al., 1999)

Decell.: decellularized; TVR: transcatheter valve replacement; TEM: tissue engineered matrix; PGA: poly glycolic acid; P4HB: poly(4-hydroxybutyrate); FD: freeze-dried; UPy: ureido-pyrimidinone.

Table 2
Clinical evaluation of surgically implanted decellularized TEHVs for in-situ regeneration in both pulmonary and aortic position.

TEHV material	Control	Patients	Age	Major results	Year/Ref.
Aortic valve replacement					
Decell. homograft	n.a.	69	19.7 ± 14.6	Withstand systemic circulation, trace of regurgitation, no dilation, no calcification, suitable for young patients	2016 (Tudorache et al., 2016)
Decell. homograft	Cryo. homograft	42 TEHV; 29 control	49 ± 17	At 10 years, freedom from reoperation is greater for cryo. Homografts than decell. Homografts (80% vs 51%)	2016 (Helder et al., 2016b)
Decell. homograft	n.a.	41	34 (0.1–71)	At 18 months, 98% freedom from reoperation, stable structural integrity, low rate of calcification, and adequate hemodynamics. Longer periods of observation are necessary	2010 (da Costa et al., 2010)
Decell. homograft	n.a.	22	53 ± 14	Antigens are successfully removed from the homograft. Panel reactive antibody results were negative in > 90% of patients. Unremarkable functionality with low transvalvular gradients.	2005 (Zehr et al., 2005)
Pulmonary valve replacement					
Decell. homograft	Cryo. homograft; GF-bovine conduits	93 per group	15.8 ± 10.2	At 10 years, 100% freedom from explantation and endocarditis for the decell. Homografts. Sustained functionality over time.	2016 (Sarikouch et al., 2016b)
Decell. porcine valve	n.a.	27	12.4 (0.8–38.7)	52% of the patients needed a new valve replacement due to failure because of stenosis with moderate to severe insufficiency. Histology showed wall thickening with severe foreign body reaction and inflammation.	2013 (Voges et al., 2013)
Decell. homograft	Cryo. homograft	29	28.6 ± 16.0	No patient required reoperation; no deterioration of the valve; good functionality but no significantly different from the cryo. Homografts.	2011 (Brown et al., 2011)
Decell. porcine valve	n.a.	61	7 (9d – 50y)	Unremarkable functionality and normal structural features, with no evidence of calcification. The intermediate-term performance of the conduits was favourable in patients with congenital heart disease	2011 (Konertz et al., 2011)
Decell. homograft	Cryo. homograft; GF-bovine conduits	38 per group	12.7 ± 6.1	Decell. homografts showed improved freedom from explantation, low pressure gradients, and exhibited adaptive growth	2011 (Cebotari et al., 2011)
Decell. porcine valve	n.a.	16	14 ± 11	Graft obstruction that led to patient re-operation occurred in 38% of the cases; histological examination revealed stenosis formation, due to inflammatory infiltration	2010 (Rüffer et al., 2010)
Decell. homograft	Cryo. Homograft	14	8.5 ± 7.9	The panel-reactive antibody level for both class I and class II antibodies are significantly lower for decell. Homografts compared to cryo. Homografts. Similar early functionality.	2003 (Hawkins et al., 2003)
Decell. homograft with EPCs	n.a.	2	11, 13	Feasible and safe; potential to remodel and grow (increase in annulus diameter), no size of degeneration	2006 (Cebotari et al., 2006)
Decell. porcine valve	n.a.	4	2.5–11	Good functioning post-operatively but sudden death for structural failure caused by severe inflammation in 3 patients	2003 (Simon et al., 2003)

Decell.: decellularized; EPC: endothelial progenitor cells; GF: glutaraldehyde fixed; Cryo.: cryopreserved; n.a.: not available.

and the requirement of open-heart surgery for these valve replacements impose significant restrictions on the applicability of this valve substitution strategy.

2.2.2. Biodegradable polymeric valves

Natural and synthetic biodegradable polymers are currently garnering a lot of attention and interest as scaffolds for in-situ application as they can be designed to exhibit the desired mechanical properties and valve geometry. The unlimited availability of both natural and synthetic polymers is a further advantage of this approach; however, natural polymers, mainly hydrogels (e.g.: collagen, gelatin, fibrin), do not usually offer sufficient mechanical properties to be suitable for in-vivo application. On the other hand, synthetic biodegradable polymers (e.g.: polyglycolic acid, polylactic acid, polycaprolacton, …), can be tailored to include 1) sufficient strength to sustain in-vivo valve function while the new tissue is formed; 2) flexibility required to implant these scaffolds via TVR; 3) controlled degradation rate; 4) rapid manufacturing, and 5) cost reduction. In addition, porosity can be configured to allow for optimal cell infiltration and the material can be functionalized using peptides, growth factors, and/or cytokines to modulate the ensuing immune response (Bouten et al., 2011; Wissing et al., 2017; Cheung et al., 2015; Fioretta et al., 2012). As a promising preclinical example of this approach, pulmonary valve replacements based on bisurea-modified poly(carbonate) (Kluin et al., 2017) and 2-ureido-4[1H]-pyrimidinone-modified poly-caprolactone (Serruys et al., 2017) implanted in sheep retained their functionality for up to 12 and 24 months, respectively. Despite the successful cell-driven scaffold degradation and remodeling in these approaches, extended long-term follow up studies are required to better understand the remodeling and functionality of these polymer-based prostheses upon complete scaffold degradation.

2.2.3. Tissue engineered matrix-based (TEM) heart valves

To eliminate dependence on donor-derived valves and support valve replacement by TVR, TEHVs based on tissue engineered matrix (i.e.: in-vitro grown ECM subsequently decellularized (Dijkman et al., 2012a)) are currently being investigated (VeDepo et al., 2017; Motta et al., 2018; Fioretta et al., 2016). Myofibroblasts and dermal fibroblasts have proven to be viable cell sources for the in vitro production of ECM (Hoerstrup et al., 2002; Hoerstrup et al., 2000; Syedain et al., 2014) and preclinical studies have so far shown good early functionality and in-vivo cell infiltration and organization (Syedain et al., 2014; Driessen-Mol et al., 2014; Schmidt et al., 2016). Furthermore, it has been shown that TEM scaffolds can be successfully implanted using the TVR approach (Driessen-Mol et al., 2014; Schmidt et al., 2010; Dijkman et al., 2012b).

In summary, the success of TEHVs is influenced strongly by scaffold architecture, hemodynamic performance and cellular infiltration and organization. Each of these factors alone can bring about the failure of a valvular prosthesis and must play a crucial role in the design and validation of a heart valve.

The aim of this review is to provide an overview of the most relevant experimental steps to test and validate a novel (tissue engineered) valve prosthesis and to approach clinical translation. Before being ready for first-in-men trials, a novel heart valve replacement should be subjected to extensive in-vitro and in-vivo testing to confirm its functionality, safety, and suitability for clinical use. TEHVs should undergo similar laboratory testing, but extra characterization is required to assess remodeling and growth potential of the replacement and confirm its safety profile over time. Within this review, we will distinguish between in-silico, in-vitro, and pre-clinical in-vivo tests that can and should be used to design and validate TEHVs.

3. In-silico valve validation

Valvular diseases are often associated with changes in hemodynamics, the physical principle controlling the distribution of blood flow and pressure (Gould et al., 2013; Secomb, 2016). Maintenance of physiological hemodynamics is, therefore, vital for normal valve functionality and to prevent the development of disease. In fact, non-physiological values of blood velocity and pressure can lead to complex changes firstly on a macroscopic scale (i.e.: higher values of blood pressure can lead to increased leaflet deformation) and then on microscopic scale (i.e.: increased leaflet deformation influences valvular interstitial and endothelial cells that can become activated, promoting maladaptive tissue remodeling) (Gould et al., 2013). Considering the importance of these forces on the physiological or pathological remodeling of the leaflet, understanding stress and strain distribution in the valve cusps is of utmost importance to predict the remodeling potential of tissue engineered constructs.

The progress in computational modeling of the past decades provides valuable information for our understanding of the complex biological processes that characterize the valve environment (i.e.: opening and closure behavior of the leaflets, flow patterns, cellular interactions, stress and strain distribution) (Chandran, 2010). Computational simulations proved to be essential also for the evaluation of novel designs of valve replacements, hence reducing the need for prototype production and animal testing (Chandran, 2010), as also recognized by the US Food and Drug Administration (FDA) in 2014 (Morris et al., 2016).

These results, in combination with the advent of non-invasive 3D cardiac imaging modalities (i.e.: echocardiography, magnetic resonance imaging (MRI), computed tomography) led to patient-specific modeling of the cardiac valves (Sun et al., 2014). Patient-specific 3D reconstruction can be useful to simulate congenital heart disease, where the structural and physiological complexity of the cardiac valves cannot be represented by standard in-vitro and in-vivo model systems (Quail & Taylor, 2013), as well as for preoperative planning of minimally invasive transcatheter procedures, where precise assessment of the valve dimensions and geometry is of utmost importance for proper valve functionality (Sun et al., 2014).

Currently, the dynamic simulation of heart valve prostheses is usually achieved by finite-element (FE) analysis, computational fluid dynamics (CFD) and fluid-structure interaction (FSI). FE analysis focuses on the characterization of stress and strain distribution in the region of interest (i.e.: the leaflets), CFD provides a quantitative description of flow characteristics, and FSI aims at modeling the interactions between valve structure and blood flow, providing information on the detailed flow dynamics past the valve (Chandran, 2010; Sun et al., 2014).

3.1. Finite element structural analysis

FE analysis can be used to optimize valve designs by performing parametric studies on valve geometry and dimensions. While most early valve models were based on simplified symmetric geometries of the valve structures, the recent use of cardiac imaging techniques allows for the development of patient-specific simulations based on a detailed three-dimensional geometry of the valve. Initially, this analysis was performed on valves in closed configuration (Sabbah et al., 1985; Ghista & Reul, 1977; Cataloglu et al., 1977) but, more recently, the dynamic simulation of the opening and closure of a heart valve has also been achieved (Sripathi et al., 2004; Gnyaneshwar et al., 2002). Due to advances in imaging and simulation technologies, it is now possible to perform patient-specific modeling of valve replacement using different prostheses, a procedure that can help the surgeon in selecting the best heart valve replacement for the specific diseased anatomy of the patient (Quail & Taylor, 2013).

The application of such a model to TEHVs is still limited but of remarkable importance. As an example, TEHVs with improved geometry were obtained by using a constraining insert during culture in the bioreactor. While in-vitro testing showed competent hydrodynamic functionality under physiological pulmonary conditions, in-silico data

revealed a considerable decrease in radial tissue compression. This result suggests that the developed TEHV is expected to be less prone to leaflet retraction, hence retaining its competence after implantation (Sanders et al., 2016). Additionally, computational modeling has been used to predict the remodeling of a TEHV subjected to both pulmonary and aortic pressure conditions. In this study, the risk of developing valvular insufficiency was also correlated to the presence of contractile cells, showing how an increase in cellular contractility can lead to the development of valvular insufficiency (Loerakker et al., 2016).

3.2. Computational fluid dynamics

By providing a measure of the blood flow, imaging techniques such as 4D MRI and echocardiography, are a powerful tool to improve our understanding of the pathophysiology of cardiovascular diseases, by quantifying and visualizing the mechanical stress on the valve walls and leaflets (Morris et al., 2016; Itatani et al., 2017). However, these methods lack spatial and temporal resolution. Compared to them, CFD is a well-established tool to calculate the flow instead of measuring it (Itatani et al., 2017). CFD allows to study the complex physiological flows of the heart, enabling the investigation of pressure and flow fields. As an example, CFD modeling is commonly used to compute wall shear stress values in a non-invasive way, providing information on the local hemodynamics and on the flow characteristics (i.e.: laminar, disturbed, turbulent) (Jin et al., 2004). By providing detailed predictions of blood flow through the valve prosthesis, CFD data are essential to optimizing valve hemodynamics and limiting the risk of blood clotting (Kelly, 2002). In fact, by understanding the flow pattern, it is possible to change and correct the designs of heart valve prostheses in order to limit the design-related thrombogenic potential (Simon et al., 2010; Yoganathan et al., 2005; Zakaria et al., 2017).

Combined with advanced imaging techniques, CFD simulations have also demonstrated their potential in modeling healthy and diseased systems and in predicting the physiological responses to a specific clinical intervention (Morris et al., 2016). CFD is therefore developing towards a clinical tool to assess heart functionality, providing important information on hemodynamic parameters to serve as non-invasive clinical diagnostic indices (Doost et al., 2016). However, this powerful computational technique should also be used to assess the flow patterns generated by (tissue engineered) valve prostheses, allowing for reduction of costs and risks associated with a novel heart valve design (Kelly, 2002).

3.3. Fluid-structure interaction model

Compared to native healthy heart valves, prosthetic valves are associated with complications often related to the non-physiologic flow patterns created by the prostheses (e.g.: regions of abnormal flow determined by the bi-leaflet design of mechanical valves induce local areas of high shear stress that can activate platelets, a major factor leading to thrombus deposition). FSI models can be used to reveal the hemodynamics of valve replacements and the interaction between blood and the implanted valve (Borazjani, 2015).

By using in-vitro derived hemodynamic parameters (e.g.: transvalvular pressure gradient, flow rate, maximum velocity, and effective orifice area) and platelet activation models, it is possible to characterize the hemodynamics and thrombogenic potential of a novel valve design. For example, this approach allows to determine platelet trajectories and their statistical distribution, indicating areas of stress accumulation, local reverse flow, and vortices. By identifying non-physiological flow patterns caused by the valve geometry, it is possible to determine which features of the valve need further design optimization (Piatti et al., 2015). In order to obtain reliable results and prevent technical problems and requirements, the most suitable approach to simulate flexible leaflets should be determined, especially for complex 3D simulations (Bavo et al., 2016). Interestingly, such an approach can also be applied to patient-specific models derived from magnetic resonance images and to assess the ventricular flow through the valve (Liang Zhong et al., 2013). These simulations can be also extremely valuable in studying the progression of disease such as the aortic valve stenosis (Sadeghpour et al., 2017) and in understanding the effects on both valve structure and cellular organization (Gould et al., 2013).

The accuracy of computational modeling depends heavily on valve geometry, material properties, and the loading and boundary conditions used, determining the level of simplification of the simulation. The use of patient-specific valve models with improved accuracy obtained by state-of-the-art imaging techniques allows the reconstruction of complex heart and valve anatomies and understanding of the specific hemodynamics. As a consequence, in-silico models can help in reducing the risks associated with the testing of a novel design, thereby reducing the number of required animals for preclinical testing. Nevertheless, valve functionality and remodeling cannot be validated only with computational modeling and further in-vitro and in-vivo assessment in suitable models is a necessity to confirm the safety, biocompatibility, and regenerative capacity of a TEHV.

4. In-vitro valve validation

4.1. Biocompatibility

Upon implantation, initial blood-material interactions coat the surface of the implant with a provisional matrix (i.e.: fibrin and platelets) that will further influence the inflammatory response and subsequent phases of healing (Anderson et al., 2008). Previous studies have shown the infiltration of host cells in tissue engineered acellular valves, inducing the anticipated remodeling response (Weber et al., 2011; Kluin et al., 2017; Weber et al., 2013). Researchers are currently using different in-vitro platforms (i.e.: microfluidic chambers, transwell systems, organ-on-a-chip technologies (Smits et al., 2014; Ballotta et al., 2014; Sidorov et al., 2017; Sanders et al., 2017)) to assess the interaction between human blood-derived cells and the implanted valve material in terms of adhesion, infiltration, and secretion potential. This aspect is of central importance to explain and to anticipate possible (mal-)adaptive remodeling phenomena determined by the initial monocyte recruitment (Roh et al., 2010). Additionally, by using human-derived cells, the assessment of likely patient-specific differences (i.e.: gender, age, disease …) in the early human host cell response can be unraveled and correlated to the remodeling potential.

Early thrombotic and thromboembolic complications post implantation are another important concern of current cardiovascular implants, making hemocompatibility a fundamental biomaterial requirement (Ekdahl et al., 2011). Foreign materials as well as exposed collagen fibers are known to initiate coagulation, allowing for platelet adhesion and activation (Farndale, 2006). Previous studies have proven that TEHV implanted as pulmonary replacement in sheep support neoendothelialization (Kluin et al., 2017; Weber et al., 2013; Reimer et al., 2017). However, in-situ endothelialization in human has been reported to be rather limited when compared to animal models (Zilla et al., 2007). Hence, full in-vitro endothelialization of the TE heart valve prior to implantation represents a potential solution to reduce the risk of early thrombosis, as already shown in clinical trials using decellularized human pulmonary valves pre-seeded with autologous endothelial cells (Cebotari et al., 2006; Dohmen et al., 2012).

In terms of regulatory aspects, the International Organization of Standardization (ISO) suggests guidelines to assess the material biocompatibility in the ISO 10993 (Biological evaluation of medical devices). Specifically, the norm proposes tests for interactions with blood (part 4), suggesting in-vitro assays to obtain information on the effects of the biomaterial on blood and blood components, such as hemolysis (i.e.: damaging effects on leukocytes and erythrocytes during whole blood incubation with the material), complement activation, and thrombogenicity (i.e.: platelet adhesion, clotting time). In addition,

tests for in vitro cytotoxicity (part 5) are also recommended to assess potential cytotoxic reactions (i.e.: via cell incubation together with material extracts).

4.2. Functionality

To determine valve functionality in-vitro, TEHVs are subjected to hydrodynamic studies aiming at characterizing the valve performance by measuring parameters such as pressure difference, regurgitation, and durability. Measures for flow, backflow leakage, and pressure gradients, together with accurate imaging of the opening and closure behavior of the valve can be obtained using pulse duplicator systems to assess the hydrodynamic pulsatile performance of the valve replacements. Valve durability testers, on the other hand, are fundamental to determine the fatigue behavior of the valve (Sanders et al., 2016; Buse et al., 2016; Black et al., 1994) via accelerated durability tests. To further mimic the physiological environment, certain parameters can be adjusted in order to better mimic the blood density (e.g.: by adding Polyacrylamid or Xanthan gum to the saline solution to replicate the complex viscoelastic behavior of blood (Pohl et al., 1996)). By using this precaution, the influence of blood-like rheological properties on leakage flow and volume can be better determined. To simulate long-term in-vivo performance, accelerated opening and closing cycle settings (i.e.: at 10 Hz) are available in the durability tester. However, several precautions are also needed to ensure the correct opening and closing behavior of the valve (i.e.: by analyzing slow-motion recording) to prevent incorrect loading of the leaflets that could affect valve durability (Sanders et al., 2016).

Specifically for heart valve replacements, the ISO 5840 (Cardiovascular implants: cardiac valve prostheses) provides general requirements to test valves for human implantation and it defines operational requirements of a valve prosthesis. Additionally, it presents a selection of tests and methods suitable to assess the physical, chemical, biological, and mechanical properties of heart valve substitutes and of their materials and components.

4.3. Feasibility

After having proven the prosthesis functionality in a simplified heart valve tester, the assessment of valve performance inside a realistically performing heart will provide further information on the operability of the product. To this end, researchers have developed the cardiac biosimulator platform, a novel in-vitro set-up that simulates cardiovascular device real operating conditions in a physiological-like environment (Leopaldi et al., 2015). This approach consists of a mock apparatus combined with an entire explanted (ovine, porcine, …) heart, capable of simulating the pumping function of the heart through external pressurization of the ventricle (Leopaldi et al., 2015). By preserving the valvular anatomy, the cardiac biosimulator platform allows to test novel valve prototypes, to simulate surgical or transcatheter procedures, and to train physicians in novel surgical techniques (Leopaldi et al., 2018). Additionally, this set-up is compatible with advanced imaging techniques and will enable hemodynamic analysis and valve imaging in physiological settings (Leopaldi et al., 2012).

Despite the advances in in-vitro model systems, it is not yet possible to replicate important physiological phenomena in these set-ups that, by definition, are a simplification of the in-vivo host environment. While the use of blood-derived mononuclear cells to determine the immunocompatibility of a material is an established method, the results will be limited by the exclusion of certain cell fractions (i.e.: granulocytes and, particularly, their sub-population neutrophils) that may also play a role in the inflammatory process. Similarly, the use of whole blood in-vitro requires blood exposure to different surfaces and the use of anti-coagulants that will invariably influence the coagulation cascade. Finally, the ISO norms apply only to non-regenerative mechanical and bioprosthetic valves, suggesting the need for an imminent update to better assess the performance of tissue engineered valve prostheses that, by definition, will change by in-vivo remodeling upon implantation. Hence, the durability assessment will most likely lead to a potential underestimation of the durability of the valve for degenerative phenomena associated with the testing conditions.

5. In-vivo (preclinical) valve evaluation

Despite the recent advances in both in-vitro and in-silico models to test the functionality and biocompatibility of heart valve replacements, in-vivo experiments are a mandatory step in the preclinical evaluation of such a prosthesis. Additionally, valve remodeling, self-repair and, eventually, growth – fundamental characteristics of a TEHV – can only be tested and verified in-vivo. While small animal models have been extensively used to assess integration, remodeling, and functionality of tissue engineered vascular grafts (Roh et al., 2010; Hibino et al., 2011; Lee et al., 2014), TEHVs are usually tested in large animal models. The heart anatomy among mammals is very similar, but the orientation of the heart and of the great arteries differs between animals and human. While the non-human primate is the animal model that most closely resembles the human cardiovascular system, other mammalian species, such as pigs and sheep, have been used for preclinical evaluation of regenerative prostheses.

Ideally, the perfect animal model should have a cardiovascular anatomical structure with similar size and geometry to the one of humans, as well as comparable hemodynamics, thrombogenicity, and immune response. Even if none of the available models can fully replicate human physiology, they exhibit anatomical and functional features similar to humans, making them adequate candidates for the evaluation of novel regenerative prostheses.

The ISO norms provide guidelines for the design and execution of animal tests, with recommendations to facilitate the reduction of the overall number of animals used, to reduce or eliminate pain or distress in animals, and to find in-vitro replacements for animal tests (ISO 10993, Biological evaluation of medical devices; part 2: Animal welfare requirements). Further information is provided by the ISO 5840 (Cardiovascular implants - Cardiac valve prostheses) that also recommends tests for preclinical in-vivo evaluation and clinical evaluation of the final heart valve substitute. However, there is not yet a clear standard for the development and testing of TEHVs.

5.1. Non-human primates

Non-human primates are the animal model that most closely resembles anatomical and physiological human features. Similar to humans, they have a slow growth curve which makes them ideal candidates for extended long-term studies. However, their use is prohibited in countries where other animal models are available and, even if possible, the use of non-human primates is strictly regulated and associated with prohibitive costs (Rashid et al., 2004; Gallo et al., 2017). Due to these circumstances, few studies reporting the use of non-human primates for the testing of TEHVs are available. Specifically, Weber et al. implanted via minimally invasive procedure off-the-shelf available TEHVs in a baboon model for up to 8 weeks (Weber et al., 2013). Valve functionality was retained throughout the follow-up, even if mild to moderate insufficiency, caused by leaflet shortening, was detected. When compared to human decellularized valves, these TEHVs showed a rapid cellular repopulation, confirming the remodeling potential of such acellular tissue engineered materials.

5.2. Pigs

Pigs are a popular choice for cardiovascular experiments as they share a similar anatomy and physiology to that of humans (Gallo et al., 2017). However, they have a fast growth curve, gaining up to 75 kg in 8 weeks (Rashid et al., 2004) which makes them unsuitable for the

assessment of regenerative prostheses because of potential size mismatch. To overcome this limitation, researchers have optimized the in-vivo testing of TEHVs in a smaller swine breed, the Vietnamese pig (Gallo et al., 2017). In these studies, Gerosa and his team optimized decellularized porcine aortic roots (Bottio et al., 2010) and implanted them as replacement of the right ventricular outflow tract in Vietnamese pigs (Gallo et al., 2012; Gallo et al., 2016). After 15 months in-vivo, extended functional performance, cell repopulation, de-novo extracellular matrix synthesis and no evidence of calcification suggest that these valve replacements have the potential to remodel upon implantation.

The porcine model presents some clear advantages for preclinical cardiovascular research (i.e.: similarities to humans in immune system, coagulation cascade, and endothelialization potential (Gallo et al., 2017)). Despite the limited use of the swine model for the in-vivo testing of TEHVs, research has shown that the pig can be considered as a valid experimental choice for the preclinical evaluation of regenerative prostheses.

5.3. Sheep

The sheep is the most widely accepted and used animal model to test heart valve replacements because of mechanical properties of the valves and hemodynamic flow parameters similar to that of humans (Rashid et al., 2004). Additionally, the juvenile sheep (up to 12 months, when bone growth and maturation mostly occur) represents the “the worst-case scenario” (Taramasso et al., 2015) for testing the durability and performance of valve prostheses because of the high levels of calcium and phosphorous in the serum which may accelerate the calcification of heart valve prostheses (Barnhart et al., 1982).

Hence, the ovine model has been extensively used for the evaluation of TEHV functionality and remodeling, for pulmonary and aortic valve replacements with both surgical and transcatheter implantation procedures (Table 1). Importantly, the sheep model has a moderate growth curve that proved to be suitable to study the growth potential of both tissue engineered vascular (Reimer et al., 2017; Kelm et al., 2012) and valvular prostheses (Zafar et al., 2015; Hoerstrup et al., 2000; Reimer et al., 2017; Quinn et al., 2016; Hennessy et al., 2017). The use of lambs as animal model is, therefore, becoming the gold-standard for the development and assessment of novel regenerative cardiovascular solutions capable of growing within the recipient body.

6. In-vivo clinical evaluation

With the goal of improving the durability of currently available xenogenic bioprostheses by avoiding fixation in glutaraldehyde, researchers have developed TEHVs based on porcine valves deprived of cells. Decellularization preserves the native valve geometry and the gross integrity of the tissue structure, while eradicating the cellular components responsible for adverse host responses and, hence, limiting xenograft antigenicity without resorting to chemical fixation (O'Brien et al., 1999; Erdbrügger et al., 2006). Despite the promising preclinical results in a juvenile sheep model (O'Brien et al., 1999) (Table 1), clinical transposition of such an approach into pediatric patients led to a catastrophic outcome, with three sudden deaths and one prophylactic explantation due to severe inflammatory responses to the implanted xenogenic material (Simon et al., 2003) (Table 2). By translating the decellularization approach to allografts, researchers have obtained good clinical outcomes, with freedom from re-operation and adaptive growth in the pulmonary position (Table 2). Extended follow-up studies are still needed for a complete assessment of decellularized homografts in aortic position, as the promising early data [42] could not be corroborated after 10 years (Helder et al., 2016b). Clinical evaluation of decellularized homografts in the aortic setting is currently ongoing (ARISE program, clinical trial number NCT02527629).

While the use of fresh decellularized homograft is, so far, the ideal solution in terms of functionality, integration and immune response, and may even allow to reduce reoperation rates in children and young adults (Cebotari et al., 2011), the paucity of this material makes it an unsuitable source for the increased demand of prostheses. On the other hand, polymer-based bioresorbable TEHVs have raised great interest because of their tuneable mechanical and geometrical properties, reduced cost and potential to regenerate upon implantation (Kluin et al., 2017; Serruys et al., 2017). Vascular grafts based on this same technology have already been tested in pediatric patients with positive outcome up to one year (Bockeria et al., 2017). Based on these successful results, a first-in-man clinical trial to evaluate bioresorbable polymeric valves (Xplore, clinical trial number NCT03022708) will soon be initiated. TEHVs based on decellularized tissue engineered matrix are not yet applied in clinical settings even though small calibre vascular prostheses based on this technology are currently under clinical investigation for hemodialysis access (clinical trial number NCT01744418 and NCT01840956).

7. Future perspectives and conclusions

Recently, novel minimally-invasive techniques like TVR are being extended to younger low-risk patients, as is evident from the ongoing clinical trials (PARTNER3: NCT02675114, Evolut R low risk: NCT02701283, NOTION 2: NCT02825134, LRT Study: NCT02628899), suggesting the extension of the current clinical indication for TVR to these patients in the near future. Despite this dramatic evolution in the surgical field, with specific ISO norms that apply to this minimally invasive technique (ISO norm 5840 on Cardiovascular implants - Cardiac valve prostheses, Part 3: Heart valve substitutes implanted by transcatheter techniques), limited changes have been implemented to the valve prostheses used for this approach. In particular, only glutaraldehyde-fixed xenogenic bioprostheses are currently suitable for TVR, as the valve replacement needs to be sutured on a metal stent and crimped into a delivery device before the implantation. Little is known about the failure mode of TVR-compatible bioprostheses given that the currently available clinical data for TVR, so far, cover a time span of only 10 years. However, as these valves are analogous to the surgically implanted bioprostheses, we can expect a similar failure mode, based on degeneration and calcification. This will result in long-term morbidity and the need for multiple re-interventions, in particular for younger patients (Saleeb et al., 2014). Tissue engineered heart valve replacements with regenerative potential are therefore proposed as a potential solution to obtain life-long prostheses. However, despite encouraging preclinical results, few of these concepts have advanced into clinics (Table 2) and are not yet compatible with TVR techniques. The open challenges are multifaceted: technical and logistical complexity; long-term safety and efficacy; controlled tissue remodeling to prevent valvular dysfunction, and long-term preclinical evaluation in appropriate animal models. In addition, inconsistencies and a lack of internationally congruent regulations regarding TE constructs are a key player in preventing the efficient translation of TE into clinical application (Emmert et al., 2017). Due to the heterogeneous multitude of TEHVs and the wide variation in biologically active ingredients and delivery methods, categorization and classification of TE constructs is a complex task and substantial efforts in this direction have been and are being undertaken (Bertram et al., 2013; Bayon et al., 2015). Harmonization of the nation-specific guidelines for classification of tissue engineered medicinal products (TEMPs), as recently instated in the European Medical Device Regulation and the introduction of GMP (good manufacturing practice) and GLP (good laboratory practice) practices are, for example, steps in the direction of facilitating the clinical translation of TEMPs (Emmert et al., 2017). However, the ISO norm 5840 was, for example, established in reference to mechanical and bioprosthetic heart valves and its extensibility to regenerative TEHVs is questionable. We are, thus, a long way from establishing international guidelines as regulatory and technical aspects tend to be

neglected while scientific and/or clinical challenges are being tackled.

In order to achieve standardization guidelines for regenerative heart valve prostheses exact definitions of clinical requirements (e.g.: clinical indications, inclusion and exclusion criteria, monitoring processes and bailout strategies), technical prerequisites and infrastructure needs are mandatory (Emmert & Hoerstrup, 2016).

Clinical translation of TEHVs has become a reality for homograft-based prostheses (Table 2), and it is imminent for novel bioresorbable polymer-based valve replacements (Xplore clinical trial). These studies will provide important insights in the remodeling potential of TEHV in humans and set the bases for the successful translation of other heart valve TE approaches, especially those combined with minimally invasive TVR techniques.

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Declaration of interest

The authors have no relevant affiliation or financial involvement that could led to conflict of interests.

References

Anderson, J.M., Rodriguez, A., Chang, D.T., 2008. Foreign body reaction to biomaterials. Semin. Immunol. 20 (2), 86–100.

d'Arcy, J.L., Prendergast, B.D., Chambers, J.B., Ray, S.G., Bridgewater, B., 2011. Valvular heart disease: the next cardiac epidemic. Heart 97 (2) (Jan 15). (91 LP-93. Available from:). http://heart.bmj.com/content/97/2/91.abstract.

Ballotta, V., Smits, A.I.P.M., Driessen-Mol, A., Bouten, C.V.C., Baaijens, F.P.T., 2014. Synergistic protein secretion by mesenchymal stromal cells seeded in 3D scaffolds and circulating leukocytes in physiological flow. Biomaterials 35 (33), 9100–9113. (Nov [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/25112932.

Barker, C.M., Reardon, M.J., 2017. Should TAVR replace surgery for aortic stenosis in low- to intermediate-risk patients? Can J Cardiol 33 (9), 1124–1128. (Available from:). http://www.sciencedirect.com/science/article/pii/S0828282X17303276.

Barnhart, G.R., Jones, M., Ishihara, T., Chavez, A.M., Rose, D.M., Ferrans, V.J., 1982. Bioprosthetic valvular failure. Clinical and pathological observations in an experimental animal model. J. Thorac. Cardiovasc. Surg. 83 (4), 618–631. (Apr [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/7062773.

Bavo, A.M., Rocatello, G., Iannaccone, F., Degroote, J., Vierendeels, J., Segers, P., 2016. Fluid-structure interaction simulation of prosthetic aortic valves: comparison between immersed boundary and arbitrary lagrangian-eulerian techniques for the mesh representation. PLoS One 11 (4), e0154517. cited 2018 Jan 18. (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/27128798.

Bayon, Y., Vertès, A.A., Ronfard, V., Culme-Seymour, E., Mason, C., Stroemer, P., et al., 2015. Turning regenerative medicine breakthrough ideas and innovations into commercial products. Tissue Eng Part B Rev. 21 (6), 560–571. Available from: https://doi.org/10.1089/ten.teb.2015.0068.

Benjamin, E.J., Blaha, M.J., Chiuve, S.E., Cushman, M., Das, S.R., Deo, R., et al., 2017. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. In: Circulation. 135(10). pp. e146–603. (Mar 7). (Available from:). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5408160/.

Bertram, T., Hellman, K.B., Bayon, Y., Ellison, S., Wilburn, S.R.S., 2013. The regulatory imperative: international perspective. Tissue Eng Part B Rev. 19 (3), 191–193. Available from: https://doi.org/10.1089/ten.teb.2012.0654.

Black, M.M., Hose, D.R., Lamb, C.J., Lawford, P.V., Ralph, S.J., 1994. In vitro heart valve testing: steady versus pulsatile flow. J Heart Valve Dis. 3 (2), 212–215. (Mar [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/8012641.

Bockeria, L., Svanidze, O., Kim, A., Shatalov, K., Makarenko, V., Cox, M., et al., 2017. Total cavopulmonary connection with a new bioabsorbable vascular graft: first clinical experience. J. Thorac. Cardiovasc. Surg. 153 (6), 1542–1550.

Borazjani, I., 2015. A review of fluid-structure interaction simulations of prosthetic heart valves. J. Long-Term Eff. Med. Implants 25 (1–2), 75–93. [cited 2018 Jan 18]. (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/25955008.

Bottio, T., Tarzia, V., Dal Lin, C., Buratto, E., Rizzoli, G., Spina, M., et al., 2010. The changing hydrodynamic performance of the decellularized intact porcine aortic root: considerations on in-vitro testing. J Heart Valve Dis. 19 (4), 485–491. (Jul [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/20845897.

Bouten, C.V.C., Dankers, P.Y.W., Driessen-Mol, A., Pedron, S., Brizard, A.M.A., Baaijens, F.P.T., 2011. Substrates for cardiovascular tissue engineering. Adv. Drug Deliv. Rev. 63 (4), 221–241. (Available from:). http://www.sciencedirect.com/science/article/pii/S0169409X11000111.

Brown, J.W., Ruzmetov, M., Eltayeb, O., Rodefeld, M.D., Turrentine, M.W., 2011. Performance of SynerGraft decellularized pulmonary homograft in patients undergoing a Ross procedure. Ann. Thorac. Surg. 91 (2), 416–423. (Available from:). http://www.sciencedirect.com/science/article/pii/S000349751002415X.

Buse, E.E., Hilbert, S.L., Hopkins, R.A., Converse, G.L., 2016. Pulse Duplicator Hydrodynamic Testing of Bioengineered Biological Heart Valves. Cardiovasc. Eng. Technol. 7 (4), 352–362. (Dec 21 [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/27443841.

Capulli, A.K., Emmert, M.Y., Pasqualini, F.S., Kehl, D., Caliskan, E., Lind, J.U., et al., 2017. JetValve: Rapid manufacturing of biohybrid scaffolds for biomimetic heart valve replacement. Biomaterials 133, 229–241. (Jul [cited 2018 Jan 18]). Available from: http://linkinghub.elsevier.com/retrieve/pii/S0142961217302685.

Cataloglu, A., Clark, R.E., Gould, P.L., 1977. Stress analysis of aortic valve leaflets with smoothed geometrical data. J. Biomech. 10 (3), 153–158. ([cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/858719.

Cebotari, S., Lichtenberg, A., Tudorache, I., Hilfiker, A., Mertsching, H., Leyh, R., et al., 2006. Clinical application of tissue engineered human heart valves using autologous progenitor cells. Circulation 114 (Suppl. 1), 132–138.

Cebotari, S., Tudorache, I., Ciubotaru, A., Boethig, D., Sarikouch, S., Goerler, A., et al., 2011. Use of fresh decellularized allografts for pulmonary valve replacement may reduce the reoperation rate in children and young adults: early report. Circulation 124 (11 Suppl. 1), 115–124.

Chandran, K.B., 2010. Role of computational simulations in heart valve dynamics and design of valvular prostheses. Cardiovasc. Eng. Technol. 1 (1), 18–38. (Mar 18 [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/20606715.

Cheung, D.Y., Duan, B., Butcher, J.T., 2015. Current progress in tissue engineering of heart valves: multiscale problems, multiscale solutions. Expert. Opin. Biol. Ther. 15 (8), 1155–1172. (Jun 1). (Available from:). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4883659/.

da Costa, F.D.A., Costa, A.C.B.A., Prestes, R., Domanski, A.C., Balbi, E.M., Ferreira, A.D.A., et al., 2010. The early and midterm function of decellularized aortic valve allografts. Ann. Thorac. Surg. 90 (6), 1854–1860. (Dec [cited 2018 Jan 18]). (Available from:). http://linkinghub.elsevier.com/retrieve/pii/S0003497510018722.

Dijkman, P.E., Driessen-Mol, A., Frese, L., Hoerstrup, S.P., Baaijens, F.P.T., 2012a. Decellularized homologous tissue-engineered heart valves as off-the-shelf alternatives to xeno- and homografts. Biomaterials 33 (18), 4545–4554. (Available from:). http://www.sciencedirect.com/science/article/pii/S0142961212002876.

Dijkman, P.E., Driessen-Mol, A., de Heer, L.M., Kluin, J., van Herwerden, L.A., Odermatt, B., et al., 2012b. Trans-apical versus surgical implantation of autologous ovine tissue-engineered heart valves. J Heart Valve Dis 21 (5), 670–678. (Sep [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/23167234.

Dohmen, P.M., Lembcke, A., Holinski, S., Kivelitz, D., Braun, J.P., Pruss, A., et al., 2007. Mid-term clinical results using a tissue-engineered pulmonary valve to reconstruct the right ventricular outflow tract during the ross procedure. Ann. Thorac. Surg. 84 (3), 729–736. (Available from:). http://www.sciencedirect.com/science/article/pii/S0003497507009228.

Dohmen, P., da Costa, F., Yoshi, S., Lopes, S.V., da Souza, F.P., Vilani, R., et al., 2012. An experimental study of decellularized xenografts implanted into the aortic position with 4 months of follow up. J Clin Exp Cardiolog. s4. (Jan 19 [cited 2018 Jan 18]). (Available from:). https://www.omicsonline.org/an-experimental-study-of-decellularized-xenografts-implanted-into-the-aortic-position-with-4-months-of-follow-up-2155-9880.S4-004.php?aid=3933.

Doost, S.N., Ghista, D., Su, B., Zhong, L., Morsi, Y.S., 2016. Heart blood flow simulation: a perspective review. Biomed. Eng. Online 15 (1), 101. (Aug 25). (Available from:). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5000510/.

Driessen-Mol, A., Emmert, M.Y., Dijkman, P.E., Frese, L., Sanders, B., Weber, B., et al., 2014. Transcatheter implantation of homologous “off-the-shelf”; tissue-engineered heart valves with self-repair capacity: long-term functionality and rapid in vivo remodeling in sheep. J. Am. Coll. Cardiol. 63 (13), 1320–1329. (Apr 8 [cited 2018 Jan 18]). (Available from:). http://linkinghub.elsevier.com/retrieve/pii/S0735109713063742.

Ekdahl, K.N., Lambris, J.D., Elwing, H., Ricklin, D., Nilsson, P.H., Teramura, Y., et al., 2011. Innate immunity activation on biomaterial surfaces: a mechanistic model and coping strategies. Adv. Drug Deliv. Rev. 63 (12), 1042–1050. (Sep 16 [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/21771620.

Emmert, M.Y., Hoerstrup, S.P., 2016. Tissue engineered heart valves: moving towards clinical translation. Expert Rev Med Devices. 4440 (April), 1–3. Available from: https://doi.org/10.1586/17434440.2016.1171709.

Emmert, M.Y., Hoerstrup, S.P., 2017. Regenerative transcatheter valves. Eur. Heart J. 38 (36), 2710–2713. (Sep 21). (Available from:). https://doi.org/10.1093/eurheartj/ehx476.

Emmert, M.Y., Weber, B., Wolint, P., Behr, L., Sammut, S., Frauenfelder, T., et al., 2012. Stem cell–based transcatheter aortic valve implantation. JACC Cardiovasc Interv. 5 (8), 874–883. (Aug [cited 2018 Jan 18]). Available from: http://www.ncbi.nlm.nih.gov/pubmed/22917460.

Emmert, M.Y., Weber, B., Behr, L., Sammut, S., Frauenfelder, T., Wolint, P., et al., 2014. Transcatheter aortic valve implantation using anatomically oriented, marrow stromal cell-based, stented, tissue-engineered heart valves: technical considerations and implications for translational cell-based heart valve concepts. Eur J Cardio-Thoracic

Surg. 45 (1), 61–68. (Jan [cited 2018 Jan 18]). Available from: http://www.ncbi.nlm.nih.gov/pubmed/23657551.
Emmert, M.Y., Fioretta, E.S., Hoerstrup, S.P., 2017. Translational challenges in cardiovascular tissue engineering. J. Cardiovasc. Transl. Res. 10 (2).
Erdbrügger, W., Konertz, W., Dohmen, P.M., Posner, S., Ellerbrok, H., Brodde, O.-E., et al., 2006. Decellularized xenogenic heart valves reveal remodeling and growth potential in vivo. Tissue Eng. 12 (8), 2059–2068. (Aug [cited 2018 Jan 18]). Available from: http://www.ncbi.nlm.nih.gov/pubmed/16968148.
Farndale, R.W., 2006. Collagen-induced platelet activation. Blood Cells Mol. Dis. 36 (2), 162–165. (Mar [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/16464621.
Fioretta, E.S., Fledderus, J.O., Burakowska-Meise, E.A., Baaijens, F.P.T., Verhaar, M.C., Bouten, C.V.C., 2012. Polymer-based scaffold designs for in situ vascular tissue engineering: controlling recruitment and differentiation behavior of endothelial Colony forming cells. Macromol. Biosci. 12 (5).
Fioretta, E.S., Dijkman, P.E., Emmert, M.Y., Hoerstrup, S.P., 2016. The future of heart valve replacement: recent developments and translational challenges for heart valve tissue engineering. J. Tissue Eng. Regen. Med. http://dx.doi.org/10.1002/term.2326. [Epub ahead of print].
Gallo, M., Naso, F., Poser, H., Rossi, A., Franci, P., Bianco, R., et al., 2012. Physiological performance of a detergent decellularized heart valve implanted for 15 months in Vietnamese pigs: surgical procedure, follow-up, and explant inspection. Artif. Organs 36 (6), E138–50. (Jun [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/22512408.
Gallo, M., Bonetti, A., Poser, H., Naso, F., Bottio, T., Bianco, R., et al., 2016. Decellularized aortic conduits: could their cryopreservation affect post-implantation outcomes? A morpho-functional study on porcine homografts. Heart Vessel. 31 (11), 1862–1873.
Gallo, M., Poser, H., Bottio, T., Bonetti, A., Franci, P., Naso, F., et al., 2017. The Vietnamese pig as a translational animal model to evaluate tissue engineered heart valves: promising early experience. Int J Artif Organs 40 (4), 142–149. (May 9 [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/28362047.
Ghista, D.N., Reul, H., 1977. Optimal prosthetic aortic leaflet valve: design parametric and longevity analyses: development of the Avcothane-51 leaflet valve based on the optimum design analysis. J. Biomech. 10 (5–6), 313–324. ([cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/893470.
Gnyaneshwar, R., Kumar, R.K., Balakrishnan, K.R., 2002. Dynamic analysis of the aortic valve using a finite element model. Ann. Thorac. Surg. 73 (4), 1122–1129. (Apr [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/11996252.
Goecke, T., Theodoridis, K., Tudorache, I., Ciubotaru, A., Cebotari, S., Ramm, R., et al., 2018. In vivo performance of freeze-dried decellularized pulmonary heart valve allo- and xenografts orthotopically implanted into juvenile sheep. Acta Biomater. 68, 41–52. (Dec 2 [cited 2018 Jan 18]; Available from:). http://www.ncbi.nlm.nih.gov/pubmed/29191508.
Gottlieb D, Kunal T, Emani S, Aikawa E, Brown DW, Powell AJ, et al. In vivo monitoring of function of autologous engineered pulmonary valve. J. Thorac. Cardiovasc. Surg.. 2010;139(3):723–7. (Available from:) http://www.sciencedirect.com/science/article/pii/S0022522309014330
Gould, S.T., Srigunapalan, S., Simmons, C.A., Anseth, K.S., 2013. Hemodynamic and cellular response feedback in calcific aortic valve disease. Circ. Res. 113 (2), 186–197. (Jul 5 [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/23833293.
Hawkins, J.A., Hillman, N.D., Lambert, L.M., Jones, J., Di Russo, G.B., Profaizer, T., et al., 2003. Immunogenicity of decellularized cryopreserved allografts in pediatric cardiac surgery: comparison with standard cryopreserved allografts. J. Thorac. Cardiovasc. Surg. 126 (1), 247–253.
Helder, M.R.K., Kouchoukos, N.T., Zehr, K., Dearani, J.A., Maleszewski, J.J., Leduc, C., et al., 2016a. Late durability of decellularized allografts for aortic valve replacement: a word of caution. J. Thorac. Cardiovasc. Surg. 152 (4), 1197–1199. (Oct [cited 2018 Jan 18]). (Available from:). http://linkinghub.elsevier.com/retrieve/pii/S0022522316300241.
Helder, M.R.K., Kouchoukos, N.T., Zehr, K., Dearani, J.A., Maleszewski, J.J., Leduc, C., et al., 2016b. Late durability of decellularized allografts for aortic valve replacement: a word of caution. J. Thorac. Cardiovasc. Surg. 152 (4), 1197–1199. (Oct [cited 2018 Jan 18]). Available from: http://linkinghub.elsevier.com/retrieve/pii/S0022522316300241.
Hennessy, R.S., Go, J.L., Hennessy, R.R., Tefft, B.J., Jana, S., Stoyles, N.J., et al., 2017. Recellularization of a novel off-the-shelf valve following xenogenic implantation into the right ventricular outflow tract. In: Aikawa, E. (Ed.), PLoS One. 12(8). pp. e0181614. (Aug 1 [cited 2018 Jan 18]). Available from: https://doi.org/10.1371/journal.pone.0181614.
Hibino, N., Yi, T., Duncan, D.R., Rathore, A., Dean, E., Naito, Y., et al., 2011. A critical role for macrophages in neovessel formation and the development of stenosis in tissue-engineered vascular grafts. FASEB J. 25 (12), 4253–4263. Available from: https://doi.org/10.1096/fj.11-186585.
Hoerstrup, S.P., Sodian, R., Daebritz, S., Wang, J., Bacha, E.A., Martin, D.P., et al., 2000. Functional living trileaflet heart valves grown in vitro. Circulation 102 (19 Suppl 3), III44–9. (Nov 7 [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/11082361.
Hoerstrup, S.P., Zünd, G., Cheng, S., Melnitchouk, S., Kadner, A., Sodian, R., et al., 2002. A new approach to completely autologous cardiovascular tissue in humans. ASAIO J. 48 (3), 234–238.
Iop, L., Bonetti, A., Naso, F., Rizzo, S., Cagnin, S., Bianco, R., et al., 2014. Decellularized allogeneic heart valves demonstrate self-regeneration potential after a long-term preclinical evaluation. PLoS One 9 (6).
Itatani, K., Miyazaki, S., Furusawa, T., Numata, S., Yamazaki, S., Morimoto, K., et al., 2017. New imaging tools in cardiovascular medicine: computational fluid dynamics and 4D flow MRI. Gen. Thorac. Cardiovasc. Surg. 65 (11), 611–621. (Nov). (Available from:). https://doi.org/10.1007/s11748-017-0834-5.
Iung, B., Vahanian, A., 2011. Epidemiology of valvular heart disease in the adult. Nat. Rev. Cardiol. 8 (3), 162–172. (Available from:). https://doi.org/10.1038/nrcardio.2010.202.
Iung, B., Baron, G., G Butchart, E., Delahaye, F., Gohlke-Bärwolf, C., W Levang, O., et al., 2003. A prospective survey of patients with valvular heart disease in Europe: the euro heart survey on valvular heart disease. Eur. Heart J. 24, 1231–1243.
Jana, S., Tefft, B.J., Spoon, D.B., Simari, R.D., 2014. Scaffolds for tissue engineering of cardiac valves. Acta Biomater. 10 (7), 2877–2893. (Available from:). https://doi.org/10.1016/j.actbio.2014.03.014.
Jana, S., Tranquillo, R., Lerman, A., 2016. Cells for tissue engineering of cardiac valves. J. Tissue Eng. Regen. Med. 10 (10), 804–824.
Jin, S., Yang, Y., Oshinski, J., Tannenbaum, A., Gruden, J., Giddens, D., 2004. Flow patterns and wall shear stress distributions at atherosclerotic-prone sites in a human left coronary artery - an exploration using combined methods of CT and computational fluid dynamics. Conf Proc IEEE Eng Med Biol Soc. 5, 3789–3791. (Available from:). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3644397/.
Kelly, S.G.D., 2002. Computational fluid dynamics insights in the design of mechanical heart valves. Artif. Organs 26 (7), 608–613. (Jul 1). (Available from:). https://doi.org/10.1046/j.1525-1594.2002.07083.x.
Kelm, J.M., Emmert, M.Y., Zürcher, A., Schmidt, D., Begus Nahrmann, Y., Rudolph, K.L., et al., 2012. Functionality, growth and accelerated aging of tissue engineered living autologous vascular grafts. Biomaterials 33 (33), 8277–8285. Available from: https://doi.org/10.1016/j.biomaterials.2012.07.049.
Kheradvar, A., Groves, E.M., Dasi, L.P., Alavi, S.H., Tranquillo, R., Grande-Allen, K.J., et al., 2015. Emerging trends in heart valve engineering: part I. solutions for future. Ann. Biomed. Eng. 43 (4), 833–843. (Available from:). https://doi.org/10.1007/s10439-014-1209-z.
Kluin, J., Talacua, H., Smits, A.I.P.M., Emmert, M.Y., Brugmans, M.C.P., Fioretta, E.S., et al., 2017. 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.
Komiya, T., 2015. Aortic valve repair update. Gen. Thorac. Cardiovasc. Surg. 63 (6), 309–319. (Available from:). https://doi.org/10.1007/s11748-015-0523-1.
Konertz, W., Angeli, E., Tarusinov, G., Christ, T., Kroll, J., Dohmen, P., et al., 2011. Right ventricular outflow tract reconstruction with decellularized porcine xenografts in patients with congenital heart disease. J Hear Valve Dis. 20 (3), 341–347.
Kvidal, P., Bergström, R., Malm, T., Ståhle, E., 2000. Long-term follow-up of morbidity and mortality after aortic valve replacement with a mechanical valve prosthesis. Eur. Heart J. 21 (13), 1099–1111. (Jul 1). (Available from:). https://doi.org/10.1053/euhj.2000.1862.
Langer, R., Vacanti, J.P., 1993. Tissue engineering. Science 260 (May), 920–926 80-.
Lee, Y.-U., Yi, T., Tara, S., Lee, A.Y., Hibino, N., Shinoka, T., et al., 2014. Implantation of inferior Vena Cava interposition graft in mouse model. J. Vis. Exp. 88 (Jun 4 [cited 2018 Jan 18]). Available from: http://www.ncbi.nlm.nih.gov/pubmed/24961688.
Leopaldi, A.M., Vismara, R., Lemma, M., Valerio, L., Cervo, M., Mangini, A., et al., 2012. In vitro hemodynamics and valve imaging in passive beating hearts. J. Biomech. 45 (7), 1133–1139. (Apr 30 [cited 2018 Jan 18]). Available from: http://linkinghub.elsevier.com/retrieve/pii/S0021929012001078.
Leopaldi, A.M., Vismara, R., van Tuijl, S., Redaelli, A., van de Vosse, F.N., Fiore, G.B., et al., 2015. A novel passive left heart platform for device testing and research. Med. Eng. Phys. 37 (4), 361–366. (Apr [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/25666402.
Leopaldi, A.M., Wrobel, K., Speziali, G., van Tuijl, S., Drasutiene, A., Chitwood, W.R., 2018. The dynamic cardiac biosimulator: A method for training physicians in beating-heart mitral valve repair procedures. J. Thorac. Cardiovasc. Surg. 155 (1), 147–155. (Jan [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/29074049.
Liang Zhong, L., Boyang Su, B., Jun-Mei Zhang, J.-M., Hwa Liang Leo, H.L., Ru San Tan, R.S., 2013. FSI simulation of intra-ventricular flow in patient-specific ventricular model with both mitral and aortic valves. In: 2013 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). IEEE, pp. 703–706. cited 2018 Jan 18. (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/24109784.
Loerakker, S., Ristori, T., Baaijens, F.P.T., 2016. A computational analysis of cell-mediated compaction and collagen remodeling in tissue-engineered heart valves. J. Mech. Behav. Biomed. Mater. 58, 173–187. (Available from:). https://doi.org/10.1016/j.jmbbm.2015.10.001.
Maganti, K., Rigolin, V.H., Sarano, M.E., Bonow, R.O., 2010. Valvular heart disease: diagnosis and management. Mayo Clin. Proc. 85 (5), 483–500. (May). (Available from:). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2861980/.
Marijon, E., Mirabel, M., Celermajer, D.S., Jouven, X., 2012. Rheumatic heart disease. Lancet 379 (9819), 953–964. (Available from:). http://www.sciencedirect.com/science/article/pii/S0140673611611719.
Miyazaki, Y., Soliman, O., Abdelghani, M., Katsikis, A., Naz, C., Lopes, S., et al., 2017. Acute performance of a novel restorative transcatheter aortic valve: preclinical results. EuroIntervention 13 (12), e1410–7. Available from: https://www.pcronline.com/eurointervention/127th_issue/225.
Morris, P.D., Narracott, A., von Tengg-Kobligk, H., Silva Soto, D.A., Hsiao, S., Lungu, A., et al., 2016. Computational fluid dynamics modelling in cardiovascular medicine. Heart 102 (1), 18–28. (Jan 1). (Available from:). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4717410/.

Motta, S.E., Lintas, V., Fioretta, E.S., Hoerstrup, S.P., Emmert, M.Y., 2018. Off-the-shelf tissue engineered heart valves for in situ regeneration: current state, challenges and future directions. Expert Rev. Med. Devices 15 (1), 35–45. (Jan 2). (Available from:). https://doi.org/10.1080/17434440.2018.1419865.

Nkomo, V.T., Gardin, J.M., Skelton, T.N., Gottdiener, J.S., Scott, C.G., Enriquez-Sarano, M., 2006. Burden of valvular heart diseases: a population-based study. Lancet 368 (9540), 1005–1011. (Available from:). http://www.sciencedirect.com/science/article/pii/S0140673606692088.

O'Brien, M.F., Goldstein, S., Walsh, S., Black, K.S., Elkins, R., Clarke, D., 1999. The SynerGraft valve: a new acellular (nonglutaraldehyde-fixed) tissue heart valve for autologous recellularization first experimental studies before clinical implantation. Semin. Thorac. Cardiovasc. Surg. 11 (4 Suppl 1), 194–200. (Oct [cited 2018 Jan 18]). Available from: http://www.ncbi.nlm.nih.gov/pubmed/10660192.

Piatti, F., Sturla, F., Marom, G., Sheriff, J., Claiborne, T.E., Slepian, M.J., et al., 2015. Hemodynamic and thrombogenic analysis of a trileaflet polymeric valve using a fluid-structure interaction approach. J. Biomech. 48 (13), 3641–3649. (Oct 15 [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/26329461.

Piazza, N., Kalesan, B., van Mieghem, N., Head, S., Wenaweser, P., Carrel, T.P., et al., 2013. A 3-center comparison of 1-year mortality outcomes between transcatheter aortic valve implantation and surgical aortic valve replacement on the basis of propensity score matching among intermediate-risk surgical patients. JACC Cardiovasc. Interv. 6 (5), 443–451. (Available from:). http://www.sciencedirect.com/science/article/pii/S193687981300602X.

Pohl, M., Wendt, M.O., Werner, S., Koch, B., Lerche, D., 1996. In vitro testing of artificial heart valves: comparison between Newtonian and non-Newtonian fluids. Artif. Organs 20 (1), 37–46. (Jan [cited 2018 Jan 18]). Available from: http://www.ncbi.nlm.nih.gov/pubmed/8645128.

Quail, M.A., Taylor, A.M., 2013. Computer modeling to tailor therapy for congenital heart disease. Curr Cardiol Rep. 15 (9), 395. (Sep 24 [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/23881579.

Quinn, R.W., Bert, A.A., Converse, G.L., Buse, E.E., Hilbert, S.L., Drake, W.B., et al., 2016. Performance of allogeneic bioengineered replacement pulmonary valves in rapidly growing young lambs. J. Thorac. Cardiovasc. Surg. 152 (4), 1156–1165.e4. (Oct [cited 2018 Jan 18]). Available from: http://linkinghub.elsevier.com/retrieve/pii/S0022522316304895.

Rashid, S.T., Salacinski, H.J., Hamilton, G., Seifalian, A.M., 2004. The use of animal models in developing the discipline of cardiovascular tissue engineering: a review. Biomaterials 25 (9), 1627–1637. (Apr [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/14697864.

Reimer, J., Syedain, Z., Haynie, B., Lahti, M., Berry, J., Tranquillo, R., 2017. Implantation of a tissue-engineered tubular heart valve in growing lambs. Ann. Biomed. Eng. 45 (2), 439–451.

Roh, J.D., Sawh-Martinez, R., Brennan, M.P., Jay, S.M., Devine, L., Rao, D.A., et al., 2010. Tissue-engineered vascular grafts transform into mature blood vessels via an inflammation-mediated process of vascular remodeling. Proc. Natl. Acad. Sci. U. S. A. 107 (10), 4669–4674. (Mar 9 [cited 2018 Jan 18]). Available from: https://doi.org/10.1073/pnas.0911465107.

Rüffer, A., Purbojo, A., Cicha, I., Glöckler, M., Potapov, S., Dittrich, S., et al., 2010. Early failure of xenogenous de-cellularised pulmonary valve conduits - a word of caution!. Eur. J. Cardiothorac. Surg. 38 (1), 78–85.

Sabbah, H.N., Hamid, M.S., Stein, P.D., 1985. Estimation of mechanical stresses on closed cusps of porcine bioprosthetic valves: effects of stiffening, focal calcium and focal thinning. Am. J. Cardiol. 55 (8), 1091–1096. (Apr 1 [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/3984872.

Sadeghpour, F., Fatouraee, N., Navidbakhsh, M., 2017. Haemodynamic of blood flow through stenotic aortic valve. J Med Eng Technol. 41 (2), 108–114. (Feb 17 [cited 2018 Jan 18]). Available from: http://www.ncbi.nlm.nih.gov/pubmed/27629019.

Saleeb, S.F., Newburger, J.W., Geva, T., Baird, C.W., Gauvreau, K., Padera, R.F., et al., 2014. Accelerated degeneration of a bovine pericardial bioprosthetic aortic valve in children and young adults. Circulation 130 (1), 51–60.

Sanders, B., Loerakker, S., Fioretta, E.S., Bax, D.J.P., Driessen-Mol, A., Hoerstrup, S.P., et al., 2016. Improved geometry of Decellularized tissue engineered heart valves to prevent leaflet retraction. Ann. Biomed. Eng. 44 (4).

Sanders, B., Driessen-Mol, A., Bouten, C.V.C., Baaijens, F.P.T., 2017. The effects of scaffold remnants in decellularized tissue-engineered cardiovascular constructs on the recruitment of blood cells. Tissue Eng Part A. 23, 19–20. (Oct 1). (Available from:). https://doi.org/10.1089/ten.tea.2016.0503.

Sarikouch, S., Horke, A., Tudorache, I., Beerbaum, P., Westhoff-Bleck, M., Boethig, D., et al., 2016a. Decellularized fresh homografts for pulmonary valve replacement: a decade of clinical experience. Eur J Cardio-Thoracic Surg 50 (2), 281–290. (Aug [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/27013071.

Sarikouch, S., Horke, A., Tudorache, I., Beerbaum, P., Westhoff-Bleck, M., Boethig, D., et al., 2016b. Decellularized fresh homografts for pulmonary valve replacement: a decade of clinical experience. Eur. J. Cardiothorac. Surg. 50 (2), 281–290.

Sayk, F., Bos, I., Schubert, U., Wedel, T., Sievers, H.-H., 2005. Histopathologic findings in a novel decellularized pulmonary homograft: an autopsy study. Ann. Thorac. Surg. 79 (5), 1755–1758. (Available from:). http://www.sciencedirect.com/science/article/pii/S0003497504002139.

Schmidt, D., Achermann, J., Odermatt, B., Breymann, C., Mol, A., Genoni, M., et al., 2007. Prenatally fabricated autologous human living heart valves based on amniotic fluid-derived progenitor cells as single cell source. Circulation 116 (11 SUPPL. 1), 64–71.

Schmidt, D., Dijkman, P.E., Driessen-Mol, A., Stenger, R., Mariani, C., Puolakka, A., et al., 2010. Minimally-invasive implantation of living tissue engineered heart valves. J. Am. Coll. Cardiol. 56 (6), 510–520. (Aug 3 [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/20670763.

Schmidt, B., Spriestersbach, H., h-Ici, D., Radtke, T., Bartosch, M., Peters, H., et al., 2016. Percutaneous pulmonary valve replacement using completely tissue-engineered off-the-shelf heart valves: six-month in vivo functionality and matrix remodelling in sheep. EuroIntervention 12 (1), 62–70. (May 16). (Available from:). https://www.pcronline.com/eurointervention/98th_issue/12.

Secomb, T.W., 2016. Hemodynamics. In: Comprehensive Physiology. John Wiley & Sons, Inc, Hoboken, NJ, USA, pp. 975–1003. cited 2018 Jan 18. (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/27065172.

Serruys, P., Miyazaki, Y., Katsikis, A., Abdelghani, M., Leon, M., Virmani, R., et al., 2017. Restorative valve therapy by endogenous tissue restoration: tomorrow's world? Reflection on the EuroPCR 2017 session on endogenous tissue restoration. EuroIntervention 13 (AA), AA68–AA77. (Sep 24 [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/28942388.

Shinoka, T., Shum-Tim, D., Ma, P.X., Tanel, R.E., Isogai, N., Langer, R., et al., 1998. Creation of viable pulmonary artery autografts through tissue engineering. J. Thorac. Cardiovasc. Surg. 115 (3), 536–546. (Available from:). http://www.sciencedirect.com/science/article/pii/S0022522398703150.

Sidorov, V.Y., Samson, P.C., Sidorova, T.N., Davidson, J.M., Lim, C.C., Wikswo, J.P., 2017. I-wire heart-on-a-chip I: three-dimensional cardiac tissue constructs for physiology and pharmacology. Acta Biomater. 48, 68–78. (Jan 15 [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/27818308.

Simon, P., Kasimir, M.T., Seebacher, G., Weigel, G., Ullrich, R., Salzer-Muhar, U., et al., 2003. Early failure of the tissue engineered porcine heart valve SYNERGRAFT in pediatric patients. Eur. J. Cardiothorac. Surg. 23 (6), 1002–1006. (Jun [cited 2018 Jan 18]). (discussion 1006. Available from). http://www.ncbi.nlm.nih.gov/pubmed/12829079.

Simon, H.A., Ge, L., Sotiropoulos, F., Yoganathan, A.P., 2010. Simulation of the three-dimensional hinge flow fields of a Bileaflet mechanical heart valve under aortic conditions. Ann. Biomed. Eng. 38 (3), 841–853. (Mar 4). (Available from:). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2841271/.

Smits, A.I.P.M., Ballotta, V., Driessen-Mol, A., Bouten, C.V.C., Baaijens, F.P.T., 2014. Shear flow affects selective monocyte recruitment into MCP-1-loaded scaffolds. J. Cell. Mol. Med. 18 (11), 2176–2188. (Nov [cited 2018 Jan 18]). Available from: http://www.ncbi.nlm.nih.gov/pubmed/25103256.

Sparks, C., 1969. Autogenous grafts made to order. Ann. Thorac. Surg. 8 (2), 104–113.

Sripathi, V.C., Kumar, R.K., Balakrishnan, K.R., 2004. Further insights into normal aortic valve function: role of a compliant aortic root on leaflet opening and valve orifice area. Ann. Thorac. Surg. 77 (3), 844–851. (Mar [cited 2018 Jan 18]). (Available from:). http://linkinghub.elsevier.com/retrieve/pii/S0003497503015182.

Sun, W., Martin, C., Pham, T., 2014. Computational modeling of cardiac valve function and intervention. Annu. Rev. Biomed. Eng. 16, 53–76. (Jul 11). (Available from:). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481457/.

Supino, P.G., Borer, J.S., Preibisz, J., Bornstein, A., 2006. The epidemiology of Valvular heart disease: a growing public health problem. Heart Fail. Clin. 2 (4), 379–393. (Available from:). http://www.sciencedirect.com/science/article/pii/S155171360600078X.

Syedain, Z.H., Meier, L.A., Lahti, M.T., Johnson, S.L., Tranquillo, R.T., 2014. Implantation of completely biological engineered grafts following decellularization into the sheep femoral artery. Tissue Eng Part A 20 (11 − 12), 1726–1734. (Available from:). https://doi.org/10.1089/ten.tea.2013.0550.

Syedain, Z., Reimer, J., Schmidt, J., Lahti, M., Berry, J., Bianco, R., et al., 2015. 6-Month aortic valve implantation of an off-the-shelf tissue-engineered valve in sheep. Biomaterials 73, 175–184. Available from: https://doi.org/10.1016/j.biomaterials.2015.09.016.

T Kasimir, M., Rieder, E., Seebacher, G., Silberhumer, G., Wolner, E., Weigel, G., et al., 2003. Comparison of different decellularization procedures of porcine heart valves. Int. J. Artif. Organs 26, 421–427.

Taramasso, M., Emmert, M.Y., Reser, D., Guidotti, A., Cesarovic, N., Campagnol, M., et al., 2015. Pre-clinical in vitro and in vivo models for heart valve therapies. J. Cardiovasc. Transl. Res. 8 (5), 319–327.

Tarantini, G., Purita, P.A.M., D'Onofrio, A., Fraccaro, C., Frigo, A.C., D'Amico, G., et al., 2017. Long-term outcomes and prosthesis performance after transcatheter aortic valve replacement: results of self-expandable and balloon-expandable transcatheter heart valves. Ann Cardiothorac Surg 6 (5), 473–483. (Sep 19). (Available from:). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639218/.

Thourani, V.H., Kodali, S., Makkar, R.R., Herrmann, H.C., Williams, M., Babaliaros, V., et al., 2016. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Lancet 387 (10034), 2218–2225. (Available from:). http://www.sciencedirect.com/science/article/pii/S0140673616300733.

Townsend, N., Wilson, L., Bhatnagar, P., Wickramasinghe, K., Rayner, M., Nichols, M., 2016. Cardiovascular disease in Europe: epidemiological update 2016. Eur. Heart J. 37 (42), 3232–3245 (Available from: +).

Tudorache, I., Horke, A., Cebotari, S., Sarikouch, S., Boethig, D., Breymann, T., et al., 2016. Decellularized aortic homografts for aortic valve and aorta ascendens replacement. Eur. J. Cardiothorac. Surg. 50 (1), 89–97.

VeDepo, M.C., Detamore, M.S., Hopkins, R.A., Converse, G.L., 2017. Recellularization of decellularized heart valves: progress toward the tissue-engineered heart valve. J Tissue Eng 8 (Aug 25). (2041731417726327. Available from:). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5574480/.

Voges, I., Bräsen, J.H., Entenmann, A., Scheid, M., Scheewe, J., Fischer, G., et al., 2013. Adverse results of a decellularized tissue-engineered pulmonary valve in humans assessed with magnetic resonance imaging. Eur. J. Cardiothorac. Surg. 44 (4), 272–279.

Weber, B., Scherman, J., Emmert, M.Y., Gruenenfelder, J., Verbeek, R., Bracher, M., et al., 2011. Injectable living marrow stromal cell-based autologous tissue engineered heart

valves: first experiences with a one-step intervention in primates. Eur. Heart J. 32 (22), 2830–2840. (Nov [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/21415068.

Weber, A., Noureddine, H., Englberger, L., Dick, F., Gahl, B., Aymard, T., et al., 2012. Ten-year comparison of pericardial tissue valves versus mechanical prostheses for aortic valve replacement in patients younger than 60 years of age. J. Thorac. Cardiovasc. Surg. 144 (5), 1075–1083. (Available from:). http://www.sciencedirect.com/science/article/pii/S002252231200027X.

Weber, B., Dijkman, P.E., Scherman, J., Sanders, B., Emmert, M.Y., Grünenfelder, J., et al., 2013. Off-the-shelf human decellularized tissue-engineered heart valves in a non-human primate model. Biomaterials 34 (30), 7269–7280. (Oct [cited 2018 Jan 18]). (Available from:). http://www.ncbi.nlm.nih.gov/pubmed/23810254.

Wissing, T.B., Bonito, V., Bouten, C.V.C., Smits, A.I.P.M., 2017. Biomaterial-driven in situ cardiovascular tissue engineering—a multi-disciplinary perspective. npj Regen Med 2 (1), 18. (Available from:). http://www.nature.com/articles/s41536-017-0023-2.

Yoganathan, A.P., Chandran, K.B., Sotiropoulos, F., 2005. Flow in prosthetic heart valves: state-of-the-art and future directions. Ann. Biomed. Eng. 33 (12), 1689–1694. (Available from:). https://doi.org/10.1007/s10439-005-8759-z.

Zafar, F., Hinton, R.B., Moore, R.A., Baker, R.S., Bryant, R., Narmoneva, D.A., et al., 2015. Physiological growth, remodeling potential, and preserved function of a novel bioprosthetic tricuspid valve: tubular bioprosthesis made of small intestinal submucosa-derived extracellular matrix. J. Am. Coll. Cardiol. 66 (8), 877–888.

Zakaria, M.S., Ismail, F., Tamagawa, M., Aziz, A.F.A., Wiriadidjaja, S., Basri, A.A., et al., 2017. Review of numerical methods for simulation of mechanical heart valves and the potential for blood clotting. Med. Biol. Eng. Comput. 55 (9), 1519–1548. (Available from:). https://doi.org/10.1007/s11517-017-1688-9.

Zehr, K.J., Yagubyan, M., Connolly, H.M., Nelson, S.M., Schaff, H.V., 2005. Aortic root replacement with a novel decellularized cryopreserved aortic homograft: Postoperative immunoreactivity and early results. J. Thorac. Cardiovasc. Surg. 130 (4), 1010–1015. (Available from:). http://www.sciencedirect.com/science/article/pii/S0022522305007865.

Zilla, P., Bezuidenhout, D., Human, P., 2007. Prosthetic vascular grafts: wrong models, wrong questions and no healing. Biomaterials 28 (34), 5009–5027. (Dec [cited 2018 Jan 18]). (Available from:). http://linkinghub.elsevier.com/retrieve/pii/S0142961207005510.