Recent progress in biomaterials for heart valve replacement: Structure, function, and biomimetic design

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Abstract
Heart diseases caused by structure and function degradation is troubling millions of people all over the world. With the extension of human lifespan, the demand for heart valve replacement is rapidly increasing. However, the currently used prostheses of heart valve in clinic such as mechanical and tissue valves all have serious limitations over long-term stability after implanting. Therefore, novel artificial heart valves with outstanding durability and low degradation risk are still in great demands, despite of numerous studies in the literature. The sophisticated, multiscale structure of native heart valve is believed to be the key to its mechanical and biological durability during long-term cyclic motion. In this review, we discussed the complex structure of the native heart valve as well as their contributions to the valve’s cyclic work. In addition, representative and state of the art studies of biomimetic heart valves inspired by the natural valve are also introduced. Based on these, the structural and functional design of future novel biomimetic heart valves are proposed.

KEYWORDS
biomimetic materials, fatigue resistance, heart valve prosthesis, native heart valve, polymeric heart valve
1 | INTRODUCTION

Heart disease, including coronary artery disease, valvular heart disease, and many other diseases, has long been one of the leading threats to human health. Valvular heart disease, which is related to the stenosis and regurgitation of heart valves, is troubling people all over the world, especially individuals over 65 years old. The disorder of aortic valve, including aortic stenosis and aortic regurgitation, contributes more than half of the valvular diagnoses, and is the leading cause of death from valvular heart disease.1–4 Statistically, in the ten years from 1999 to 2009, nearly 150,000 people died because of aortic heart disease.1 Besides, more than 100,000 heart valve surgeries are performed each year in the United States and over 300,000 operations are performed worldwide, with most of them are replacement of the mitral or aortic valves.5 Based on simulation, the number of elderly patients with calcific aortic stenosis is projected to more than double by 2050 in both the United States and Europe.6 Therefore, the demand for heart valve replacement will rapidly increase, and the development of ideal heart valve prostheses is also discussed. More importantly, recent studies on the biomimetic heart valves are summarized, which we believe would inspire the development of more efficient and durable heart valve replacement in the future.

2 | MICROSTRUCTURE OF NATIVE HEART VALVE

As the name implies, native heart valves act as “valve” inside human body. They normally allow blood to flow in only one direction through the heart, and thus maintain the stability of the blood circulation. The performance of aortic valve largely affects the whole blood circulation of human body and further affects our health. The aortic valve locates between the left ventricle (LV) and the ascending aorta (AA),6 it opens when the left ventricle contracts and closes when the left ventricle is at the diastolic state. At each cycle, around 3-5 L of blood flows from the heart through the aortic valve to the aorta at a pressure of about 80 mm Hg and the speed of blood is about 1.35 m/s.7,8 This cyclic opening and closing occurs over 30 million times a year. In other words, as a passive tissue directed by the inertial forces of blood flow, the aortic valve undergoes complex load without stop for hundreds of millions of times throughout its life. Therefore, a qualified replacement for aortic valve needs to sustain this cyclic stress without large performance degradation, which remains challenging for the existing aortic valve prostheses, especially in the complicated flowing blood environment. As a result, even though the artificial heart valve has been developed for decades, there still remains many drawbacks in these currently used prosthesis, such as the calcific degeneration of tissue valves and the blood coagulation caused by mechanical heart valves. Obviously, it is both painful and costly for patients to replace their heart valve every few years due to their limited durability.

In this review, we will first introduce the structure and mechanical properties of the native aortic valves, which always provide inspirations for the structure and function design of the artificial valves. The microstructure and function of the valve leaflet are discussed in detail as one of the main stress bearing part of the aortic valve. The advantages and limitations of the currently used aortic valve prostheses are also discussed. More importantly, recent studies on the biomimetic heart valves are summarized, which we believe would inspire the development of more efficient and durable heart valve replacement in the future.
The microstructure of native aortic valve. (A) The trilaminar microstructure of the native aortic valve. The fibrosa lays on the aortic side of the valve and the ventricularis lays on the ventricular side of the valve with the spongiosa between the two outer layers. (Reproduced from CC-BY open access publications. [11] Copyright © 2014 Chester, El-Hamamsy, Butcher, Latif, Bertazzo, Yacoub, licensee Bloomsbury Qatar Foundation Journals) (B) SEM images of the elastic fibers inside the spongiosa layer in different regions. Scale bar = 200 μm. (Reproduced with permission. [10] Copyright 2007, Elsevier)

Flexible structure can be divided into three layers, which is, from the ventricle side to the artery side, the fibrosa, the spongiosa and the ventricularis (Figure 2A). Lying on the outflow side of the aortic valve, the fibrosa layer, as the name implied, is mainly consisted of a network of circumferential aligned collagen fibers, which could provide tensile strength. According to histological study, this layer takes nearly half of the leaflet’s thickness. The ventricularis is on the inflow side of the aortic valve, consisting of a dense sheet of elastic fibers that are mainly radially orientated. Between these two layers is the spongiosa layer, which is rich in glycosaminoglycans (GAGs) and proteoglycans (PGs) and can resist compression and lubricate shear stress from the outer layers. Additionally, it is noteworthy that the three microlayers of the leaflet are not separated with each other. Instead, they are closely interconnected and function together to maintain the stability of the heart valve. Elastin fibers, an important component of the leaflet, forming a fibrous, porous network that extended through all the three micro-layers of the valve leaflet. In the ventricularis, elastic fibers form a smooth dense sheet, while in the other layers, the elastic fibers are arranged loosely. These elastic fibers in the three layers are interconnected with each other, and
work together during the motion of the valve, instead of working separately. In the fibrosa layer, the interconnected elastic fibers lie around the circumferential collagen fibers, working as a sheath surrounding the collagen fibers. The structure and function of the elastic fibers in the spongiosa layer, the middle layer of the leaflet with the main components of GAGs and PGs were investigated by Hubert Tseng et al. They divided the leaflet into three parts—the hinge, the belly, and the coaptation, which respectively refer to the attachment to the aortic root, the center of the leaflet, and the region where the three leaflets meet to close the valve. As shown by the scanning electron microscopy (SEM) image in Figure 2B, inside the spongiosa layer, the elastic fibers in the hinge and coaptation regions show rectilinear pattern, and are radially oriented in the belly region. The thickness of the spongiosa layer has also been studied through immunohistochemistry, showing a much thicker elastin network in the two outer regions, and the thickness gradually decreases when moving toward the belly region.

3 | MECHANICAL PROPERTIES OF NATIVE HEART VALVE

3.1 | Stress on the aortic valve leaflets during the cardiac cycle

As a “valve,” the aortic valve works in cyclic opening and closing motion between the aorta and the left ventricle. This cyclic work is associated with the systole and diastole of the left ventricle, that is, the cardiac cycle. When the heart is at the systolic state, liters of blood is pumped out of the left ventricle at a relatively high speed, the aortic valve would open under this fast blood flow. Specifically, one theory indicates that when the ventricular pressure increases and equal to the aortic pressure, the inter-commissurral leaflet distances would increase and a tangential tension would generate on the leaflets to pull them open. And the later impetus is dependent on the forward blood flow velocity.\(^{18}\) Shear stress is thus caused by the high-speed fluid when blood is flowing through the three opening leaflets. On the other hand, when the left ventricle is in its diastolic state and its pressure is lower, the aortic valve would close to prevent the blood from flowing back to the heart from the aorta. The pressure difference across the leaflets would thus cause large tensile stress of the whole leaflet. Additionally, flexural stresses occur because of the fluctuating liquid during the process of opening and closing, even though this process could always complete in really short period of time (reported as less than 1/60 s\(^{18}\)). Briefly, the aortic valve works under a complex cyclic shear-flexural-tensile load in the blood environment, which requires outstanding and stable mechanical properties.

Many simulations have been done to understand the stress distribution within the aortic valve during the cardiac cycle, which could provide strong guidance for the design of the biomimetic aortic valve prosthesis.\(^{13,19–26}\) Coulter et al simulated a cardiac cycle with a finite element computational analysis.\(^{24}\) The simulation was carried out by applying a uniform static pressure over the entire valve surface in the direction of the blood flow and tuning the temporal evolution of applied pressure. When the aortic valve is considered as a homogeneous membrane, as shown in Figure 3A, the stress distribution within the leaflets was found to depend strongly on the state of the valve. When the heart is in systolic state and blood is flowing through the three valve leaflets, high stress would develop mostly along the attaching line of the leaflet and the inter-leaflet triangle, while the leaflets remains nearly stress free. On the contrary, when the heart is at diastolic state and aortic valve closes to prevent flood from backflowing, a much higher stress would occur in the entire aortic valve leaflet. In addition, the stress is not distributed uniformly on the leaflet, but concentrated along an imaginary line running across the middle height of the leaflet that connects to the uppermost attachment points of the leaflet triangles. Therefore, as the stress develop in the leaflet during the diastolic state is much higher than that develop in the systolic state, the stress throughout the leaflet when the aortic valve is closed would largely influence the leaflet’s long-term performance.

3.2 | The function of the leaflet’s multilayered microstructure

Under the complex loading environment, aortic valve develops sophisticated microstructure. As mentioned in previous sections, the aortic valve leaflet is not a homogeneous matrix, but has complex and highly specialized, functionally adapted cells and extracellular matrix.\(^{27}\) The mechanical properties of the aortic valve leaflet are closely related with its anisotropic structure. The circumferentially aligned collagen fibers in fibrosa layer work together with the radially aligned elastic fibers in ventricularis layer and the glycosaminoglycans in spongiosa layer to ensure the stability of the aortic valve’s cyclic opening and closing. Balguid et al.\(^{28}\) investigated the relationship between the microstructure and the mechanical properties of the human aortic heart valve leaflets through uniaxial tensile tests, cutting the aortic valve into strips both along circumferential and radial direction. The stress-strain curves showed obviously different mechanical properties of the aortic valve leaflets in different directions. Owing to the
FIGURE 3  The aortic valve's stress distribution during the cardiac cycle. (A) Stress distribution over the native aortic valve as well as the opening area and pressure of the aortic in a simulated cardiac cycle when take the leaflets as homogenous matrix. GOA refers to the geometric orifice area. (Reproduced with permission. [24] Copyright 2019, Elsevier) (B) The contribution of multiscale structure and elastic fibers to heart valve’s function. (a) Illustration of the deformation of the multiscale structure of native aortic valve during the cardiac cycle. (Reproduced with permission. [27] Copyright 1999, John Wiley and Sons) (C) A biomechanical model reflecting the stress of both the collagen and elastic fibers in cardiac cycle. (Reproduced with permission. [27] Copyright 1999, John Wiley and Sons)

orientation of the stronger and stiffer collagen fibers along the circumferential direction, tensile modulus of the strips cut in this direction is clearly larger than those cut in the radial direction. On the other hand, the radially aligned elastin fibers in ventricularis layer is much more stretchable and less stiff than collagen fibers, resulting in a less small tensile strength and modulus in the radial direction. Therefore, the fibrosa layer is considered as the main bear loading layer of the leaflet due to its aligned collagen fibers.

The function of aligned collagen fibers of the aortic valve leaflets was also studied for further understanding of aortic valve’s function. Marom et al.13 investigated the influence of aortic valve with collagen fiber network on hemodynamics and the relating stress distribution throughout the valve leaflets. In their simulation, two different models of aortic valve have been studied – one model is an asymmetric model where the orientation of the collagen fiber in the three cups were copied from a native aortic valve and are not identical, another is a simplified model which is strictly symmetric. When the function of collagen fibers is taken into consideration, stress distribution throughout the leaflets during a cardiac cycle would largely change and concentrate in these aligned fibers. What’s more, they found that the internal stress and flow shear stress would rise when the collagen fiber is less dense in one cup of the asymmetric model. This is considered to be one reason of the damage of valve leaflets.

In a normal cardiac cycle, aortic valve leaflets need to withstand a strain of about 40% when closed and then return to the undeformed state when blood is flowing through the artery. However, when stretched, collagen fibers would yield at a small strain of about 1-2%, 29 which obviously does not meet the aortic valve’s requirement of stable cyclic work. Therefore, there must be some other strategies for the aortic valve to maintain its mechanical properties’ stability. In fact, the leaflets of aortic valve develop many other structure features in different scales to ensure the stability during long-term work. First, when in the systolic state, fibrosa layer is corrugated along the circumferential direction, and the collagen fibers are not straightly arranged, but are crimped inside the fibrosa layer, making the leaflets’ surface ripples. The crimps in two size scales would disappear in diastolic state, providing the leaflets extra space to stretch in both radial and
circular circumferential directions without destroying the micro- and macrostructure of the leaflets. As illustrated in Figure 3B, when the aortic valve is closing, the corrugations and collagen crimps would extend first, and when at diastolic state, the collagen fibers would be fully unfolded and become the main bearing loading element, the leaflets would thus be stiffened. Besides, during the extending process of the leaflets when the valve is closing, the collagen fibers’ rotation also needs to be taken into consideration. Billiar et al.30 tested the mechanical properties of the native aortic valve cusp through biaxial tensile test. As they apply load on the circumferential axis and radial axis at the same time, the circumferential axis would show a much stiffer mechanical performance while the radial axis would show a much stretchable performance. The large strain and final stiffen of the radial axis are considered as the result of the rotation of circumferential aligned collagen fibers.

As another important composition of the aortic valve’s multilayered structure, the function of the elastin fibers also needs to be considered. Because of the much smaller strength and modulus, these elastin fibers certainly could not act as a bearing loading structure, especially during diastolic state. As the biomechanical model in Figure 3C shows,27 the elastic fiber network closely works together with the aligned stiff collagen fibers during the motion of the aortic valve. Specifically, when the leaflet is stretched in a relatively small strain, the elastic fibers would bear the small load while the collagen fibers are unfolding and the crimps are straightening. Once straight, the much more stiffer collagen fibers would then take up large proportion of the tensile load. What’s more, as mentioned in the second section, the three microlayers of the aortic valve are not strictly separated, but closely interconnected with each other, and the major interconnecting component between layers is elastic fibers with high extensibility.6 Observations of the microstructure of leaflets through electron microscopy,11,15,16,27,29,31–34 micro-computed tomography,35 small angle light scattering15,27,36,37 and other approaches have shown that there is a fine elastic fiber network emanating from ventricularis layer and connecting into fibrosa layer. Michael Scott et al.29 suggested one of the function of the elastin fibers by studying the microstructure of them. This structure model suggests that the intra- and inter-fiber elastic fibers running from one collagen scrim to the next or from one collagen fiber to another. What’s more, when the heart is in the systolic state, because of their elasticity, the elastic fibers would recoil to return the collagen fibers back to the undeformed shape and orientation quickly, opening the valve and preparing for the next cardiac cycle. Thus, the elastic fibers in the fibrosa layer provide a “return-spring mechanism” for the stiff collagen fibers. In addition, when the aortic is open and the leaflets flex to the outflow direction, the dense network in the ventricularis layer formed by elastic fibers are able to bear the shear stress caused by fast flowing blood.

Besides, as mentioned in the second section, elastic fibers in spongiosa layer have different microstructure in different regions.6 The thicker elastic fibers with a rectilinear pattern in the hinge and coaptation regions are considered to be benefit to the flexing of the leaflets and could dampen vibrations when the valve is closing. The aligned elastic fibers in the belly region contribute to the bending performance of the leaflet. This elastic network cooperates with GAGs - which is hydrophilic and readily absorb water to swell and from a gel38 – to function as buffering and lubricant between the outer two layers.

4 | CURRENTLY USED HEART VALVE PROSTHESIS

4.1 | Advantages and shortcomings of existing artificial heart valve

Mechanical and bioprosthetic valves are the most frequently used heart valve prostheses in clinic.39 Mechanical valves, including both lateral flow valves such as ball-cage valves, and central flow valves such as single-tilting disc valves and bileaflet valves,2,40–43 are more like “machine parts” instead of a tissue. They aimed at maintaining native heart valve’s function but not mimicking their morphology. Mechanical valves have good durability but requiring lifelong anticoagulation therapy. Problems such as potential bleeding, valve embolism, pannus formation, perivalvular leakage, and infective endocarditis, which sometimes could be fatal or require another surgery because of the large stress caused by the valve.40,42,44–46 Bioprosthetic valves with biological tissue of either allogeneic or xenogeneic origin47–51 – in the current market mainly made of mammal tissues such as bovine pericardium or porcine heart valve45,52 – on the other hand, show superior hemodynamic properties.24 Patients implanted with this kind of heart valve prosthesis only need to receive anticoagulation therapy for a short term53 when the patients do not have other cardiovascular diseases. As a result, anticoagulation-related complications54 could be largely avoided and thereby largely improve the patients’ life quality after the surgery. Unfortunately, bioprosthetic valves can’t service for a long term55 – usually about 10–15 years21,44,56 – because of structure and function degeneration,45 and sometimes requiring another surgery, which is quite painful for patients.57,58 The reason for the degeneration includes calcific degeneration,19 infective endocarditis (IE),44 and thrombosis.59 What’s more, structure degeneration is associated with the stress level of the leaflet, positions with higher stress tend to degenerate
faster. The stress caused by the flowing blood may lead to exposure or fracture of the fibers in the prostheses’ tissues.\textsuperscript{60}

Prospective studies have been conducted to evaluate the benefits and risks of implanting bioprosthetic aortic valves in patients under 60 years old, including the long-term structural changes and hemodynamic performance.\textsuperscript{58} The younger patients are found to be more susceptible to suffer structural valve degeneration (SVD) of bioprosthetic valves.\textsuperscript{60} Therefore, according to recommendations,\textsuperscript{61} implanting bioprosthetic valves require the patient should be at least 60 years old. The 2017 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines on valvular heart disease updates that bioprosthetic valves can be recommended in patients over the age of 50 years, and patients at the age between 50 to 70 are recommended to implant both mechanical and tissue valves.\textsuperscript{62} Despite of the short lifespan, more patients tend to choose bioprosthetic valves for heart valve replacement, especially for older patients at the age from 55 to 64 years.\textsuperscript{44,57,63}

Regardless of the progress in heart valve prosthesis, prostheses of heart valve could not fully meet the clinical requirements yet.\textsuperscript{64} A more suitable and durable heart valve is still in great demand.

### 4.2 Characteristics of an ideal heart valve prosthesis

Some parameters have been taken to assess the performance of the valve, for example, the open area of aortic valve orifice (or the effective orifice area, EOA), forward blood flow velocity, and the pressure gradient from left ventricle to aortic side during the systolic state\textsuperscript{18,65} and the fraction of backflowing blood (or the regurgitation fraction, RF) during the diastolic state.\textsuperscript{24,66,67} As a replacement of the failed heart valve, the overriding demand of artificial valve from the patients and doctors would be the stability. The implanted prosthesis needs to work inside human body like the native heart valve – the valve should have a long lifespan without distinct performance loss to avoid another painful surgery. This requires the artificial heart valve to have outstanding fatigue-resistant ability, which is among the most essential requirements. To be specific, the overall performance of the prosthesis – such as mechanical properties (elastic modulus, tensile or flexural strength...), hemodynamic characteristics (transvalvular pressure gradient, effective orifice area, regurgitation fraction...), surface properties – need to be stable enough over a long period of time, which for young patients could be as long as tens of years.

In addition, an ideal prosthesis for heart valve also needs to meet the following requirements: (1) The prostheses should have properties close to the native ones. For instance, its modulus needs to be moderate – not too hard for the blood flow to open it but not too soft to be unable to prevent the blood from backflowing; (2) The valve should have enough effective orifice area (EOA) and the blood should have no obvious turbulence while flowing through the valve. The transvalvular pressure of the valve needs to be low enough; (3) There should be no or little regurgitation phenomenon when valve is close (low regurgitation fraction(RF)); (4) The artificial heart valve needs to eliminate drawbacks of the existing prostheses, e.g. calcific degeneration and blood coagulation; (5) The implanted valve needs to have a good biocompatibility so that it would not destroy the normal blood components or be rejected by the immune system; (6) The implanted heart valve as well as its tent should not cause any damage to the vascular wall or endothelium; (7) The stability of aortic root (including ventricular-arterial junction (VAJ), sinuses of Valsalva, STJ, aortic annulus) and valve is essential to keep the hemodynamic environment stable and thus reduce the chance of fatigue damage.\textsuperscript{68} Therefore, the prosthesis needs to be able to customized to fit different patient’s aortic root; (8) The implanting process of the prosthesis needs to be convenient for surgeon; (9) The morphology and structure could totally recover without any fatal damage after collapse when used in transcatheter heart valve implant; (10) The cost of the prosthesis should be affordable for general people.

### 5 BIOMIMETIC HEART VALVE

As introduced in the above sections, the currently used aortic valve prosthesis has some drawbacks limiting their long-term usage inside the human body, such as thrombogenicity of mechanical valves and calcification of tissue valves. Therefore, development of novel artificial aortic valve prostheses is still in great demands. With the rapid development of material science, polymeric aortic valves are considered to be a competitive candidate for the aortic valve prosthesis that could eliminate shortcomings of the existing artificial heart valves.\textsuperscript{2,3,20,46,69–78} Researchers have been trying to develop ideal polymeric heart valve for decades. Trace back to the 1960s, the first polymeric heart valve has been implanted into the human body. This valve was fabricated with polyurethane (PU), and was used as the replacement of the mitral valve, which is a valve located between the left atrium and the left ventricle.\textsuperscript{79} However, because of the limitation of the raw materials and other technology, the polymeric valve could not sustain for a long time.\textsuperscript{3} In the following tens of years, countless concepts of the novel polymeric valves with different materials and structures have been...
proposed, including molecular design and modification of existing polymers, composition with nanomaterials and other methods. However, due to durability, calcification degradation, and many other problems, there still remains a long way to go before the clinical usage of these polymeric aortic valve prostheses.

On the other hand, it is widely believed that the outstanding and stable performance of the native aortic valve largely comes from its sophisticated multilayered structure, which has been discussed in the third section in detail. In short, the circumferentially aligned collagen fibers with a much larger modulus and strength are believed to be able to bear large proportion of load and thus contribute to the long-term cyclic motion of native aortic valves. By mimicking the structure or function of natural materials with outstanding mechanical and other properties, biomimetic materials are always believed to have modified performance than those materials without optimization. Therefore, in this section, we will introduce some recently reported biomimetic attempts on artificial heart valve. Besides, it is worth mentioning that native heart valve is a complex system. It is really hard and even impossible to mimic this whole system artificially. As the main load-bearing structure, leaflets’ microstructure and function is always the main target to mimic in the biomimetic designs of heart valve. The prostheses mentioned in this section were fabricated through different methods with different materials, but all tried to mimic the microstructure or other aspects of the native aortic valves, especially the leaflets.

### 5.1 Molecular orientation of polymer

Injection molding is a commonly used method to fabricate products with complex architecture, referring to a method of injecting the polymer into a prepared mold at specific pressure and temperature. The flow of the polymer inside the mold would largely influence its molecular orientation and further influence the corresponding morphologies and mechanical properties of the material. The flow’s influence would be prominent when the polymer itself could assemble to anisotropic microstructure, for example, due to the segregation of the styrenic and elastomeric blocks, the styrenic triblock copolymers with a styrene content of about 20% to 33% can self-assemble into cylindrical microstructure with well-defined diameter and spacing. When under melted processing, these polymers molecular could be orientated by the flow and produce structural anisotropy in the obtained materials. According to this, Joanna Stasiak et al. reported a slow injection molding method to achieve ordered microstructure of cylindrical block copolymers. By carefully designing the geometry of the mold and controlling the injecting speed and temperature, the block copolymer – in this work is poly(styrene-block-isoprene-block-styrene) containing 30 wt% styrene – could exhibit specific molecular orientations. As an example, a representative sample was prepared by injecting block copolymer from the center of a disc mold made of two parallel plates with a diameter of 80 mm at 160°C with an injecting speed ten times slower than the industrial injection (Figure 4A), and the orientation of molecular was characterized by Small Angle X-ray Scattering (SAXS). A typical two-dimensional SAXS image in Figure 4B shows a pair of meridional reflections and a pair of equatorial reflections, corresponding to the cylindrical aligned and radial aligned domains, respectively. What’s more, the molecular orientation throughout the whole sample was obtained by integrating the SAXS profile scanned from different points of the sample, and was plotted in terms of vector in Figure 4C, where the direction of the vector represents the orientation direction of the molecular and the length of the vector is proportional of the degree of orientation. Obviously, the whole sample basically shows perpendicular orientation (circumferential aligned and radial aligned) except for the close vicinity of the injection point, and the degree of orientation does not vary significantly with position. This complex bi-directional orientation is considered as the balance of shear and extensional flow in the different regions of the sample during the injection process. In short, because of the relatively slow injection speed, the copolymer flow between the two plates can be considered as a fully developed laminar flow. In the case of injection molding with a disc mold, the two outer layers show radial alignment under shear flow, while the inner layer exhibits circumferential orientation under extensional flow, as illustrated in Figure 4D.

On the basis of the above study with a simple round disc mold, a more complex three-dimensional mold with the geometry of heart valve is designed. By slowly injecting SIS from the center point of the top of the leaflet, a polymeric heart valve prosthesis with molecular orientation analogous to the fiber alignment of native heart valve could be fabricated. The modeled velocity flow map inside the mold and molecular orientation in the leaflet as well as the experimental orientation of the leaflet scanned from SAXS are shown in Figure 4E. Clearly, a biomimetic polymeric heart valve could be obtained through carefully controlling the mold’s geometry and the injection condition. This fabrication of polymeric heart valve has been developed over the recent years. A novel heart valve prosthesis with the feasibility study has been reported recently, and Figure 5A shows the rigorously designed mold for injection and the obtained polymeric heart valve. These prototypes of heart valve with controlled molecular orientation...
were fabricated from the styrenic triblock copolymers poly(styrene-block-ethylene/propylene-block-styrene) (SEPS) and poly(styrene-block-ethylene/butylene-block-styrene) (SEBS) with the slow injection molding method. Figure 5B shows an orientation map of the artificial heart valve leaflet obtained by SAXS, again, the direction and the length of the vector represent the orientation direction of the molecular and the proportional of the degree of orientation, respectively. As the map shows, the biomimetic polymeric heart valve has leaflets with regional aligned cylinder molecular, which is close to the fiber orientation in the native aortic valve, and is believed to be crucial...
FIGURE 6 Biomimetic heart valve – Eggshell membrane reinforced hydrogels. (A) Optical image of original eggshell membrane. (B) SEM image of eggshell membrane showing a network with collagen fibers. (C) Illustration of the structure of the fiber reinforced hydrogel. (D) Stress-strain curve of both the two components. (E) Nonlinear regime of the ESM’s stress-strain curve. (F) Elastic modulus of composites with different thickness and different direction of ESM. (Reproduced with permission. [70] Copyright 2017, American Chemical Society)

to the total valve’s performance. What’s more, durability of the heart valve prostheses, which could be regarded as one of the most important assessment criteria, has been tested according to the ISO standard 5840:2015. In specific, the durability was conducted with an accelerated fatigue tester at a frequency of 30 Hz with water at 37°C as working fluid, and the pressure difference across the aortic valves is required to be 100 mmHg for at least 5% of each cycle. When the pressure was traced to be abnormal, the valve would be visually inspected to identify whether it is failed. The number of cycles in Figure 5C exhibits the durability of different valve prototypes, and the latest version of design is shown to have sustained over 1.2 billion cycles without failure, equivalently to work over forty years inside the human body.

5.2 Fiber reinforced matrix

Structurally, the native aortic valve could be regarded as a matrix reinforced by collagen and elastic fibers. Therefore, reinforcing the matrix with fibers is considered to be an effective way to mimic the aortic valve’s microstructure and further improve the overall performance of the artificial heart valve. The fibrous structure has been applied in many designs of biomimetic heart valve. For example, Qian Li et al. [70] introduced eggshell membrane (ESM) – a thin membrane between the eggshell and egg white (Figure 6A) – into the design of polymeric heart valve. Figure 6B shows an SEM image of this natural protein fibrous network. Similar to the extracellular matrix of the aortic valve leaflets, the eggshell membrane consists of fibers with collagen-rich core and glycoprotein-rich mantel. This eggshell membrane reinforced polymeric aortic valve is fabricated by immersing the glutaraldehyde (GA) cross-linked eggshell membrane into the prepolymer solution of poly (ethylene glycol) diacrylate (PEGDA), following by photo crosslink to form a PEGDA hydrogel and the crosslink between the eggshell membrane and the hydrogel (Figure 6C). For comparison, samples containing different layers of ESM have been fabricated. In order to investigate the feasibility of the composition, the mechanical properties of each component were tested through uniaxial tension. Similar to natural fibrous materials, as shown in Figure 6D, the stress-strain curve of original ESMs included a linear regime and a nonlinear regime, and the nonlinear regime could be further divided into a “toe” and a “heel” region (Figure 6E), correlating to the reorganization of unstretched fibrous network and the stretch of the protein’s telopeptide terminals and triple helical structure, respectively. Besides, the PEGDA hydrogel shows a linear performance when stretched, showing good elasticity and homogeneity. Figure 6F shows the elastic modulus of the samples with different layers of ESMs calculated from the tensile curves, where the marks “latitudinal” and “hemispherical” refer to the testing direction of the ESMs. It could be concluded that the samples with similar volumetric percentages of ESMs have a close modulus and there is little difference between the modulus of samples along the latitudinal and hemispherical direction of ESMs. The
modulus of this composition is close to that of the native aortic valves, which is about 3–15 MPa along the circumferential direction. In addition to uniaxial tensile tests, the authors also conducted in vitro calcification and enzymatic degradation tests of the composition. The results showed that this composition of natural eggshell membrane and PEGDA hydrogel shows abilities of preventing calcification and enzymatic degradation because of the basically unchanged surface when soaked into the calcified media and the similar elastic modulus before and after treated by type I collagenase and pepsin.

Another example takes the anisotropic properties of native valves into consideration. Guo et al. reported a bioinspired polymeric fabricated heart valve by assembling electrospinning silk fibroin membranes with PEDGA hydrogel. In this study, two types of silk fibroin membranes – isotropic silk fibroin (ISF) membrane and directional aligned silk fibroin (DSF) membrane – were prepared with a baffle receiver and a rotating cylindrical receiver, respectively. By combining the ISF membrane and DSF membrane through collecting silk fibers with the two collectors successively, a membrane with anisotropic structure (ASF) could be obtained. The obtained silk fibroin membranes were then immersed into PEGDA solution and then exposed to ultraviolet light to cross-link the hydrogel and form composite with the thickness of about 400 μm. The composites with different microstructure were then cut into specific shapes and then fixed with a 3D printed stent (Figure 7A). The SEM images in Figure 7B show the morphologies of the silk fibroin membranes – ISF membrane consists of randomly oriented silk fibers, DSF membrane consists of silk fibers aligned in one direction, and ASF membrane has two tightly bounded layers with different silk fiber orientation. The feasibility of this prosthesis was mainly assessed through the tests of mechanical properties and hemodynamic properties. The performance of different composites under these tests is compared with the native aortic valve in Figure 7C. It could be concluded that the combination of ASF membrane with PEGDA hydrogel provides the biomimetic heart valve with similar mechanical and hemodynamic properties with the native ones.

5.3 Additive manufacturing

Additive manufacturing, or in other words, three-dimensional printing, is a rapidly developing method for material fabrication, providing people ability to design and manufacture materials with complex three-dimensional structure with the assistance of computer. Fergal B. Coulter et al. presented a hybrid multi-axis additive manufacturing process for fabricating customizable,
fiber-reinforced heart valve prosthesis, including design of the mandrel and fabrication process, as illustrated in Figure 8A. In specific, the manufacture of the biomimetic heart valve starts with imaging aortic root’s geometry of the patient through computed tomography (CT) or other ways and then convert it into a digital mesh. Two mandrels for 3D printing – one representing the inner surface of aortic valve (Mandrel I) and one fitting the scanned aortic root (Mandrel II) – were created before additive manufacturing. After designing the whole structure of the aortic valve system as well as the toolpaths for manufacturing, the three-dimensional printing process could start. Firstly, a sprayable silicone ink was diluted and deposited onto the surface of Mandrel I, after solvent evaporation and photo-curing, three soft silicone leaflets with specific thickness could be obtained. Afterward, the stripes of medium-stiffness silicone were extruded onto the soft leaflet surface to act as the reinforcing fiber. The following fabrication process of this heart valve system including the deposition of inter-leaflet triangles and the extrusion of an auxetic mesh pattern with the assistance of Mandrel II to fit the patient’s aortic root.

The orientation of the reinforcing fiber in this study is simplified into two representative architectures: 1) a horizontal design with circumferential aligned fibers (relative angle of 0°); 2) a bioinspired design with fiber oriented along the direction of maximal principal stress while diastole (relative angle of 30°). What’s more, a model with homogeneous structure but is much thicker is taken into comparison as well (Figure 8B). The stress distribution throughout these three samples and their hemodynamic performance during the cardiac cycles is simulated through finite element analysis. According to their simulation, as shown in Figure 8C, increasing the leaflets’ thickness could significantly reduce the maximum stresses, but also increase the minimum transvalvular pressure needed for opening the valve. The contradictory demand of facile opening and lower stress could be reconciled by the introduction of reinforcing fibers. With the stiffer fibers bearing most of the load, both the designs of fiber architectures could reduce the stress levels of the heart valve leaflets. In vitro hemodynamics tests with an applied frequency of 70 Hz have been done for assessment. Three valves with a thickness of 200 μm but with different designs of reinforcing fibers were tested and showing similar hemodynamic behavior. Besides, the two fiber-reinforced valves were more stable than the unstructured reference one while opening. The effective orifice area (EOA) and relative regurgitation volume (RV) of these valves during the cardiac cycle were also calculated, all the valves could fulfill the requirements in the standard ISO 5840.

6 | DISCUSSION

With the urgent demand of aortic valve prostheses with long lifespan, numerous conceptions of novel artificial valves have been reported, with the exquisite multilayered architecture of the native aortic valve leaflets providing inspirations for the structural and functional design. As summarized in Figure 9, these biomimetic aortic valves
are fabricated through different methods, such as injection molding and additive manufacturing. In addition to these biomimetic polymeric heart valves mentioned above, many novel methods have been taken into the fabrication of artificial heart valve. For instance, regenerative heart valve involving mesenchymal stem cells are also promising candidates for artificial heart valves. Attempts have been made with autologous mesenchymal stem cells derived from bone marrow. The complex of cells and biodegradable scaffold was experimented for several weeks in vitro and later implanted into the pulmonic valve location of sheep, and was observed uneventfully after 8 months. But unfortunately, none of the reported artificial heart valves meet all the requirements for an ideal heart valve prosthesis, after being developed and improved for many years. Additionally, due to the complex manufacturing process, the existing heart valve prostheses are still expensive. Even though some polymeric valves have been designed for low-income patients, they are mainly aimed at the rheumatic heart disease instead of calcific valve disease. Actually, there still remains a long way to go before these polymeric aortic valves could be widely used in clinical practice. In the above sections, we discussed the complex microstructure of aortic valve, especially the load-bearing leaflets in detail, hoping that this natural structure developed through a long period of evolution could provide new ideas for the design of artificial heart valve. In this section, we will discuss the progress as well as the challenges of the existing polymeric heart valve prostheses. Some suggestions for the designing of a more practical and durable aortic valve will also be proposed.

The leading requirement of an artificial heart valve is its stability, or the fatigue resistant ability. But it is extremely hard for the synthetic materials to maintain long-term stability under complex cyclic loads, especially in the blood environment. In recent years, fatigue performance of elastic materials such as hydrogels has been reported by many researchers. They found that comparing with some natural materials such as muscle and heart valve, synthetic materials always have weaker fatigue resistant ability, which could be reflected by the relationship between the toughness and threshold of the materials. Figure 10 shows a threshold-toughness chart, where toughness refers to the total energy release of a material under monotonic load and threshold corresponds to an energy release rate of cyclic load, under which the material would present no fatigue phenomenon such as crack propagation. Clearly, all the materials locate under the diagonal of the chart because the threshold is always lower than the toughness. Besides, those commonly used tough materials mostly have threshold lower than their toughness by one or two orders of magnitude.

Inspired by the elegant microstructure of the native heart valve, many novel biomimetic heart valves have been reported recently. As the simulation of stress distribution and hemodynamics of the aortic valve conducted by Coulter et al. indicated, the addition of fibers onto the leaflets’ surface could largely decrease the stress level...
throughout the valve at the diastolic state and at the same time guarantee a low minimum transvalvular pressure needed for opening the valve. The aligned collagen fibers are considered as the most important structure of the leaflet in almost all these studies. According to this, one of the main designing conceptions of the biomimetic heart valves is to reinforce a soft matrix with stiff fibers. Besides, although the injection molding of block copolymers did not introduce another component into the design, the controlled orientation of molecular are considered to play the same role as the collagen fibers in the native valves. Thus, the aligned structure for load bearing is believed to disperse the stress and thereby improve the overall performance and extend the lifespan of the aortic valve.

But the natural materials always have a complex structure in multi-scales. The collagen fibers do take important roles in the motion of the native aortic valve, but the contribution of structure features in other scales and other components to aortic valve’s performance should not be neglected. As discussed above, the flexibility and fatigue resistance of the native valves are believed to come from the cooperation of components like collagen fibers, elastic fibers, GAGs, and the corresponding structures in different scales. When the valve begins to close, the relatively stronger collagen fibers would not immediately bear the load. The extension of scrimps as well as the elastic fibers allow collagen fibers to have a small strain when the valve is totally closed, which largely reduce the energy released by the collagen fibers and thereby reduce their likelihood of fatigue damage. On the contrary, the role of multiscale structures was rarely taken into consideration in these reported biomimetic heart valves, and the reinforcing fibers would always function as load-bearing structure during the opening process because of their larger modulus. This cyclic motion with large strain is always closely related to the material’s fatigue damage. As a result, if the material used as the artificial valve’s leaflets is working beyond its threshold (which may be related to a low strain especially for the stiff reinforcing material), fatigue damage would definitely occur and thus influence the valve’s mechanical and hemodynamics properties. Therefore, the structural design of heart valve prosthesis in different scales is essential for keeping the valve working under all the components’ threshold to avoid catastrophic fatigue damage of the valve.

From another aspect, the studies on fatigue performance of elastic materials provide some strategies for us to improve the materials’ threshold. For example, anti-fatigue-fracture hydrogels could be obtained by increasing the crystallinity of polyvinyl alcohol (PVA) hydrogels by extending the annealing time after freeze-thawing and air drying. By mechanical training, aligned nanofibrillar architectures would be developed inside the freeze-thawed PVA hydrogels to achieve a high fatigue threshold. Except for some anti-fatigue design of specific materials, some principles of fatigue resistance of general materials have been proposed. These principles require a matrix reinforced by stiff fibers, which is consistent with some design conceptions of biomimetic heart valves. In addition, strong interface adhesion between the two components and the matrix’s high resistance to shear deformation are also required for stretchable and fatigue-resistant materials. What’s more, the natural materials with complex multiscale structure are believed to have multiscale toughening mechanism, for example, the nanofibrous structure as well as the crystalline structures inside the nanofibers of the muscle are considered to be able to absorb large amount of energy to prevent the propagation of cracks, which is also important to the material’s fatigue-resistant performance.

More importantly, these reported biomimetic heart valves are based on the existing knowledge of the structure and function of native heart valves. However, we need to acknowledge that this knowledge is far from comprehensive and thorough. More structural and functional studies should be performed on both healthy and failed native heart valve for a comprehensive understanding of their mechanical and hemodynamic properties as well as their failure mechanism. This requires collaboration among researchers from multiple fields including medical, material, engineering, and computer science.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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