Valvular Heart Diseases: Insights and Perspectives

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Abstract

Heart valves maintain the unidirectional blood flow ensuring effective cardiac functioning. Currently, over 74 million people worldwide suffer from valvular heart ailments such as regurgitation and stenosis. This review focuses on the structures and mechanisms of the four major valves, aortic, mitral, tricuspid, and pulmonary valves comprehending the biology and clinical aspects of both congenital and acquired valvular diseases. This manuscript reviews emerging updates in transcatheter mitral valve repair, transcatheter aortic valve replacement, and stem cells based approaches for the management of various valvular diseases. Additionally, the article provides insights into computational models and artificial intelligence in next generation valvular therapies.

Introduction

The human heart consists of four chambers, left and right ventricles and left and right atriums (Figure 1). The heart valves ensure unidirectional flow of blood by facilitating the movement of deoxygenated blood into the lungs and circulating oxygenated blood throughout the body[1]. Impairment in the functions of heart valves significantly affects the pumping efficiency and heart function. Common valve diseases include valvular stenosis, valvular regurgitation, ventricular dysfunction, arterial dilation, and atresia. Clinically, valve diseases arise congenital or acquired. Congenital valve disease includes abnormal valve shape, size, structure, and formation of leaflets[1], whereas acquired heart diseases include rheumatic fever, infective endocarditis, and aging[2]. Regurgitation refers to the backward flow of blood resulting from inadequate closure of the valve. Stenosis is characterized by the thickening of the valve leaflets. Atresia describes the absence of a valve. Among these valve dysfunctions, mitral regurgitation(MR) is an especially important case, involving mitral arrhythmias or heart failure. This dysfunction may require surgical intervention, such as valve repair or replacement. During mitral valve regurgitation, the valve leaflets do not close properly, causing the backward flow of blood Individuals with this condition often experience an irregular and rapid heartbeat, higher blood pressure, and congestive heart failure. Although it appears to be mild and progress slowly, it can still pose serious health risks[3].

Valves are responsible for opening and closing to ensure blood flows in the correct direction, also known as “one-way valves”. They allow blood, carrying oxygen and nutrients, to be delivered to the cells while also removing waste products. The sound of a heartbeat is created by their opening and closing. For the heart to function efficiently, its valves need to function properly; otherwise, the heart is forced to exert more energy to pump blood, or diseases may develop. One of the major challenges of valvular diseases is heart failure, as the heart must pump harder to compensate for poorly functioning valves[4].

Valves Biology

The heart contains four main types of valves: the tricuspid valve, pulmonary valve, mitral valve, and aortic valve (Table 1) (Figure 1). Each valve plays a crucial role in regulating blood flow through different chambers and vessels of the heart. The tricuspid valve regulates blood flow between the right atrium and the right ventricle, while the pulmonary valve regulates blood flow from the right ventricle to the pulmonary artery. The mitral valve manages blood flow

between the left atrium and left ventricle, and the aortic valve controls blood flow from the left ventricle into the aorta.

Generally the valve function depends on the contraction and relaxation of the heart muscle, causing the opening and closing of the valves, which allows unidirectional flow[5]. The four valves are being separated into two categories: Atrioventricular valves (tricuspid and mitral) and semilunar valves (Aortic and Pulmonary).

The tricuspid consists of three cusps or leaflets: the anterior, posterior, and septal leaflets. The base of each cusp is anchored to a fibrous ring called the annulus that provides stability. Thin, string-like structures, called chordae tendineae, connect the edges of the valve leaflets to the papillary muscles in the right ventricle, preventing the valve leaflets from being pushed backward into the right atrium that causes backward blood flow. The papillary muscles pull on the chordae tendineae, ensuring the integrity of valve leaflets The mitral valve has the similar structure as the tricuspid valve, but has two leaflets: anterior and posterior. The aortic valve has three cusps: right, left, and posterior and annulus located at the base of the valve to stabilize it. Unlike the atrioventricular valves, the aortic valve does not require chordae tendineae for support. Instead, the cusps are stabilized by the pressure of the blood flowing through the valve. There are small pockets behind each cusp known as aortic sinuses that help to maintain the valve's shape and function. The pulmonary valve has the similar structure characteristics as the aortic valve[6].

Heart Valve	**Anatomy**	**Function**
Tricuspid Valve	Three leaflets (anterior, posterior, and septal); supported by chordae tendineae and papillary muscles.	Regulates blood flow from the right atrium to the right ventricle and prevents backflow.
Pulmonary Valve	Composed of three semilunar cusps (anterior, left, and right); located between the right ventricle and pulmonary artery.	Regulates blood to flow from the right ventricle into the pulmonary artery and prevents backflow.
Mitral Valve	Two leaflets (anterior and posterior); supported by chordae tendineae and papillary muscles.	Regulates blood flow from the left atrium to the left ventricle and prevents backflow.
Aortic Valve	Composed of three semilunar cusps (left, right, and posterior); located between the left ventricle and aorta.	Regulates blood flow from the left ventricle to the aorta and prevents backflow.

Table 1: Overview of heart valves.

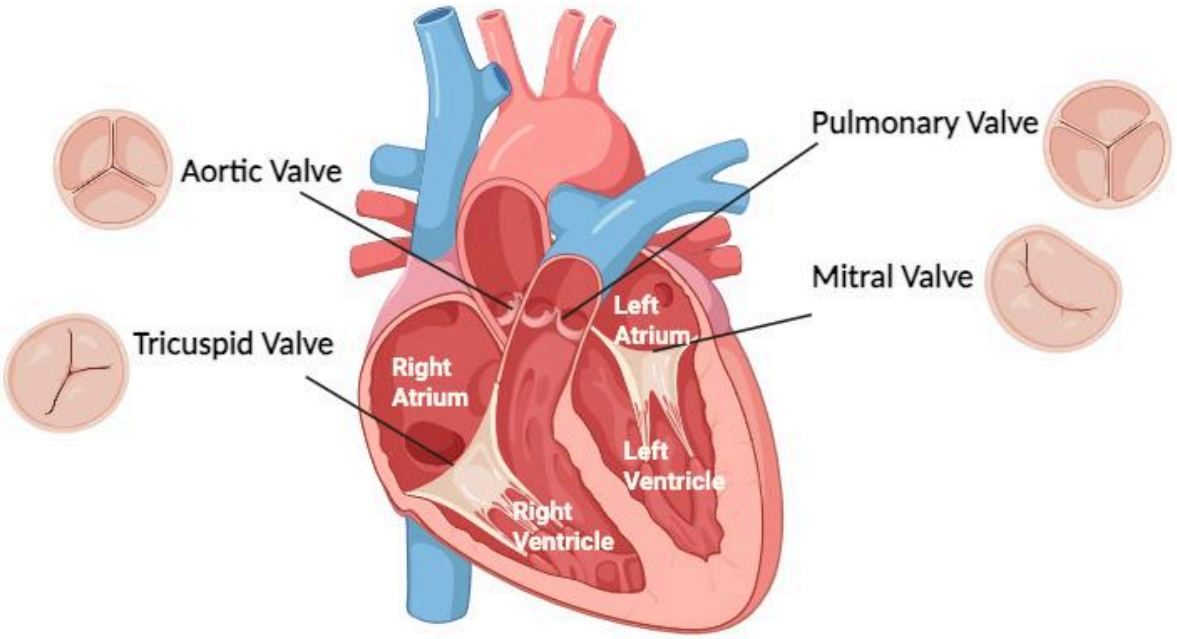

Figure 1: Anatomy of heart and valves

Valvular Pathology

A valvular disease develops whenever there is a dysfunction (Table 2) [7].Tracking to embryology, the heart has the role of pumping blood, which creates the circular pattern of blood flow. In the United States, there are about 500,000 adults who have congenital heart disease[8]. There is a 5 to 6 percent chance of congenital heart defects caused by the abnormality of an infant's chromosomes, a 3 to 5 percent cause from single gene defects, and a 2 percent cause from environmental factors[9]. 1 in every 100 children have congenital heart defects caused by genetic or chromosomal abnormalities[8]. Congenital valve disease mainly emerges from an abnormal valve development during the embryonic period, within the first six weeks of pregnancy, when the heart is developing from a simple tube-like structure into a more structured heart[10]. Also, seizure disorders, phenylketonuria, insulin-dependent diabetes, during pregnancy have been reported to have a higher risk for congenital heart disease[9]. Additionally, heart valve defects include stenosis, heart muscle abnormalities, a hole located on the wall of the heart, heart failure, and atherosclerosis aggravates the pathology. Congenital valve disease occurs when the valves do not develop properly before birth. It can be difficult to detect until middle age. Symptoms include chest pain, dizziness, fatigue, shortness of breath, and heart murmurs[11]. Types of congenital valve disease include aortic valve stenosis, coarctation of the aorta, Ebstein's anomaly, patent ductus arteriosus, pulmonary valve stenosis, and more[12].

Acquired valve diseases refers to conditions that develop after birth, especially aortic and mitral valves are the most common sites for valvular heart diseases. Aging and pre-existing diseases also leads to acquired valvular disease characterized by hardening of the tissue and restriction in blood flow. Two major clinical problems are regurgitation and stenosis. For

example, aortic stenosis results in a compromised blood flow that impairs cardiac function resulting in ventricular hypertrophy[13].

Treatment of valve disease starts with changing to a healthy lifestyle or medications. Eventually, in severe cases, the heart valve request repaired or replaced. Medications diuretics and vasodilators help with controlling blood pressure thereby relieving valvular workload. Surgical approach has been prescribed for fixing valve leaflets including positioning, reshaping, reattaching or separating the leaflets.

Type of Valve Disease	Causes	Symptoms	Treatments
Congenital Valve Disease	Genetic mutations, abnormal valve development during fetal life.	Shortness of breath, fatigue, heart murmur, cyanosis.	Medications, surgery (valve repair or replacement), minimally invasive procedures.
Acquired Valve Diseases	Aging, other heart conditions, infection, calcification.	Shortness of breath, chest pain, fatigue, dizziness, and swelling in legs.	Medications, surgery (valve repair or replacement), minimally invasive procedures.

Table 2: Types of valve diseases.

Challenges

Early diagnosis of valvular diseases are challenging because they remain asymptomatic; however, early interventions improve the chances of recovery[14]. Diagnostic tests, such as echocardiogram, chest X-ray, stress test, and screening tests are necessary for detection. Unfortunately, many patients often attribute their symptoms to easier causes such as lack of rest or high levels of stress[15]. As a result, patients experience serious complications including heart failure, stroke, thrombogenesis, arrhythmias, infection, pulmonary hypertension, and death in severe cases[16].

Additionally, the risk factors include age, poor hygiene and nutrition, and hurdle valve treatment. In the United States, approximately 13.2% of individuals aged 75 years or above are experiencing modern to severe valvular heart disease[17]. In many developing countries, access to treatments is limited due to underdeveloped healthcare systems or financial struggles. Therefore, improvements in healthcare practices are warranted[18]. Surgical challenges include, heart valve infections, excessive bleeding, transient ischaemic attack and kidney dysfunction. Even though the risk of mortality is about 2%, surgical interventions are likely to induce undesirable outcomes[19].

Emerging Treatments

As technology advances, innovative treatments and interventions are emerging. Transcatheter Aortic Valve Replacement (TAVR) (Figure 2) is a procedure to replace a narrowed or diseased aortic valve to treat aortic stenosis[20]. TAVR offers an alternative to traditional surgery, allowing for faster recovery. During this minimally invasive procedure, employing

catheter, artificial or xenogeneic valves are used to replace the damaged aortic valve [21]. Similarly, Transcatheter Mitral Valve Repair (TMVR) (Figure 2) is another minimally invasive procedure used to repair a damaged mitral valve. During TMVR, a catheter clips to fasten the leaflets to prevent backflow of blood and leakage. The clip closes the valve partly, allowing the blood flow[22].

Currently, mesenchymal stem cells (MSCs) (Figure 2) are emerging to regenerate damaged valve tissue. MSCs from bone marrow and fat tissue have the potential to differentiate into valvular interstitial cells (VICs) or valvular endothelial cells (VECs). VICs are abundant in fibrosa, spongiosa, and the ventricularis layers of the valve[23]. These cells are organized into five phenotypes and functions to maintain the physiological valve structure and function, allows to activate cellular repair processes (proliferation, migration, and matrix modeling), and calcification in the heart valve[24]. VECs play a crucial role in valvular leaflets integrity including protection against calcification, inflammation and fibrosis[25]. MSCs derived VICs and VECs are promising to repair or replace the damaged valve tissue through minimally invasive injection thereby avoiding complicated surgical procedures[26].

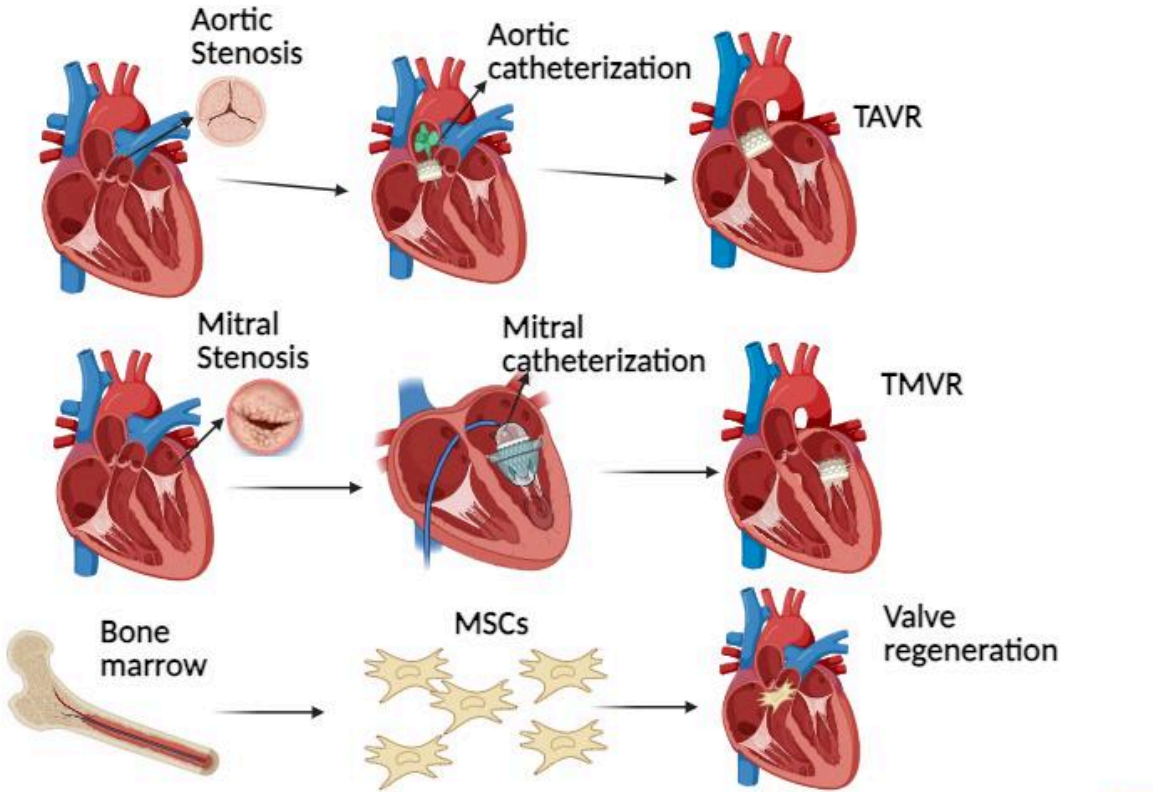

Figure 2: Approaches in valvular disease managements

Current-state-of art

Currently practiced heart valve replacements have clinical limitations. Mechanical valves require lifelong use of blood thinners, while bioprosthetic valves wear out within 10 to 20 years. Interestingly, a bioengineered valve could address these issues by lasting longer and growing with the patient. Creating a bioengineered valve involves advanced techniques such as

nanotechnology, 3D printing, and tissue engineering[27]. Researchers aim to develop bioengineered heart valves that closely mimic the function of natural heart valves. One approach is self-seeding valves, which offer a faster and more practical alternative to traditional bioengineered valves. Instead of growing patient cells in a lab prior to implantation, which is a slow and complex process, self-seeding valves are coated with antibodies that attract the host cells post-implantation[28].

X-linked cardiac valvular dysplasia is a genetic condition that affects the heart valves, causing them to thicken and malfunction. One or more heart valves become thickened and fail to function, leading to blood leaking through the affected valves, most commonly the mitral or aortic valve. Valve regurgitation induces cardiac overload, potentially causing symptoms such as chest pain and shortness of breath. Additionally, the mitral or aortic valve prolapse, further preventing proper closure and causing valve regurgitation[29].

Of the more than 300,000 heart valve replacements performed worldwide each year, 40% to 60% are xenograft bioprosthetics[30]. A xenogenic heart valve is a valve transplanted from an animal to a human, typically from pig or cow tissue[31]. Pig hearts closely resemble human hearts, allowing for direct transplantation, whereas cow heart tissue requires further modifications. Animal models, particularly pigs and sheep, are commonly used in heart valve research because their heart anatomy and valve structure closely resemble those of humans. Smaller animals such as chickens, mice, and zebrafish are used to study congenital valve disease, as their embryos can be easily manipulated to examine how specific genes or environmental factors influence valve formation. Larger animals, including sheep and pigs, are used to test new valve replacement and repair devices due to their heart size, structure, and biological responses. For example, mouse embryo models are effective to study different genes on cardiac and valve development, as well as lineage tracing of cells. Zebrafish and chicken embryos, which have transparent heart tissues, allow for high-resolution imaging of the heart and vasculature, as well as monitoring of blood flow dynamics. Chicken embryos are particularly useful for surgical interventions that alter hemodynamics in heart development[32].

An important study demonstrated for the first time that lab-created heart valves implanted in young lambs showed reduced calcification and improved hemodynamics after one year follow-up. This approach has the potential to provide a growing heart valve for children with congenital heart disease, reducing the need for multiple heart surgeries. Currently, growing heart valves are limited, demanding multiple surgeries and cost[33].

Computational models of heart valves use numerical simulations to study the mechanics, fluid dynamics, and interactions between valve structures and blood flow. Bioprosthetic heart valves (BHVs) are commonly used to replace damaged heart valves, their durability remains a challenge. Computational models help researchers understand the mechanisms behind BHV deterioration and optimize new valve designs. Key components of these models include accurate representations of valve structures, realistic biomaterial properties that change over time, and appropriate physiological conditions[34].

Future Perspective

Artificial intelligence, a revolutionary advancement in cardiovascular disease treatment, has been increasingly used in the diagnosis and treatment of valvular heart disease. AI has the ability to detect clinical signs that might be missed or misinterpreted by a physician. Evidently, AI detects audible valvular heart diseases, which is twice as accurate as physical examination by a physician. Additionally, AI assists in ECG interpretation, particularly in identifying specific

patterns associated with valvular heart disease that are yet to be achieved. Contrastingly,out of 33,371 patients, AI detected moderate to severe aortic stenosis in 1,224 cases. However, the positive predictive value was only 10%, while the negative predictive value was 99%, suggesting that AI produces a high rate of false positives. Hence, further improvements in AI algorithms are warranted. Ultimately, the use of robots in performing surgical procedures represents the most advanced application of AI in valvular heart disease treatment. Currently, these robotic systems have only been tested in animal experiments, however the field is rapidly developing[35].

Conclusion

In conclusion, congenital and acquired valvular heart diseases elicit serious threats to global cardiovascular health. Developments in diagnostic methods, surgical procedures, and stem cell therapies offer support to millions of sufferers. Early diagnosis remains a major problem and further research and advancements in artificial intelligence are required to improve treatments, especially in surgery and diagnostic accuracy. Additionally, further research into bioengineered valves and minimally invasive procedures are warranted to design personalized solutions.

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