Etiology of Valvular Heart Disease in the 21st Century

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Key Words

Valvular heart disease · Calcification · Atherosclerosis · Etiology

Abstract

A metamorphosis in the etiology of valvular heart disease (VHD) has occurred over the last 6 decades. In this review, the factors contributing to this metamorphosis, the common causes of VHD today, the relationship of valvular calcification to atherosclerosis and the interrelationship of VHD with other systems/organs are presented.

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Valvular heart disease (VHD) can be defined as a structural or functional abnormality of a cardiac valve. This is a generic term that includes several etiologic entities with different pathophysiologic mechanisms, presentations and natural histories. Disruption of the anatomic integrity of a cardiac valve may produce valvular stenosis, valvular regurgitation or a combination of the two. Structural abnormalities of a cardiac valve often produce surface phenomena, which may be associated with platelet aggregation and microorganism accumulation predisposing to thromboembolism and infective endocarditis. In addition to intrinsic valve pathologies, cardiomyopa-

thies or other causes of myocardial dysfunction can result in mitral and/or tricuspid regurgitation, even in the absence of intrinsic structural valve abnormalities, presumably due to abnormal mechanical stresses that lead to the distortion of normal valves and of the subvalvular apparatus; similarly, aortic regurgitation can develop from abnormal mechanical stresses acting on an intrinsically normal aortic valve in the setting of aortic root disease and dilatation [1, 2].

Changing Distribution of VHD Etiologies and Contributing Factors

The distribution of VHD etiologies has changed markedly over the last 60–70 years. Several factors have contributed to this alteration (fig. 1). Rheumatic fever and syphilis, very common causes of VHD in the first half of the last century, have almost disappeared in industrialized countries. Increased life expectancy over the last several decades has enabled expression of progressive structural alterations associated with aging including aortic valvular calcification and mitral valve mechanical distortion from floppy mitral valve (FMV)/mitral valve prolapse (MVP) resulting in significant aortic stenosis and mitral regurgitation, respectively [3]. The incidence of ischemic cardiomyopathy has increased as mortality

Fig. 1. Factors contributing to the metamorphosis of the etiology of VHD (modified from [2]).

from myocardial infarction has fallen, and heart failure management has improved, prolonging survival; the ventricular morphologic distortion of cardiomyopathy often causes secondary valve dysfunction, magnified in their expression associated with prolonged survival. Increased survival among patients with chronic kidney disease, especially those on dialysis, has increased the prevalence of VHD partially due to pathologic calcification of valves secondary to hyperparathyroidism that is often present in these patients. With the increasing prevalence of VHD, there has been a rapid development of and increasing application of interventions (e.g. valve replacement with prostheses and valve repair) which has replaced the original disease with a new, less morbid and lethal type. In addition, diseases that were not always recognized previously, such as acquired immune deficiency syndrome (AIDS) and Kawasaki disease, are more frequently observed and may be associated with VHD [1–3].

Recent data have suggested that certain intrinsic valve abnormalities (calcific aortic stenosis and mitral annular calcification) may be related to atherosclerosis. However, while metabolic pathways similar to those of atherosclerosis exist in the heart valves, current research suggests that these pathways deviate at a crucial point from the atherosclerotic pathways and result directly in calcification rather than atherosclerosis.

Despite the reduction of rheumatic fever in industrialized countries, VHD constitutes a major public health problem due to the relatively high incidence of heritable/congenital valve disorders, the continual aging of the population and the tendency of valve lesions to worsen with age [4–7]. Recent advances in imaging technology have allowed early detection in vivo of mild valve dysfunction (or even more severe in some cases), previously

clinically silent and undetectable until autopsy (if performed) and, even then, not necessarily detectable if the valve dysfunction was not associated with obvious structural abnormality [2–8]. In addition, advances in technology have allowed precise definition of the structural and functional abnormalities of VHD, enabling etiologic classification of VHD in vivo. Accurate etiologic classification of VHD in vivo has enabled definition of the metamorphosis of etiology of VHD over time [1, 2, 5, 9–12].

Recent epidemiologic studies in adults suggested that the prevalence of VHD increases from <1% among subjects aged <45 years to approximately 15% among those ≥75 years of age [8]. Likewise, the Framingham study suggests that in adults between 50 and 60 years of age, the prevalence of VHD (mild or greater) is approximately 19% for mitral regurgitation in both men and women, 18.4% for tricuspid regurgitation in women and 14.8% in men and 13.0% for aortic regurgitation in men and 8.5% in women [10].

In this brief review, the etiology of VHD in the 21st century, some possible molecular-pathophysiologic mechanisms underlying VHD and the interrelationship of VHD with other organs will be presented.

VHD Etiology

The major pathophysiologic entities associated with VHD are shown in table 1.

Heritable – Congenital VHD

Heritable Disorders of Connective Tissue

Connective tissue abnormalities are of etiologic importance in a broad spectrum of cardiovascular disorders. Marfan syndrome and Ehlers-Danlos syndrome represent well-known examples of this association. Many isolated cardiovascular abnormalities due to connective tissue disorders have also been identified, such as FMV/MVP, multivalvular prolapse, annuloaortic ectasia, certain types of aortic regurgitation and pulmonary artery dilatation [1–3, 11, 12].

Marfan syndrome is associated with multiple valvular abnormalities, including FMV/MVP, floppy tricuspid valve/tricuspid valve prolapse, aortic root dilatation, aortic regurgitation and aortic valve prolapse. This is an autosomal dominant disorder that is extremely pleiotropic with cardiovascular, ocular and skeletal system involvement. The phenotypic expression of the syndrome has been associated with several different mutations of the gene encoding fibrillin-1 located on chromosome 15 (15q21.1) [3, 11].

Table 1. Etiologies of VHD

I.	Heritable – congenital
i.	Heritable disorders of connective tissue (Marfan syndrome, Ehlers-Danlos syndrome, polycystic kidney disease and isolated abnormalities)
ii.	Congenital valve disease and etiology unclear (bicuspid aortic valve disease, endocardial cushion defects with mitral clefts)
iii.	Environmentally determined (pulmonic stenosis in maternal/fetal infection, e.g. rubella)
II.	Inflammatory – immunologic (rheumatic fever, syphilis, AIDS, Kawasaki disease, ankylosing spondylitis, systemic lupus erythematosus and antiphospholipid syndrome)
III.	Endocardial disorders
i.	Noninfective (NBTE)
ii.	Infective
IV.	Myocardial diseases (ischemic-nonischemic and hypertrophic cardiomyopathy) – diseases of other organs
V.	Neoplastic (carcinoid, myxoma and fibroelastoma)
VI.	Degenerative (related to aging, possible genetic and environmental predisposing factors)
VII.	Iatrogenic valve disease: surgical valve repair and interposition of devices (valvulotomy, reconstruction and valve replacement)
VIII.	Drugs and physical agents (e.g. radiation and trauma)
IX.	Infiltrative (mucopolysaccharidoses and hypereosinophilic syndrome)
X.	Idiopathic
Modified from [1] and [2].	

Ehlers-Danlos syndrome is often associated with FMV/MVP, aortic root or sinus of Valsalva enlargement and aortic regurgitation. Bicuspid aortic valve may also be present.

Adult polycystic kidney disease is associated with aortic root dilatation and aortic regurgitation, FMV/MVP, bicuspid aortic valve and tricuspid valve prolapse.

Osteogenesis imperfecta, several of the mucopolysaccharidoses and other metabolic abnormalities may also be associated with VHD.

Heritable disorders of connective tissue, as a general rule, are genetically transmitted like in Marfan syndrome, though the specific genetic variants and pattern of inheritance are often not known (as in most patients with bicuspid aortic valve). Nonetheless, the offspring of pa-

tients with these abnormalities may have the same disease and should be evaluated [1–3].

FMV associated with MVP is considered a connective tissue disorder and it is present in 2–3% of the general population. MVP occurs when one or both mitral leaflets or parts of them extend above the plane of the atrioventricular junction during left-ventricular systole. Progressive mitral regurgitation, rupture of the chordae tendinae, infective endocarditis, thromboembolic events, cardiac arrhythmias and congestive heart failure are potential sequelae of FMV/MVP that increase in frequency with age. FMV (diffuse or regional) is the central issue in the genesis of MVP-mitral valvular regurgitation. FMV/MVP is heritable with dominant transmission and different degrees of penetrance. At least three gene loci related to MVP have been identified (fig. 2). Another rare form is transmitted via chromosome X [3, 12–15].

Tricuspid valve prolapse, which also may be associated with MVP, is considered a connective tissue disorder [3, 12].

‘Annuloaortic ectasia’ describes aneurysmal dilatation of the aortic annulus and ascending thoracic aorta; in affected patients there is evidence of cystic medial degeneration (‘necrosis’) without evidence of connective tissue disease in other organs. Aortic regurgitation is usually present in this abnormality [1, 2, 12].

Congenital Valve Disease – Etiology Unclear

Bicuspid aortic valve without clinically significant aortic stenosis at birth is a common congenital abnormality in adults, with a male predominance. It is estimated that approximately 2% of live births have bicuspid aortic valve. Patients with bicuspid aortic valve may develop aortic regurgitation that is apparent relatively early in life, but more commonly, they develop aortic stenosis, generally apparent in the 4th decade of life or later. The rate of progression of aortic stenosis in patients with bicuspid aortic valve is related to the variations in bicuspid aortic valve anatomy and possibly to risk factors related to atherosclerosis. A bicuspid aortic valve often is associated with aortopathy featuring aortic root dilatation, relatively high proclivity for aortic dissection or to functional abnormalities of the aorta. Bicuspid aortic valve may also be present in patients with aortic coarctation. Bicuspid aortic valve appears to be familial and at least three gene loci have been defined (fig. 2) [16–19].

Coarctation of the aorta may be associated with bicuspid aortic valve, aortic stenosis, aortic regurgitation and aortopathy. Congenital mitral stenosis is extremely rare in adults. Mitral regurgitation may be present in atrioven-

Fig. 2. a Genetics of FMV/MVP. Arrow = proband, circle = females, squares = males, shaded symbols = family members with FMV/MVP or mitral regurgitation, diagonal slashes through symbols = deceased members (pedigree modified from [3]). b. = Year born; CHF = congestive heart failure; MVR = mitral valve regurgitation. **b** Genetics of bicuspid aortic valve disease.

tricular septal defects and corrected transposition of the great vessels. Aortic regurgitation may be present in patients with a high ventricular septal defect. Pulmonic regurgitation is often seen in patients with tetralogy of Fallot [1, 2, 20].

Environmentally Determined VHD

Congenital pulmonic stenosis, whether or not associated with other congenital anomalies, may be seen when the mother is exposed during pregnancy to an infection, especially rubella [21]. This type of valve disease is not common today in industrialized countries.

Inflammatory – Immunologic

Rheumatic fever primarily affects the mitral and aortic valves, though in some populations, particularly in South America, for unclear reasons tricuspid involvement is also relatively common [22, 23]. The initial clinical presentation of rheumatic mitral valvulitis is mitral regurgitation. The most common chronic valvular abnormality resulting from rheumatic fever is mitral stenosis. Aortic valve insufficiency is also common, sometimes associated with aortic stenosis; however, pure aortic stenosis is seldom of rheumatic etiology and some authorities claim it never occurs [24, 25]. Although the incidence of rheumatic fever has decreased dramatically in industrialized countries, it is still very common in developing countries [1, 2].

Despite the significant reduction in cardiovascular syphilis, cases still occur. Aortitis occurs in the tertiary form of syphilis in 70–80% of patients. Aortic regurgitation is the most common complication of syphilitic aortitis.

Cardiac involvement in AIDS includes myocardial, pericardial or endocardial disease with valvular involvement. The most common valvular lesion reported in patients with AIDS is nonbacterial thrombotic endocarditis (NBTE) with valvular vegetation formation that can be present on all four valves, though left-sided lesions are more common. Vegetations consist of platelets within a fibrin mesh and few inflammatory cells. Thromboembolic phenomena may occur, but clinically are underestimated compared to autopsy studies [26].

Kawasaki disease is an acute febrile illness that affects infants and young children. Vasculitis of common arteries may occur in 20% of the patients. Less often, mitral regurgitation, acute or chronic, may also be seen [27].

Aortic regurgitation, secondary to aortic dilatation, is the primary valvular abnormality seen in patients with ankylosing spondylitis. The aortic annulus is dilated and therefore the cusps cannot coapt to completely cover the area of valve outflow. Mitral valvular regurgitation can also occur.

Systemic lupus erythematosus may produce mitral valve and tricuspid valve disease (Libman-Sacks). It has been suggested that the presence of antibodies against phospholipids is associated with a higher incidence of valvular abnormalities in patients with lupus [1, 2].

Antiphospholipid syndrome is defined as elevated serum levels of antiphospholipid antibodies associated with thromboembolic phenomena without diagnostic criteria of systemic lupus erythematosus or any other disease that may be responsible for the antibodies. Studies have shown an association of this syndrome with mitral or aortic valve thickening, which may be associated with mitral or aortic regurgitation [28]. Other studies have suggested, howev-

er, that certain forms of VHD stimulate generation of antiphospholipid antibodies, which in turn predispose to thromboembolic events [29–31].

Endocardial Disorders

Noninfective Disorders

NBTE, called ‘marantic endocarditis’ in earlier literature, most often occurs in patients with malignant disease, but may also complicate other wasting diseases such as uremia and AIDS. Endothelial damage caused by circulating cytokines, tumor necrosis factor, interleukins and others, which are increased in patients with malignancy or chronic wasting diseases, may trigger platelet deposition. Sterile vegetations in Libman-Sacks endocarditis, a form of NBTE, sometimes develop in patients with systemic lupus erythematosus and the antiphospholipid syndrome [28]. NBTE used to be diagnosed at autopsy, but with current imaging techniques (e.g. 2- and 3-dimensional transesophageal echocardiography) NBTE can be identified in vivo [5].

Infective Disorders

In the 19th century, Sir William Osler defined infective endocarditis as, ‘Inflammation of the lining membranes of the heart... usually confined in the valves, so the term is practically synonymous with valvular endocarditis’ [1, 2]. Since that time, the nature of infective endocarditis has changed. Major factors have contributed to the metamorphosis of infective endocarditis over the last 5–6 decades including the almost complete disappearance of rheumatic fever and syphilis in industrialized countries (previously the two most common causes of VHD and therefore the most common predisposing factors for infective endocarditis in the past), increased life expectancy, the use of implantable cardioverter defibrillators and intracardiac leads for pacing as well as the implantation of other devices intended for more or less permanent residence in the body, the use of catheters indwelling for hours or days for hemodynamic monitoring or fluid or drug infusion, increasing numbers of patients with prosthetic valves, transplanted organs (kidney, heart and liver) and increasing numbers of immunocompromised patients for reasons other than prophylaxis for organ transplantation. Although endocarditis can develop in previously normal valves, it occurs most often when VHD or congenital heart disease already exist. An important factor in the development of infective endocarditis is the abnormal surface area of the valve rather than the leakage of the valve per se. Infective endocarditis is often seen in patients with FMV/MVP, even with

minimal or absent mitral regurgitation, but has almost never been described in patients with cardiomyopathy and significant mitral or tricuspid regurgitation, who generally have a normal valve surface area. Infective endocarditis may result in vegetations, acute valvular regurgitation and thromboembolic phenomena. In intravenous-drug abusers, acute tricuspid or pulmonic valve endocarditis is particularly common. Incidence of infective endocarditis is estimated as 4–5 cases per 100,000 person-years with a male to female ratio of 2 to 2.5:1. The incidence of infective endocarditis increases with age and is thus less common in children [1, 2, 32–34]. The distribution of infective endocarditis ranges from 24 to 45% for the mitral valve alone, from 5 to 36% for the aortic valve alone and 5 to 35% for the aortic and mitral valves combined [1, 2].

Failure to decrease the incidence of infective endocarditis in the antibiotic era may be related to aging of the population associated with pathogenetic factors not apparent in younger people, increased use of invasive procedures and prosthetic valve implantations, survival into adulthood of many patients with congenital heart disease who would have died in infancy or childhood in earlier eras, development of particularly virulent pathogens by natural selection, recurrence of infective endocarditis in patients who survived an initial episode, but continue to manifest predisposing factors (many unknown) and improving methodology for detecting the disease. This last is particularly important because infective endocarditis can present with a wide variety of symptoms and findings that can involve any other organ or system in addition to the heart. It follows that diagnosis and management require a high index of suspicion, clinical experience, clinical judgment and common sense [2].

Myocardial Diseases – Diseases of Other Organs

Mitral regurgitation and tricuspid regurgitation are common in patients with ischemic and nonischemic cardiomyopathy (fig. 3). This is related to papillary muscle displacement due to left-ventricular dilatation, papillary muscle dysfunction, fibrosis, distortion of the subvalvular apparatus and dyssynchrony of left-ventricular contraction. Annular dilatation may occur, but at the very late stages of the disease [1, 2, 35, 36]. Chronic left-ventricular dilatation alone is not a common cause of functional mitral regurgitation. Studies have shown that the prevalence of functional mitral regurgitation is very low in left-ventricular dilatation secondary to chronic aortic regurgitation. In this case, elongation of the mitral valve leaflets appears to prevent mitral regurgitation [37].

Fig. 3. Factors contributing to the development of mitral regurgitation in ischemic and nonischemic cardiomyopathy.

Mitral regurgitation is common in patients with hypertrophic cardiomyopathy. It is related to the systolic anterior motion of the mitral valve that may produce obstruction of the left-ventricular outflow tract as well as mitral regurgitation. A recent study using magnetic resonance imaging techniques demonstrated elongated mitral valve leaflets independent of other disease variables, which most likely constitutes a primary phenotypic expression of the disease and contributes to left-ventricular outflow obstruction [38].

Data also suggest that atrial fibrillation can produce mitral regurgitation that improves if sinus rhythm is restored [39].

Patients with chronic kidney disease, especially those on chronic dialysis, often have VHD. Mitral and tricuspid regurgitation have been reported in 38 and 37% of patients, respectively. Mitral annular calcification was present in 35% of the patients. Aortic calcification, which is often associated with aortic stenosis or regurgitation, is also not uncommon [40, 41]. The underlying basis for valve disease in chronic kidney disease, like the basis of the unusually high prevalence of coronary artery disease, is not well understood.

Neoplastic VHD

Cardiac abnormalities occur in 60–70% of patients with carcinoid heart disease, but clinically apparent disease is less common and predominantly involves right heart valves (only 25% of those with cardiac abnormalities develop clinically apparent right-sided VHD). The

tricuspid and the pulmonic valve are the most commonly affected in carcinoid heart disease, but, less often, left-sided VHD also has been described. Carcinoid plaques composed of fibrous connective tissue with no elastic fibers may appear on either the atrial or the ventricular side of the leaflets [42].

Intracardiac myxomas are the most frequent benign tumors of the heart. Although myxomas have been reported as originating from the mitral annulus, the mitral valve and the aortic valve, most likely, true myxomas arise only from the mural endocardium. Left- or right-atrial myxomas often mimic mitral or tricuspid stenosis [43]. Papillary fibroelastomas often arise from the cardiac valves or occasionally from the ventricular endocardium; rarely, they originate from the right-sided cardiac valves. As there is potential for cerebral or coronary embolization, surgical excision should be considered, particularly if tumors are large or mobile; however, rigorous standards to support excision are not available and, thus, clinical judgment should be applied for each individual patient. Papillary fibroelastomas may also interfere with normal valve function [2, 43].

Degenerative VHD – Related to Aging, Possible Genetic and Environmental Predisposing Factors

Calcification of the cusps of the aortic valve usually occurs after the 7th decade of life. Calcification begins at the annular base of the cusps and progresses towards the edges and apices to create aortic stenosis. Until recently, it was thought that this pattern was related to processes spe-

cifically associated with aging. However, recent developments suggest that aortic stenosis and atherosclerosis are related to the same pathophysiologic mechanisms, involving a genetic disorder of metabolic processes (discussed later). Mitral annular calcification occurs primarily in elderly patients, but may occur in younger patients with Marfan syndrome, FMV/MVP or chronic renal disease. Mitral annular calcification may interfere with normal contraction of the mitral annulus, resulting in mitral regurgitation; it is associated with a relatively high incidence of cardiovascular events, even in cases with minimal valvular dysfunction [44, 45]. Mitral annular calcification, when particularly severe, can impinge on the left-ventricular inflow path, creating mitral stenosis that can be hemodynamically important [46].

Iatrogenic Valve Disease: Surgical Valve Repair and Interposition of Devices

By definition, VHD is present after interventional therapy (balloon valvuloplasty and reconstructive surgery including valve repair or valve replacement). Balloon mitral valvuloplasty is an effective treatment for many patients with valvular mitral stenosis. Long-term results after this procedure depend on the pretherapy characteristics of the valve and of the patient. Residual mitral stenosis is present in most patients after the procedure and mitral regurgitation may also occur. Mitral valve reconstruction is possible in a high percentage of patients with mitral regurgitation due to FMV/MVP. With reconstructive surgery, many of the problems associated with a valve prosthesis may be avoided. Mitral valve repair can also be performed in some young patients with rheumatic valvular disease; however, the results of repair for rheumatic disease are often suboptimal and may worsen with time as the underlying inflammatory process progresses. Prosthetic heart valves have certain hemodynamic limitations even when they are functioning according to specifications. These devices represent a type of iatrogenic VHD. Prosthetic valves are prone to several complications such as mechanical dysfunction as well as thrombosis and endocarditis, which further compromise valve function [1–3, 47]. Finally, the inability to implant an optimally sized valve results in a condition called ‘patient prosthesis mismatch’ with resulting obstructions to flow that can be clinically obvious and can affect natural history [48].

Drugs and Physical Agents

Patients who have been treated with ergotamine products for migraine headaches may develop VHD. Mitral regurgitation in combination with mitral stenosis and/or

tricuspid stenosis with regurgitation are the most common valvular abnormalities that have been reported. These lesions are characterized by irregular proliferation of myofibroblasts within an avascular myxoid or a collagenous matrix that encases the leaflets and chordal structures. There is little disruption of the valve structure itself. The fibrotic endocardial process forms proliferative mounds similar to those seen in patients with carcinoid disease. The mechanism by which ergot alkaloid agents induce valvular disease is unclear. Indeed, the causal relation between drug use and VHD has not been rigorously defined. However, the similarities in chemical structure of serotonin, methysergine and ergotamine, and the similarities in the valvular abnormalities observed after use of these chemicals, strongly suggest common pathophysiological mechanisms for ergot-alkaloid-associated valve disease and carcinoid valve disease. Similar valve lesions have been reported in patients treated with the dopamine agonists pergoline or garbergoline for Parkinson’s disease. Benfluorex, a drug used in diabetic patients (it was withdrawn from European markets in June 2010), has been reported to increase the incidence of mitral and aortic regurgitation [49–51]. More recently, the use of 3,4-methylenedioxymethamphetamine (‘Ecstasy’) has been reported to be associated with VHD. In certain cases, drug-induced VHD may be sufficiently severe to require surgical intervention [51].

Although the heart is relatively resistant to the effects of radiation, damage to the pericardium, myocardium, endocardium, microvasculature and epicardial coronary arteries after substantial radiation exposure commonly occurs with breast cancer, Hodgkin’s disease and other thoracic neoplasms. When the endocardium is involved, fibrosis and fibroelastosis may affect the atrioventricular valves and produce mitral and tricuspid regurgitation (depending on the radiation window, the aortic valve can also be involved). The effects of radiation on the heart can be classified as acute and chronic. Acute pericarditis can occur after radiation therapy, but the more common clinical expression of radiation heart disease occurs months to years after radiation exposure, often complicated by severe calcification [52]. Surgical remediation of such valve disease is often particularly difficult because of associated radiation damage to the pleura hindering post-surgical recovery [1, 2, 52].

Aortic regurgitation is the most common clinically recognized valvular disease after chest trauma, commonly secondary to aortic valve rupture or cusp perforation. In autopsy studies, rupture of the atrioventricular valve has been reported to be more common than rupture of

the aortic valve, but this is usually associated with other significant cardiac injuries and frequently with cardiac rupture. Consequently, rupture of the aortic valve has been reported more frequently in clinical series. Isolated mitral valve rupture, however, may occur after chest trauma. Rupture of the left-sided papillary muscle results in massive mitral regurgitation and death. Survival has occurred with a lesser degree of mitral regurgitation resulting from rupture of the head of a papillary muscle, rupture of chordae tendinae or a tear in one of the leaflets. Various degrees of mitral regurgitation can also occur from simple contusion of the papillary muscle, rupture of chordae tendinae or torn leaflets [1, 2].

Infiltrative VHD

Mucopolysaccharidoses are a group of rare heritable diseases caused by a deficiency of lysosomal enzymes in the metabolism of glycosaminoglycans. Mucopolysaccharidoses have been divided into seven major types. Cardiac diseases include myocardial hypertrophy, pulmonary and arterial hypertension, valvular disease and coronary occlusion. Though VHD is not a feature of all forms of mucopolysaccharidoses, mitral, tricuspid or aortic regurgitation may be present in some [53].

Two forms of hypereosinophilic syndrome are recognized: tropical eosinophilic endomyocardial fibrosis and nontropical eosinophilic myocardial disease, which is often referred to as Löffler's syndrome. This is characterized by eosinophilia in the peripheral blood and eosinophilic infiltration of the endocardium. This results in a severe form of restrictive myocardial disease. Mitral and/or tricuspid regurgitation may also be present [54, 55].

Idiopathic VHD

In rare instances, the underlying etiology of VHD may not be determinable; however, with advances in technology today, these cases are rare.

Etiology of Isolated Valve Disease

Generally, the clinical effects of VHD develop slowly even when the valve disease is severe. In certain cases, however, an acute process may result in clinically abrupt expression of regurgitation. The pathophysiology and clinical presentation in acute valve regurgitation is different from that of chronic regurgitation. In acute VHD, depending on the severity of the lesion and hemodynamic consequences, emergency surgery may be necessary [1–3, 56, 57].

Table 2. Mitral valve and aortic valve disease

A. Mitral valve disease	
Chronic mitral regurgitation	FMV/MVP, isolated or part of recognized connective tissue disorders syndrome
Congenital	
Chronic rheumatic valvulitis	
Mitral annular calcification	
Cardiomyopathy (ischemic, nonischemic and hypertrophic)	
Diseases of other organs (renal failure and carcinoid)	
Postinterventional therapy (valvuloplasty, reconstruction and replacement)	
Drugs and physical agents (radiation and trauma)	
Acute mitral regurgitation	
Infective endocarditis	
Severe papillary muscle dysfunction or rupture	
Chordae tendineae rupture	
Mitral stenosis	
Congenital	
Rheumatic	
Postinterventional therapy	
Mitral annular calcification	
B. Aortic valve disease	
Chronic aortic regurgitation	
Congenital bicuspid valve	
Heritable disorders of connective tissue (Marfan syndrome, Ehlers-Danlos syndrome, polycystic kidney annuloaortic ectasia, floppy aortic valve, aortic valve prolapse, sinus of Valsalva aneurysm)	
Rheumatic fever	
Syphilis	
Aortitis (Takayasu)	
Ankylosing spondylitis	
Prosthetic valve malfunction	
Idiopathic aortic root dilatation	
Acute aortic regurgitation	
Infective endocarditis	
Acute aortic dissection	
Trauma	
Prosthetic valve malfunction	
Aortic stenosis	
Bicuspid aortic valve	
Coarctation of the aorta	
Calcific stenosis (possibly partly atherosclerotic)	
Prosthetic valve (malfunctioning or patient prosthesis mismatch)	

Modified from [1] and [3].

The etiologies of isolated mitral valve disease, aortic valve disease, tricuspid valve disease and pulmonic valve disease are shown in table 2 and table 3. In industrialized nations, tricuspid regurgitation is most often ‘functional’ (i.e. due to annular stretch and malcoaptation of leaflets)

resulting from pulmonary hypertension secondary to left-sided heart disease rather than from intrinsic valve structural abnormality (‘degenerative’). Surgical repair of tricuspid regurgitation was commonly avoided in the past, based on the incorrect assumption that correction of the underlying left-sided problem would largely resolve the tricuspid regurgitation without subsequent major sequelae. However, recent studies suggest that an aggressive surgical approach is needed for many patients because with increasing survival when left-sided disease is surgically resolved, the long-term sequelae of untreated tricuspid regurgitation become more apparent [1, 2, 58, 59].

Multivalvular Abnormalities and Current Common Etiologies

We have presented many different etiologies of VHD. Certain types are rare and are seldom seen in clinical practice. In practice, patients also often have more than one valve affected (multivalvular heart disease). The most common causes of VHD and multivalvular heart disease seen today are shown in table 4 [1, 2].

Vulnerable Plaque and the Vulnerable Valve

Until recently, aortic sclerosis, aortic stenosis and mitral annular calcification seen mostly in the elderly were thought to result from degeneration caused by mechanical trauma and the biological response to such injury over the years. However, there is now strong evidence to suggest that the same risk factors responsible for the pathogenesis of atherosclerosis are responsible for valve calcification and stenosis (aortic sclerosis and stenosis and mitral annular calcification).

The possible role of inflammation in ‘degenerative valve disease’ characterized by valve calcification was initially emphasized more than 4 decades ago. One early study described valves with mitral annular ‘ring’ calcification. The overall incidence of mitral annular calcification in patients older than 50 years of age was 8.5% [60]. Aortic valve calcification was present in more than 30% of those patients. Microscopic examination demonstrated ‘nonspecific inflammatory changes adjacent to calcium in about half of the cases in both sexes’. This study [60] was one of the first to suggest that inflammation may play a role in valvular calcification. More recently, epidemiologic studies have suggested that the modifiable risk factors for atherosclerosis such as smoking, hyperlipidemia, arte-

Table 3. Etiology of tricuspid and pulmonic valve disease

A. Tricuspid valve disease	
	Chronic tricuspid regurgitation
	Cardiomyopathy (ischemic and nonischemic)
	Pulmonary arterial hypertension
	Heritable connective tissue disorders
	End-stage renal disease
	Postcardiac transplantation
	Congenital (Ebstein anomaly)
	Carcinoid heart disease
	Pacemaker or defibrillator leads
	Pharmacologic agents
	Acute tricuspid regurgitation
	Infective endocarditis
	Rupture chordae tendineae
	Right ventricular infarction
	Trauma
	Tricuspid stenosis
	Congenital
	Rheumatic
	Carcinoid heart disease
B. Pulmonic valve disease	
	Chronic pulmonary regurgitation
	Congenital
	Pulmonary annular dilatation
	Acute pulmonary regurgitation
	Infective endocarditis
	Trauma
	Pulmonic stenosis
	Congenital
	Rheumatic
	Carcinoid heart disease
Modified from [2] and [58].	

Table 4. Most common causes of VHD and multivalvular abnormalities today

A. Most common causes of VHD	
	Aortic stenosis-sclerosis in the elderly
	FMV/MVP
	Bicuspid aortic valve
	Associated with other diseases (cardiomyopathy and end-stage renal disease)
	Postinterventional therapy
	Infective endocarditis
	Connective tissue disorders
	Atrial fibrillation
B. Most common causes of multivalvular abnormalities	
	Mitral regurgitation plus tricuspid regurgitation
	Cardiomyopathy
	Heritable connective tissue disorders
	Mitral regurgitation plus aortic regurgitation
	Heritable connective tissue disorders
	Mitral stenosis plus aortic stenosis
	Rheumatic
	Mitral stenosis plus tricuspid stenosis or regurgitation
	Rheumatic
Modified from [1] and [2].	

rial hypertension and metabolic syndrome also constitute risk markers (though not necessarily risk factors modifiable with reduction of valve disease) for developing aortic sclerosis and stenosis. C-reactive protein, an index of inflammation, is abnormal in both patients with aortic stenosis and atherosclerosis. Moreover, aortic sclerosis with a normal functioning aortic valve is associated with a relatively high incidence of cardiovascular events, suggesting that the same underlying mechanisms may be involved in the development of atherosclerosis and aortic sclerosis [44, 45]. Hypercholesterolemia in experimental animal models produces atherosclerotic lesions in the aortic valve similar to those seen in atherosclerosis. All this information supports the hypothesis that aortic sclerosis or stenosis in the elderly is not a simple 'degenerative' process related to aging, but an active metabolic phenomenon, possibly genetically determined. The initial event in aortic sclerosis or stenosis is quite plausibly endothelial damage due to high mechanical stress and low shear stress. If so, then lipids could be expected to penetrate the damaged endothelium, with oxidation of low-density lipoproteins, initiating an inflammatory process. T cells could then be expected to accumulate, releasing proinflammatory proteins as in atherosclerosis. In fact, monocytes, mast cells and CD3-positive leukocytes with various degrees of expression are seen in stenotic aortic valves. Inflammatory activity stimulates angiogenesis; consistent with this observation, vascular endothelial growth factor (VEGF) is present in stenotic aortic valves. Small fragile vessels develop in areas of inflammation; rupture of these vessels results in intraleaflet hemorrhage, most likely accelerating the progression of the disease [61, 62]. During the development of aortic stenosis, fibrous tissue is formed and fibroblast like-cells, referred to as 'valve interstitial cells', accumulate. Some of these cells apparently undergo a transformation into myofibroblasts that ultimately differentiate into osteoblasts, which are believed to promote calcification and bone formation. Some research suggests that osteopontin and osteocalcin are involved in this process [63–65]. Thus, even though the metabolic pathways differ from those involved in atherosclerosis, the genesis may be similar.

Inflammation in patients with aortic stenosis has been demonstrated using positron emission tomography [66, 67]. Consistent with the presence of an active process, a higher temperature was detected in the leaflets of aortic valves obtained during valve replacement from patients with aortic stenosis, but not in the leaflets of patients with aortic insufficiency [68]. The metabolic syndrome was also found to predict aortic stenosis progression with a

Fig. 4. Relationship between cardiovascular calcification and loss of bone mineral.

relatively prominent impact in younger patients and in those treated with statins [69].

Calcific VHD is seen more in the left than in the right heart. Thus, it appears that, in addition to other risk factors, pressure plays an important role in disease development. Experimental animal models have demonstrated that hypercholesterolemia results in the development of atherosclerosis in the aortic and mitral, but not in the pulmonary and tricuspid valves. Studies in humans have shown that the aortic valve expresses an osteoblastic phenotype and the mitral valve a chondrogenic phenotype. The pressure on the left-atrial side of the mitral valve is much lower compared to the pressure on the ventricular side of the aortic valve. The high pressure in the aortic valve results in bone formation while the lower pressure in the mitral valve produces cartilage. The slightly higher pressure in the mitral annulus compared to the mitral valve leaflets results in bone formation and mitral annular calcification [61, 64]. Toll-like receptors, which are overexpressed in atherosclerosis, are also overexpressed in the interstitial cells of aortic valves and much less in pulmonary valves.

Other studies have suggested that cardiovascular calcification is inversely related to bone tissue mineral density. Diseases of mineral metabolism such as osteoporosis, chronic renal failure and Paget's disease are associated with a relatively high incidence of aortic stenosis and vascular calcification (fig. 4). Epidemiologic studies also suggest that higher serum phosphate levels within the normal range are associated with valvular and annular (mitral and aortic) calcification in older adults. Thus, phosphorus may be a novel risk factor for calcific aortic stenosis [70, 71].

In summary, the initial event in the development of atherosclerosis and aortic stenosis appears to be endothelial damage due to high mechanical and low shear stress. During the development of atherosclerosis, macrophages, T cells, foam cells and vascular smooth muscle cells are accumulated. In aortic stenosis, the cells that accumulate include macrophages, T cells, valve interstitial cells, myoblasts and osteoblasts. Experimental and empirical clinical observation suggests that during the progression of aortic stenosis, inflammation, fibrosis and calcification are prominent; during the progression of atherosclerosis, inflammation, lipid deposition, plaque rupture due to lipid rich pool and thrombosis prevail. These differences may explain why statins are not effective in the late stages of aortic stenosis [72]. In atherosclerosis, statins may stabilize plaques and prevent rupture, while in aortic stenosis statins cannot prevent fibrosis and bone formation.

However, given the apparent similarities in some of the underlying processes, it remains unclear why many patients with risk factors and coronary artery disease do not develop aortic stenosis. Studies have suggested that even in the normal trileaflet aortic valve, the size of the three leaflets may vary slightly (i.e. one leaflet may be a little smaller than the other two). This minor anatomic variation may be a factor predisposing to aortic stenosis [2]. Further, it appears that there is a genetic predisposition to aortic calcification and aortic stenosis. Thus, for example, recent data indicate that variations in the gene encoding lipoprotein(a), leading to variations in lipoprotein(a) levels, is associated with aortic valve calcification and aortic stenosis [73]. Better understanding of the underlying anatomic, pathophysiologic and molecular mechanisms will assist in the management and eventual prevention of aortic stenosis.

Limited data also suggest that rheumatic valve calcification is not a random passive process, but related to an inflammatory process that is associated with osteoblast formation and osteogenesis [65].

VHD Interrelationships

VHD affects the structure and function of several other organs (fig. 5). Aortic stenosis, aortic regurgitation and mitral regurgitation, through different mechanisms, have an important effect on left-ventricular structure and function. Thickening of left-ventricular walls and concentric hypertrophy is seen in aortic stenosis; eccentric left-ventricular hypertrophy with dilatation is pres-

Fig. 5. Interrelationships of VHD, several organs and underlying disease.

ent in aortic regurgitation and mitral regurgitation. Myocardial fibrosis, which also determines the natural history of the disease, is also seen. Indeed, during the past 2 decades, it has become clear that fibrosis is not an inflammatory response due to the injury of myocytes under the mechanical stress of valve disease, but is rather a primary response of myocardial fibroblasts to myocardial stress and strain [74–77]. In addition, increased oxidative stress appears to cause myofibrillar degeneration and lipofuscin accumulation resulting in left-ventricular contractile dysfunction in mitral regurgitation [78]. Left- or right-atrial dilatation and dysfunction, which are often associated with atrial fibrillation, are present in patients with mitral and tricuspid valve disease (stenosis or regurgitation) [79, 80]. Pulmonary hypertension secondary to increased left-ventricular and/or left-atrial pressure is not uncommon in VHD. Increased venous pressure and peripheral edema are associated with tricuspid valve disease (stenosis or regurgitation). Aortic function and endothelial function are abnormal in patients with bicuspid aortic valve [17]. Aortic dysfunction (i.e. stiff aorta) may accelerate the natural history of aortic regurgitation and mitral regurgitation [81]. As previously noted, aortic sclerosis is directly associated with coronary events. In patients with FMV/MVP, nerve endings in the mitral valve may be stimulated, resulting in central nervous system responses forming a heart-brain interaction [82]. Altering preload, afterload or other hemodynamic factors may also result in a change in the severity of VHD [83]. Finally, VHD may result in a deterioration of the process underlying the valvular disorder (e.g. cardiomyopathy), which, in turn, impacts negatively on valvular function (e.g. mitral regurgitation) [2, 84, 85]. Thus, VHD may affect the circulation in a global fashion.

Conclusions

A metamorphosis in the etiology of VHD has occurred over the last 6 decades. The almost complete disappearance of rheumatic fever in industrialized countries, increased life expectancy and iatrogenic forms of VHD (postinterventional therapy) are major factors contributing to this metamorphosis. Nonetheless, VHD today constitutes an important public health problem.

The most common causes of VHD today are calcific aortic stenosis in the elderly, FMV/MVP associated with mitral regurgitation, bicuspid aortic valve, VHD associated with cardiomyopathy (ischemic and nonischemic), postinterventional therapy (iatrogenic), infective endocarditis and VHD in patients with connective tissue disorders. When mitral and tricuspid regurgitation are present, cardiomyopathy or, less often, connective tissue disorders are most commonly the underlying causes. In contrast, when mitral stenosis is one of the lesions (e.g. mitral stenosis plus aortic stenosis or mitral stenosis plus tricuspid stenosis) the finding has usually been in South Africa, China or India (where rheumatic fever remains prevalent) and the underlying etiology is most likely rheumatic fever.

Until recently, it was thought that calcific aortic stenosis was related only to aging. Recent developments, however, suggest that calcific aortic stenosis and valvular calcification in general involves an active inflammatory process in which anatomic, genetic and other risk factors associated with atherosclerosis contribute to the development of the disease.

VHD may affect the structure and function of several other organs, such as the cardiac ventricles, atria and the pulmonary circulation, central nervous system function (heart-brain interaction) and aortic function. In turn, aortic function (aortic stiffness) may accelerate the progression of mitral and aortic regurgitation. VHD may even result in deterioration of the disease underlying the VHD (e.g. cardiomyopathy), which in turn potentiates the valve disease (e.g. mitral regurgitation).

Better understanding of the genetic, anatomic, pathophysiologic and molecular mechanisms responsible for the development of VHD and the interrelationship of VHD with other systems/organs will help clinicians optimize current management and, eventually, prevent the development of VHD.

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