

PATHOLOGY OF INFLAMMATORY NATIVE VALVULAR HEART DISEASE

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Before considering some common causes of post inflammatory valve disease it is useful to review general concepts of valve related dysfunction and common causes of valve pathology. Native cardiac valves may be involved by dysfunctional states – stenosis and regurgitation – or by vegetations – infective or non-infective. Inflammatory non - thrombotic disorders will be the focus of the presentation.

Valves that are surgically excised are studied for a number of reasons:

1. To document the surgical indication;
2. To correlate pathology with pre-operative diagnosis, hemodynamics, ECHO, angiography and suspected complications;
3. To document infective endocarditis or rule this out;
4. To determine the etiology of the valvular lesion – its natural history, surgical risk, post-operative prognosis and association with systemic disease;
5. To validate new diagnostic imaging techniques;
6. To assess operative technique and whether it could be done on a similar patient;
7. To determine the etiology and pathobiology of the valvular disease.

Dysfunction of a cardiac valve results from either structural abnormalities of the valve or abnormal function of a valve. Valves that are **stenotic** almost always have some anatomic abnormality - usually fibrosis or calcification. In contrast purely **regurgitant** valves do not always have anatomic abnormalities present with the excised specimen. In regurgitation the abnormality may be related to the valve or to the surrounding supporting structures. Stenotic lesions usually take years to develop, whereas regurgitant lesions may be chronic or acute in nature.

AORTIC STENOSIS

Stenosis of the aortic valve is usually due to pathology of the valve cusps, commonly fibrosis, calcification and commissural fusion. Due to the aging population, age-related degenerative aortic valve changes will have important implications for future health care costs. The most common causes of aortic valve stenosis include:

- 1) age related degenerative (senile) changes
- 2) post-inflammatory changes – mostly rheumatic
- 3) congenitally bicuspid valve

AORTIC INSUFFICIENCY

The most common mechanisms causing valve regurgitation are annular dilatation, cusp prolapse, scar retraction of the cusps, and cusp perforation. Aortic regurgitation may be due to diseases of the aortic valve cusps or the aortic root. Diseases that produce annular dilatation include cystic medial necrosis (medial degenerative changes), forms of congenital heart disease, and aortitis. Medial

degenerative changes may be an age-related change, or may be related to connective tissue diseases including Marfan's syndrome.

The most common causes of aortic regurgitation include:

- 1) **cusp pathology**
 - a) post-inflammatory changes – mostly rheumatic
 - b) infective endocarditis
 - c) congenitally bicuspid valve
 - d) iatrogenic causes such as valvuloplasty
 - e) cusp prolapse – VSD related
 - f) medications – anorexogenic medications
- 2) **aortic root pathology**
 - a) age related medial degeneration
 - b) Marfan's syndrome or other connective tissue diseases
 - c) Aortic dissection
 - d) Aortitis, such as giant cell aortitis and syphilis

MITRAL STENOSIS

Mitral stenosis is usually due to leaflet fibrosis and calcification. Almost all cases are post-inflammatory and rheumatic in etiology. Stenosis may be associated with valve regurgitation. The mechanism of stenosis is due to leaflet fibrosis, calcification, commissural fusion, chordal fusion and shortening. The subvalvular apparatus pathology can be assessed by echocardiography and the results used to determine whether valve repair is possible or whether replacement will be necessary. Other rare causes include storage diseases and medication related pathology including some ergot and migraine medications.

MITRAL INSUFFICIENCY

The mitral valve apparatus is a complicated structure with numerous components, all of which must function to ensure valve competence. Leaflet pathology is but one component. The important components and their pathology include:

- 1) **leaflets**
 - a) perforation - infective endocarditis
 - b) scar retraction - post-inflammatory causes – rheumatic
 - c) medications – anorexogenic medications
 - d) floppy mitral valve – myxomatous degeneration
- 2) **chordae**
 - a) elongation – floppy valve
 - b) rupture – floppy valve or infective endocarditis
- 3) **mitral annulus**
 - a) left ventricular dilatation related, numerous causes
 - b) mitral annular calcification (MAC)
- 4) **left ventricle - dilatation**
 - a) ischemia
 - b) cardiomyopathy
- 5) **papillary muscles**
 - a) ischemia related dysfunction (stunned myocardium)
 - b) infarct related necrosis or fibrosis
 - c) infarct related rupture of papillary muscle

INFLAMMATORY VALVE DISEASES

Rheumatic valve disease, a chronic result of rheumatic fever, is the valve disease most think of when one refers to “post-inflammatory” valve disease. This may be short sighted, as will be discussed. Many disorders that we considered to be passive and degenerative are now recognized as being active and inflammation related. This is exciting as it raises the possibility of active intervention and prevention. This handout discusses rheumatic, serotonin associated (carcinoid, migraine, anorexogenic), senile degenerative, dialysis and floppy valves. Other inflammatory valve diseases including those associated with collagen vascular disease or vasculitis are not covered.

RHEUMATIC FEVER AND VALVE DISEASE

Rheumatic fever is a late inflammatory non-suppurative complication of pharyngitis caused by Group A beta-hemolytic Streptococcus. This multi-system disease is characterized by involvement of the heart, joints, central nervous system, subcutaneous tissues and skin. ¹ Except for the heart, most of these organs are only mildly and transiently affected. Clinical diagnosis with the Jones criteria is recommended. No symptom, sign or laboratory test is pathognomic of the disease. The Jones criteria, proposed in the 1940s, have stood the test of time and are intermittently revised. Major and minor categories of clinical and laboratory findings may fulfill the criteria for diagnosis. ² Most pathologists have seen chronic rheumatic valve disease. Many of us have not recognized an acute case, and this is also true for our clinical colleagues.

Rheumatic carditis is an important and frequent acquired cardiovascular disease in children and adolescents and an important cause of death from cardiac disease in young people in developing countries. In India there are an estimated one million new cases of rheumatic fever each year. It has been estimated that rheumatic fever related disease is responsible for 30 to 40 % of cardiovascular disease related hospital admissions in that country, and is a common indication for cardiac surgery in that country. ³ The pathoetiology of the disease is complex and the incidence and prevalence vary among countries. Environmental conditions may play a factor with some climates having an increased frequency of rheumatic fever. In addition, low socioeconomic status, malnutrition, poor hygiene, and poor access to health care have all been associated with increased prevalence and incidence. ^{1,4,5} Rheumatic fever is most frequently observed in children and adolescents, rare before age 5 and after age 25. The highest incidence is observed in children age 5 to 15. ⁶

Genetic studies suggest that there is a vulnerable population with increased risk. Related family members of patients with rheumatic fever have a higher probability of developing disease. Relationships between the development of rheumatic fever and HLA-DR subtypes have been found. These associations are variable between countries and populations. ^{1,7,8}

Important antigenic structures of the Streptococcus include proteins M, R and T. ¹ Streptococcal M-protein, which determines the serotype, extends from the cell surface as an alpha-helix with structural homology to myosin and other alpha-helix coiled molecules. ⁹ The M-protein is a virulence factor with potent anti-phagocytic activity. ⁶ In

outbreaks, bacterial colonies isolated from those with rheumatic fever tend to have a mucoid morphology with thick capsules and certain M-proteins are more common.^{5,10}

The pathogenesis of rheumatic fever is related to humoral and cellular mediated immune responses with development of autoimmunity.⁷ The clinical manifestations of rheumatic fever occur 1 to 3 weeks after the onset of Streptococcal infection. After an apparent convalescence of the pharyngitis, products of the Streptococcus have **molecular mimicry** to human tissue and are recognized by the immune system thus initiating an autoimmune response. Cross-reactivity between the M-protein and cardiac proteins is important.⁹

The acute involvement of the heart in rheumatic fever is pancarditis with inflammation of the myocardium, pericardium and endocardium. Carditis is the most severe clinical manifestation of rheumatic fever and can lead to valvular heart disease, heart failure or death. Carditis occurs in approximately 40 to 50 % of patients at the first attack.⁶ Pericarditis occurs in 5 to 10 % of patients and is characterized by chest pain, decreased heart sounds and a pericardial rub.⁶ Rarely there may be tamponade. Pericarditis rarely occurs as a sole manifestation and if encountered alone, other causes should be suspected. Myocarditis occurs in 10 % of patients and may present with heart failure, arrhythmias, pulmonary edema and cardiomegaly. Isolated myocarditis is also rare.⁶

Endocarditis and acute valve disease may be asymptomatic or present with a new murmur. In the acute phase, murmurs do not indicate a permanent valve defect and are mostly transient. The valves most affected are the mitral, aortic, tricuspid and pulmonary, in that order. Acutely, there is development of thrombi along the lines of closure of the valve (atrial side of the atrioventricular valves and the ventricular side of the semilunar valves). These small thrombi have been termed "verrucous" endocarditis and do not produce valve destruction. The leaflets may have associated edema and cellular infiltration of the leaflets. CD4 and CD8 T cell subsets are present within acute rheumatic fever valves and the major histocompatibility complex class 2 antigens are expressed on vessel endothelium and valve fibroblasts.^{6,11}

The pathogenesis of valve disease involves humoral and cell mediated immunity and molecular mimicry.⁷ Individuals develop antibodies to the carbohydrate of the Streptococcal organism and antibodies to the M-protein. The anti-carbohydrate antibodies cross react with the valvular endothelium. This produces valve injury or dysfunction with up regulation of cell adhesion molecules including VCAM. This serves as an infiltration site for activated lymphocytes into the valve. The M-protein antibodies contribute to the valve disease via molecular mimicry with myosin. Cardiac myosin is not present in the valve, but it is suggested that laminin links myosin with the valve. The cytotoxic anti-myosin antibody recognizes laminin, an extracellular matrix alpha helix coiled protein, part of the valve basement membrane structure.^{7,9}

T-cells responsive to the Streptococcal M-protein infiltrate the valve through the valvular endothelium activated by the binding of anti-Streptococcal carbohydrate antibodies cross reactive to the endothelium. Within the valve tissue the inflammatory cells are responsible for local cytokine release, and interstitial cell damage with neovascularization and chronic inflammation.⁷ Local production of tumor necrosis factor is thought to have an important role. Destruction of the valve tissue may expose more antigens and thus the process may be progressive.⁴ Patients with rheumatic fever also have increased serum cytokines, including interleukin 6, interleukin 8 and tumour necrosis factor, and increased CD4 and CD8 lymphocytes in the peripheral blood.¹²

The inflammatory component of the valve disease results from the infiltration of valves with T-cells and macrophages leading to scarring of the valve and alteration in

cardiac function. Within the valve, the T-cells produce cytokines including tumour necrosis factor and interleukins. Macrophages are activated and attract T cells.¹³

In support of this mechanism, structural and immunological mimicry between the Streptococcal M-protein and cardiac myosin has been shown in the Lewis rat model.⁹ T cells isolated directly from these cardiac valves react with Streptococcal M-protein peptides.⁹ In addition, T-cells have been cloned from human heart valves and have been found to recognize M-protein peptides and heart tissue derived proteins.^{8,9,13}

The chronically scarred, inflamed and neovascularized valve is most commonly encountered by the pathologist. Chronically, rheumatic fever leads to neovascularization, chronic inflammation, commissural fusion, valve thickening and calcification. Scarring, important in the progression of valvular disease, is accompanied by neovascularization of the otherwise avascular valve. For initial entry into the valve, transendothelial migration of the lymphocytes through the endothelial surface plays an important role. Once the valve is inflamed and there is neovascularization, lymphocytes can infiltrate the valve both through the valve surface as well as through the neovascularization channels. Even in old calcified rheumatic valves, lymphocytes and neovascularization are still present, indicating progression or persistence of disease in the valve.¹¹

By gross examination these rheumatic valves have fibrosis, with or without calcification. The commissures are often fused. Valve tissues may be thickened and show scar retraction. The chordae are often thick and shortened. The sub-valvular chordal space may seem to disappear with short thick chords attached almost directly to the papillary muscles. At the commissures of mitral valves there is often loss of surface endothelium and erosion with overlying thrombus material. This does not seem to be as common in the aortic position. Sections show neovascularization, chronic inflammation and fibrosis with alteration of the underlying valve architecture. Large fibrous endocardial onlays are present.

Other systemic manifestations of rheumatic fever are more self limited. Arthritis is frequent and least specific manifestations of rheumatic fever. The arthritis is transient, migratory and self-limiting, usually involving large joints.^{1,6} Sydenham's chorea (Saint Vitus dance) occurs in approximately 10 % of patients with rheumatic fever. It presents with hypo and hyperkinetic manifestations with brief, random and voluntary non-rhythmic movements, dysarthria and speech abnormalities. Emotional changes are also noted. This may be a late manifestation of rheumatic fever and is usually self-limited.⁶ Other features of rheumatic fever include erythema marginatum and subcutaneous nodules.¹

CARCINOID VALVE DISEASE AND SEROTONIN - RELATED VALVE DISEASE

Serotonin related valve disorders include carcinoid valve disease and disease associated with serotonin agonists such as migraine and diet medications. The valvulopathy associated with these agents is hyperplastic in nature with hyperplastic and endocardial lesions.¹⁴

An injured valve may respond by the accumulation of extracellular matrix, increased valve interstitial cells, chronic inflammation and calcification. The myofibroblast form of the interstitial cell is a major participant in valve repair. This cell expresses alpha smooth muscle actin and can proliferate, migrate, make and remodel matrix.^{15,16} Many adult valve diseases have in common proliferation and accumulation of myofibroblasts and interstitial cells.¹⁵⁻¹⁷

Carcinoid syndrome and the resultant valve disease are thought to relate to increased serum levels of serotonin. Serotonin has been found to induce TGF beta

expression. TGF beta can induce valvular endothelial cells and interstitial cells to trans-differentiate into myofibroblasts.^{17,18} Serotonin up-regulates TGF beta expression and increases erk signaling via MAP kinase.¹⁹

The pathogenesis of carcinoid valve disease is thought to involve valve serotonin receptors (5HT-2A and 5HT-2B receptors).^{14,19,20} The addition of serotonin to cultured valve interstitial cells increases TGF beta expression and increased extracellular matrix probably through this serotonin receptor mechanism.^{17,19} Addition of serotonin to sheep aortic valve interstitial cells increases TGF beta mRNA and TGF beta activity with an increase in collagen synthesis.¹⁴ Excised carcinoid valves show increased amounts of latent TGF beta associated peptide and latent TGF beta binding protein present in the interstitial cells and extracellular matrix.¹⁴

Carcinoid heart disease is seen in approximately 50 % of patients with carcinoid syndrome.²¹ The affected valves commonly are the pulmonary and the tricuspid valves. Left-sided disease may occur rarely if there is a patent foramen ovale. The plaques involve the cusps of the semilunar valves and the leaflets, chords and papillary muscles of the atrioventricular valves. Carcinoid heart disease usually produces regurgitant valves, most commonly the pulmonary valve, with mixed pulmonary stenosis and pulmonary insufficiency. The endocardial plaques cause valve thickening and retraction leading to regurgitation and stenosis.

The valve thickening is due to cellular proliferation of myofibroblast like cells and accumulation of extracellular matrix in the endocardial onlay plaque lesions. These onlays or plaques tend to occur on the arterial surface of the pulmonary valve and both surfaces of the tricuspid valve, but predominantly the ventricular side. Carcinoid plaques do not destroy the underlying valve architecture. The matrix is rich in collagen and ground substances and some studies have found small amounts of elastin. In a study of surgically excised carcinoid valves from the Mayo Clinic, 94 % had neovascularization, 94 % had chronic inflammation including lymphocytes, plasma cells and macrophages and 64 % of valves had mast cell inflammation associated with neovascularization.²¹ Prior autopsy studies also noted a high degree of neovascularization and the presence of chronic inflammation. An autopsy study of 18 patients with carcinoid syndrome by Thorson found 94 % valves were neovascularized, and 67 % had inflammation.²² Mast cells are variable in numbers in the reported studies, some finding abundant cells, others none. Mast cells tend to be in areas of neovascularization and they may also be in adjacent valve tissue and not actually in the endocardial plaque.

ANOREXOGENIC MEDICATIONS AND OTHER DRUGS

Medications, including anorexogenic drugs, and ergotamine and methysergide (migraine medications) have been found to produce carcinoid like valve disease. The mechanism is thought to be via activation or agonist activity of 5HT-2B receptors. Medications have been screened for activity at serotonin receptor subtypes by ligand binding studies and functional assays.²³ Fenfluramine metabolites, ergotamine, and methysergide have high affinity for these receptors and these drugs have been associated with serotonin related valve disease.

Ergot alkaloid drugs include methysergide and ergotamine, both used for treatment of migraine headaches. Ergotamine associated valve disease chiefly affects the mitral valve and produces a carcinoid like gross appearance that may be severe. Mitral stenosis and regurgitation have been seen. Valve leaflets are typically very thick with chordal fusion and shortening and commissural fusion. Large “myxoid collagenous” myofibroblast rich plaques are stuck on the underlying valve proper without underlying valve leaflet destruction.^{24,25} Methysergide, a migraine medication, has also had

morphologically similar mitral valve disease described, chiefly causing mitral regurgitation. This medication has been associated with retroperitoneal and pleuropulmonary fibrosis. With these drugs inflammatory cell infiltration has not been reported to be prominent.^{24,25}

The anorectic diet medications have previously been used as monotherapy for short duration therapy for many years. The combination of fenfluramine and phentermine (Fen-Phen) was introduced in North America in 1996. Over a million prescriptions were written, and not all were for severe obesity. No information concerning effectiveness or chronic effects was known.²⁶ Connolly et al, from the Mayo Clinic, reported heart valve shortly thereafter in 1997.²⁷ There is still some debate as to the risk and incidence of the valvulopathy associated with anorexogenic agents, but it is probably low.²⁸ Susceptibility or risk of valvulopathy may depend upon the dose, the duration of treatment and individual risk factors including the presence of pre-existing valve disease and concomitant medication use.²⁹

Grossly and microscopically the valve disease or valvulopathy associated with anorexogenic drugs has been reported to be similar morphologically to that of carcinoid valve disease.^{27,30} The left sided valves are affected more often with aortic insufficiency being the most common clinical manifestation.²⁷ White plaques are noted grossly. There may be chordal encasement and fusion, but not rupture. The commissures are not fused, in contrast to rheumatic disease. Doming or hooding of the mitral leaflets is not seen, in contrast to floppy valve disease. By microscopic examination, the valves have myofibroblast and glycosaminoglycan rich onlay endocardial lesions with preservation of the underlying valve architecture. These onlay lesions are “neo-tissue” of glycosaminoglycan, collagen, and myofibroblasts that are superficial to the valve elastic membrane but deep to the surface endothelium. The “downstream” side of the valve (ventricular side of mitral valve and the aortic side of the aortic valve) are most commonly involved. The valve proper may have myxoid degeneration with accumulation of glycosaminoglycans. The onlays also may contain chronic inflammatory cells (CD3 positive lymphocytes and CD68 positive macrophages) and there is neovascularization within the onlay lesions and in the valve proper.³¹ Mast cells have also been noted.³⁰

A careful and detailed digital imaging assisted study of geometry and composition reported interesting findings to aid in the distinction of anorexogenic disease from floppy mitral valves, rheumatic and carcinoid disease.³² The size and number of the onlay lesions, the amount of glycosaminoglycans in the onlay lesions and the valve proper, as well as the location of the inflammation and neovascularization are important in this distinction.

Carcinoid valves have large onlays with preservation of the underlying valve proper architecture. The valve proper and the onlays are glycosaminoglycan rich and there may be chronic inflammation throughout the valve. Floppy mitral valves have medium numbers of onlays, but these have no significant neovascularization. The valve proper also usually has little neovascularization but there is accumulation of glycosaminoglycan in the spongiosa layer. Rheumatic valves have large fibrous onlays that are few in number. Vascularization of the valve proper is prominent. The valve proper and the onlays show fibrosis.³² Anorexogenic valves had the most variable findings perhaps reflecting variability in dose, duration of exposure, and individual susceptibility. These valves have the largest amount of glycosaminoglycan of all the valve groups. The onlays were small, numerous and glycosaminoglycan rich. Chronic inflammation may be present. Interestingly, both the valve proper and the onlays are neovascularized. There appears to be some similarities between the valve groups, but

there are significant morphological trends and differences to assist in the separation of the categories.³²

There remains much unknown and poorly understood about these disorders. Why fenfluramine produces aortic regurgitation, whereas ergotamine and methylsergide produce mitral valve disease is unknown. Why methylsergide associated valve disease is more symptomatic is unknown. Why methylsergide can produce extracardiac fibrosis with pleural fibrosis and pericarditis in addition to valvular disease is unknown.²³

Similar carcinoid like valve disease has also been noted recently with pergolide.^{33,34} This is an ergot derived dopamine receptor agonist used for Parkinson's disease. Pericardial, retroperitoneal and pleural fibrosis have been reported. Valve disease in these patients has been reported as being fibroproliferative with preserved underlying valve architecture. Tricuspid and mitral valve regurgitation have been reported. The valve disease was described in 2002, even though the drug has been marketed for 20 years.^{33,34} Pergolide may activate serotonin 5HT-2B receptors. It also influences potassium channels in pulmonary artery smooth muscle cells causing vasoconstriction. Thus monitoring of individuals taking this drug for pulmonary arterial hypertension, similar to the anorexic drugs, has been suggested.³⁴

The saga of serotonin related valve disease continues. "Ecstasy", MDMA (3,4-methylenedioxymethamphetamine), an illicit street drug, has been found to induce proliferative actions of cardiac valve interstitial cells, again via 5HT-2B receptors.³⁵

DEGENERATIVE AORTIC VALVE DISEASE – AN OLD PROBLEM REVISITED

Age related (senile) degenerative change of aortic valves is the most common cause of adult aortic valve stenosis encountered in North America. With an aging population this will not likely change, and the disease will be commonly encountered at autopsy or as a surgical specimen by many pathologists.

Traditionally the valve calcification process was thought to be passive in nature representing dystrophic calcification of degenerative material in the valve. Wear and tear was postulated. Increasingly, this theory has been shown to be incomplete. An early event appears to be endothelial dysfunction from wear and tear, flow and low shear stresses. After this, numerous active mechanisms ensue including lipid accumulation, inflammation, alteration of cytokines, growth factors and valve matrix metalloproteinases.³⁶

The process of valve calcification in prostheses and native valves is an active process with much in common with atherosclerosis and bone formation.³⁷⁻³⁹ Progression of aortic valvular disease in patients from the general population has been associated with many of the traditional risk factors for atherosclerotic disease including systemic arterial hypertension, hyperlipidemia and diabetes mellitus.⁴⁰⁻⁴²

The process of vascular and valvular calcification is a highly coordinated and active with a mechanism similar to physiologic bone formation.^{37,39} This process involves the expression of non-collagenous matrix proteins such as osteopontin, osteonectin, osteocalcin, bone sialoprotein and bone morphogenic protein. The expression of these collagenous and non-collagenous matrix proteins has been demonstrated in native cardiac valves and arteries.^{37,39,43,44} Calcification of bone is a tightly regulated process that starts with osteoblasts producing a matrix of predominately type 1 collagen. The collagen is subsequently mineralized by hydroxyapatite, which is thought to initially form within the osteoblasts and move to the matrix via vesicles. The question remains as to how bone cells gain entry into the endothelium and cardiac

valves. The myofibroblasts of the valve have been shown to trans-differentiate into osteoblast like cells.³⁶

If one histologically sections calcified valves, rather than only examining them grossly, the calcified valves may have a variable degree of inflammatory infiltrate including macrophages, plasma cells, and lymphocytes.^{39,43} These cells are capable of synthesizing osteopontin, which may act to hold surrounding cells to the calcified deposits.⁴⁵ Osteopontin has effects on chemotaxis, cellular proliferation, inflammation and mineralization. It is strongly associated with macrophages and has been reported to influence macrophage invasion, migration and phagocytosis.⁴⁶ The accumulation of T cells within the cardiac valves is a likely source of cytokines important for the recruitment of more inflammatory cells.⁴⁷ Expression of cytokines such as tumor necrosis factor (TNF) alpha has been noted in stenotic valves.⁴⁷ Metalloproteinases are also altered in the valve matrix.⁴⁸ The inflammatory cells may activate growth factors such as TNF, that in turn stimulate the valve myofibroblasts to proliferate and express matrix metalloproteinases which remodel the valve matrix.⁴⁷ Mast cells may influence matrix metalloproteinases, release proangiogenic peptides and activate cytokines and growth factors.³⁹ Lymphocytes are found in congenitally bicuspid aortic valves, as well as in degenerative tricuspid valves.³⁸

Diseased valves may progressively accumulate lipid and some have postulated a common link between degenerative valve disease and atherosclerosis.⁴⁰ Stenotic aortic valves have a larger amount of lipid compared to non-stenotic valves.⁴⁹ The lipid may oxidize and attract inflammatory cells. These cells may release cytokines and contribute to neovascularization and the bone morphogenic protein mechanism.

With coronary atherosclerosis, lipid lowering therapy with statin medications (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) have effects thought to stabilize arterial plaques. These include reduction in the proteolytic activity of macrophages, increased plaque collagen content, reduction of the size of the lipid core, reduction in the degree of inflammation, restoration of endothelial function, and a decrease in tissue factor expression thus decreasing propensity for thrombosis.^{50,51} Repression of Major Histocompatibility Complex Class II expression, blockage of LFA-1 (leukocyte function antigen -1) / ICAM-1 (intercellular adhesion molecule 1) interaction and inhibition of CD40-CD40L signaling are all molecular mechanisms that have been described to explain the pleiotropic effects of the statins.⁵² In clinical trials designed for lipid lowering, one of the unexpected observations was the occurrence of fewer coronary events in the treated patients.^{49,53-55} Statins may cause slower progression or regression of atheroma.

Animal studies have demonstrated that hypercholesterolemic rabbits develop valve disease similar to human aortic valve disease.⁴⁶ Treatment with statin medications was found to decrease the extent of the lipid deposits in the animal valves.^{56,57} One could speculate that statins might be useful for prevention and treatment of valvular heart disease. Clinical trials are underway and those reported so far are mostly positive, but others have conflicting results.⁵⁸⁻⁶²

VALVE DISEASE IN END - STAGE RENAL DISEASE PATIENTS

There is an increased incidence of native valve calcification and stenosis in patients with end - stage renal disease (ESRD) as compared to the general population.^{63,64} Native valve calcification/stenosis seems to progress more rapidly in renal failure patients.^{65,66} The presence of multiple risk factors for atherosclerosis may explain the more rapid progression of aortic stenosis; however, the uremic environment,

hyperphosphatemia, hypercalcemia and a high calcium phosphate product have also been implicated in the increased risk of cardiac and vascular calcification.^{63,64,67}

In a recent study to determine if valvular calcification in patients with ESRD is similar to patients without ESRD, we examined surgically excised native cardiac valves of hemodialysis patients and while under blind, valves were compared pathologically to age, gender and valve type controls without renal failure. We found inflammation, neovascularization and bone morphogenic proteins in degenerative valves from both the normal and the dialysis populations. The demonstration of both osteopontin and bone morphogenic protein in the valves of patients with ESRD and from the general population supports the notion that native valve calcification is an active process analogous to bone formation. Interestingly, when the results were un-blinded, the patients with dialysis seemed to have more neovascularization and chronic inflammation as compared to the non-dialysis patients.⁶⁸ Enhanced inflammation in patients with ESRD is consistent with the marked elevation of acute phase reactants in patients with ESRD compared to the general population. The elevation of a reactant such as C-reactive protein (CRP) has been associated with vascular calcification scores and with an increased risk of death from all cause and cardiovascular specific mortality.^{69,70}

MITRAL VALVE PROLAPSE – DEGENERATIVE, INFLAMMATORY OR BOTH ?

Mitral valve prolapse may be seen with myxomatous valve degeneration as a degenerative age related change or in association with syndromes such as Marfans, Ehlers Danlos or osteogenesis imperfecta individuals. These are the classic large redundant, thickened “floppy” valves with endocardial fibrous thickening and accumulation of ground substances, glycosaminoglycans, in the valve spongiosa layer. It should be recognized that this is not the only cause of mitral valve prolapse. Mitral prolapse may also be seen with Turners syndrome, hypertrophic cardiomyopathy, atrial septal defect, ischemic heart disease and chest trauma. Aortic valve prolapse may be noted in many disorders including ventricular septal defect, aortoannular ectasia, Marfans, aortic dissection and infective endocarditis. Tomaru et al. described the entity of “post-inflammatory” valve prolapse.^{71,72} They studied 42 aortic and mitral valves that were removed for prolapse and found fibrosis, neovascularization and chronic inflammation in over 50 %. These valves were scarred.

There may be some overlap between rheumatic/ post-inflammatory changes and floppy myxomatous valves if one takes the effort to examine these valves by histology. By gross examination one is commonly called upon to distinguish between rheumatic valves and floppy mitral valves. The rheumatic valve is fibrotic and firm with thickened and fused leaflets and commissures. The ostium is elongated and funnel shaped due to chordal fusion. Calcification and rigidity are seen. Chordal ruptures are not common. By contrast the floppy myxomatous valve is thickened and redundant. The valve remains soft and pliable and tends to dome above the valve insertion. Chordal rupture and attenuation are common. The ruptured chords may fuse in a random irregular fashion on the underside of the valve leaflets. The commissures are not fused.⁷³

This seems simple. Unfortunately, it is not always simple if one examines the valves carefully and especially if one histologically examines the valves. In classic rheumatic valves one sometimes finds some ground substance accumulation. More commonly, in classic myxomatous valves one sometimes sees some chronic inflammation and neovascularization. With changes in chordal tension the valve endothelium may be disrupted and the valve interstitial cells may alter their expression of cytokines and growth factors.⁴⁸ It may not be as clean cut as we would like.

SUMMARY

Inflammatory cardiac valve disease encompasses many disorders and should not be solely equated with rheumatic valve disease. Granted, rheumatic disease remains an important cause, especially if one considers a global perspective, but with increased understanding of the pathoetiology of valve disease and valve injury it is evident that inflammation may play a role in many valve disorders. Cellular immunity, humoral immunity and direct cell activation via pharmacological agents may all contribute. We are only beginning to understand these complex processes. Pathologists have made many contributions to this field. With increasing knowledge that many of these processes are active, there may be opportunity for intervention or even prevention.

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