

VALVE DISEASE

Worldwide perspective of valve disease

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Valvar heart disease is a paradigm of the changing aetiology of human disease. In particular, we have witnessed dramatic changes in the incidence of rheumatic heart disease (fig 1); such changes have been limited mostly to industrialised countries, highlighting the role of factors other than microorganisms in this disease. Interestingly, the frequency of valvar heart disease is still high in industrialised countries, as new types of valve disease become increasingly prevalent (fig 2). The most important of them is degenerative valve disease, which relates directly to the increased lifespan of people living in industrialised countries compared to those in developing countries. On the other hand, aetiologies related to the relative wealth of industrialised countries have also appeared, the most dramatic example being valve disease related to appetite suppressant drugs.

Rheumatic valve disease

Although rheumatic fever was thought to be nearly eradicated from developed countries, it continues to be a challenge because of its high prevalence in the developing world. In addition, new aspects have emerged and are a cause of concern, as indicated by the recent outbreaks in industrial countries.

A variety of epidemiologic studies have shown that the incidence of rheumatic fever and the prevalence of rheumatic heart disease have declined dramatically over the last decades in the developed countries. A number of reasons (table 1) have been postulated to explain such a decrease: improvement in living standards, better access to medical care, wider use of antibiotics, as well as natural changes in the streptococcal strains.

In the USA, in the mid 1980s the medical community was surprised by the resurgence of a disease that had been considered to have virtually disappeared. Although the first outbreak was documented in the Intermountain area,¹ a nationwide survey of paediatric cardiologists indicated that a definite increase in rheumatic valve disease had occurred in 24 states. The resurgence was very intense in certain areas, where the incidence was similar to that occurring in the early 1960s. After the outbreak, a general decline in new cases was observed, but the disease did not totally disappear. Some disturbing features of the outbreak were that in the majority of cases there was not the antecedent of a sore throat, and that in some patients who had the typical symptomatology,

they had taken the recommended treatment for streptococcal pharyngitis (oral penicillin for 10 days). In contrast with what might be expected, the resurgence was not restricted to socioeconomically deprived groups. The unresolved questions are whether the disease returned because of an emergence of modified strains, a breakdown of immunity, or simply a slackening of public health vigilance. The most likely explanation for the outbreak is that highly rheumatogenic strains of group A streptococci accounted for local increases in acute rheumatic fever.² Viewed now in retrospect, through the enormous publicity that accompanied the outbreak, a nationwide survey of all children's hospitals and general hospitals of more than 600 beds in the USA revealed that rheumatic fever was no more common than Kawasaki disease, with approximately 5000 cases of each occurring over four years (from 1984 to 1987), and with no increasing trend.

In the developing countries, the situation is similar to that of industrialised nations in the early 20th century, when rheumatic fever was still one of the leading causes of death and disability in young people. An accurate evaluation of trends of rheumatic fever in these countries is not possible because of a lack of reliable health statistics, but there is overwhelming evidence that the disease continues unabated. The existing information indicates that the magnitude of the problem may not have changed during the last years or may have actually increased in the last 50–60 years. Worldwide estimates of chronic rheumatic heart disease in school age children and young adults range from 4.9 to 30 million.³ Hospital statistics from most developing nations reveal that about 10–35% of all cardiac admissions are for patients with rheumatic fever or chronic rheumatic heart disease (table 2). Accordingly, valve replacement accounts for the majority of cardiac surgery in these countries.

Unfortunately, the notion that rheumatic fever is a disease of the poor and the underprivileged is still true at the beginning of the new millennium. The absence of factors that account for the sharp decline of the disease in the industrialised countries explains its persistence in the developing world. The difficulties in accessing health care rapidly may explain why streptococcal sore throat (the most important primary cause of this disease) is not treated adequately. A report from Costa Rica shows that a single dose of penicillin benzathine administered to all patients with sore throat could reduce significantly the incidence of rheumatic fever.⁴ Another additional problem is that secondary prophylaxis is rarely done, and recurrences are frequent. Changes in the standard of living in these countries, with crowding in urban areas with poor living status (slum areas), has accelerated the propagation of the disease, since streptococcal infection spreads in these type of conditions. At the present time, prevalence of rheumatic heart disease is higher among the urban poor than the rural poor population.

Fortunately, group A streptococcus remains sensitive to penicillin, but it may be only a mat-

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ter of time before it becomes resistant (resistance to erythromycin, the second drug of choice, is common and seems to be increasing). Recently, important progress towards the development of an effective vaccine to protect against streptococcal nasopharyngeal infection opens up the possibility of better control of rheumatic fever.⁵

Degenerative valve disease

Although there has been a dramatic reduction in rheumatic valve disease in the industrialised countries over the past 30 years, there has not been a similar reduction in valve surgery. This is because the types of patients being referred for surgery have changed. The significant increase in life expectancy in developed countries partly accounts for this change in aetiology, especially in aortic valve disease. In one surgical series over a five year period (from 1981 to 1985), it was found that while the proportion of patients with congenitally bicuspid aortic stenosis remained stable (from 37% to 33%), postinflammatory valve disease decreased from 30% to 18% while degenerative valve disease increased from 30% to 46%.⁶

Although the incidence of degenerative valve disease increases with age, aging does not seem to be the only factor, as valve disease is not present universally in the elderly (25–45% of octogenarians do not have aortic calcification). Moreover, and most intriguing, the initial lesion of calcific aortic valve disease appears to involve an active process with some similarities to atherosclerosis, including lipid deposition (apo B, apo(a), and apo E), macrophage infiltration, and production of osteopontin and other proteins.^{7–9} In the Cardiovascular Health Study⁷ the relation between aortic sclerosis or aortic stenosis and clinical risk factors for atherosclerosis was evaluated in 5201 subjects aged 65 years or more; aortic valve sclerosis was found in 26% and aortic stenosis in 2% of the entire cohort. Independent clinical factors associated with both types of degenerative valve disease included age (twofold increased risk for each 10 year increase in age), male sex (two fold excess risk), and a history of hypertension (20% increase in risk); other significant factors included high lipoprotein Lp (a) and low density lipoprotein (LDL) cholesterol concentrations.

Another study found an association between atherosclerotic risk factors and mitral annulus calcification, and stenotic and non-stenotic aortic valve calcification.⁸ The analysis was done from a prospective database of 8160 consecutive patients and showed that age (odds ratio (OR) varying from 5.78 to 10.4, depending on age class), hypertension (OR 2.38), diabetes mellitus (OR 2.85), and hypercholesterolaemia (OR 2.95) were strongly and significantly associated with aortic valve calcification, as were age (OR varying from 8.82 to 67, depending on age class), hypertension (OR 2.72), diabetes mellitus (OR 2.49), and hypercholesterolaemia (OR 2.86) with mitral annu-

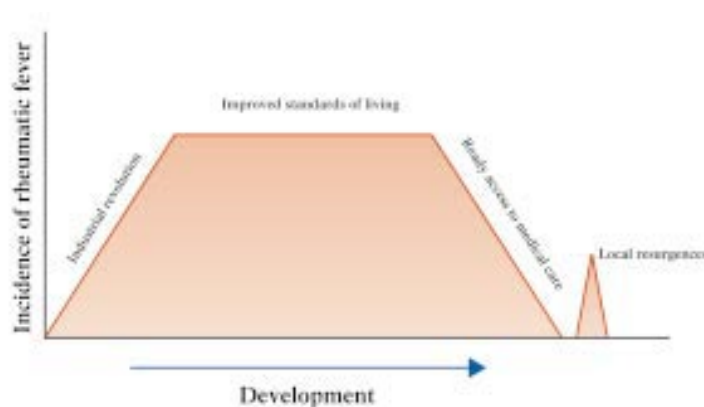


Figure 1. Changes in the incidence of rheumatic fever. Rheumatic fever increased during the period of the industrial revolution, possibly because of overcrowding in urban areas. Later on, it reached a steady state as living standards began to improve. Finally, in the postindustrial period, the decline in incidence was associated with an easier access to medical care, widespread use of antibiotics, and reduced overcrowding. At the present time, when the disease is considered to be nearly eradicated, isolated outbreaks continue to occur.

lar calcification. The most important consequence of this process is aortic calcification and/or aortic stenosis, but the same calcific deposits may be located in the undersurface of the posterior mitral leaflet and, if extensive enough, can cause mitral incompetence and, more rarely, mitral stenosis.

The results of these studies suggest that degenerative valve disease does not have to be regarded as an inevitable consequence of aging, and that these findings might be translated to preventive measures. Taking into consideration that atherosclerotic heart disease, at least coronary heart disease, is to a certain extent a preventable condition, in which efforts have to be made to modify the natural (or unnatural course), the same principles would apply to degenerative valve disease. Accordingly, early forms of aortic stenosis and, probably, of aortic sclerosis and mitral annulus calcification should be considered as indicators to implement measures generally used to treat atherosclerotic vascular disease, including diet modification, tobacco consumption cessation, plasma lipid determinations, and blood pressure control.

The prevalence of degenerative valve disease is not known in underdeveloped countries. Presumably, it is low as life expectancy is much shorter and atherosclerotic heart disease is much less prevalent than in industrialised countries.

Emerging valve disease

During the last 20 years, the medical community has witnessed the appearance of new forms of cardiac valve disease. There are three main sources of these “modern” types of valve involvement: (a) new infectious diseases such as AIDS; (b) drug related diseases resulting from the overuse of drugs that, in many cases, are specifically linked to problems only found in developed countries (for example, appetite suppressant drugs); and (c) new types of

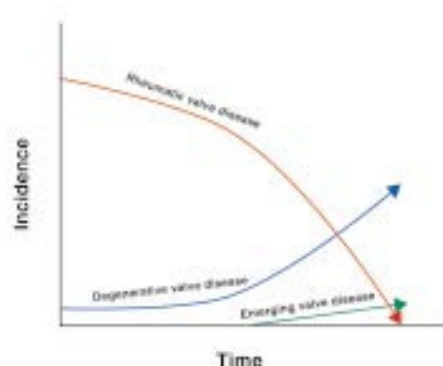


Figure 2. Evolution of different types of valve disease in the developed world. Rheumatic valve disease has witnessed an abrupt decline, which has been matched in part by an increase in degenerative valve disease, related to aging. Meanwhile, new types of valve disease have emerged, although they account for a minority of all cases in comparison with the old incidence of rheumatic valve disease or the current incidence of degenerative valve disease.

idiopathic diseases (for example, the antiphospholipid syndrome).

Infectious diseases: AIDS

Cardiac disease is not a common complication of AIDS, but the incidence of AIDS related heart involvement will increase as this infection becomes more prevalent and patients live longer.^{10 11} Valve involvement is less common than myocardial or pericardial disease in AIDS patients, unless a predisposing factor such as intravenous drug abuse exists.¹² In these cases, endocarditis is caused by *Staphylococcus aureus* or *Streptococcus pneumoniae*, but can also be caused by fungi or HACEK (*Haemophilus* species, *Actinobacillus actinomycetencomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species). It has been reported that the degree of immunosuppression caused by the HIV infection increases the severity of valve disease and the resulting mortality.¹³

The other type of valve involvement is non-bacterial thrombotic or marantic endocarditis, in a manner similar to other wasting diseases such as cancer. The incidence ranges from 4–7% in necropsy series. Vegetations are composed of sterile verrucae attached to coaptation points of the valves and comprise fibrin-platelet masses. When vegetations reach a size

greater than 2 mm they can be detected and the condition diagnosed by means of echocardiography. Any valve can be involved and, from a clinical viewpoint, the most common phenomena are embolic. There is no specific treatment.

Drug related diseases

Ergot alkaloid heart disease

Methysergide and ergotamine are two classical drugs that are used in the prophylaxis and treatment of migraine headaches. Ergotamine is believed to relieve migraine by inducing vasoconstriction of the cerebrovascular bed, while methysergide achieves a similar effect by its antiserotonergic properties. They are ergot alkaloid derivatives, and both share a common chemical structure to the neurohormone serotonin. Serotonin is the agent responsible for valve disease in the carcinoid syndrome, involving endocardial fibrosis.

It has been reported that chronic ingestion of methysergide or ergotamine can induce endocardial thickening that results in valve dysfunction.¹⁴ The endocardial involvement comprises a fibrotic reaction that coats valves, chordae, papillary muscles, and all the endomyocardial surface. Fibrosis causes valve and chordae retraction that results in either stenosis or regurgitation. The process is similar to that described in the carcinoid syndrome, but while carcinoid associated valve disease is restricted to the right sided valves (except in the case of bronchial carcinoid), in ergot alkaloid associated valve disease, although all four valves can be involved, the aortic and mitral valves are most often damaged.

The pathophysiologic underlying mechanism that explains why these lesions develop after the chronic ingestion of these drugs is unknown. Ergot alkaloid valve heart lesions only occur after very prolonged exposure: all patients diagnosed had received this treatment for a minimum of six years (usually 20 years). The incidence and importance of cardiac lesions are directly correlated to doses and time of exposure.

The incidence of this type of valve disease is unknown because no studies have evaluated large numbers of ergot alkaloid consumers, just sporadic cases. Thus, there are no reports on the natural history of the condition. A small series from the Mayo Clinic included five patients symptomatic enough to require valve surgery.¹⁴ All the patients developed symptoms after long periods of drug consumption but, once the symptomatology was established, its progression was rapid, to the point of requiring valve replacement within six months to four years. One patient that continued using ergot alkaloid suppositories after mitral and aortic surgery developed severe tricuspid involvement shortly after, which was not present preoperatively.

The treatment of ergot alkaloid valve disease is very simple. The most important measure is, of course, to stop the drug treatment. Occasionally, the interruption of therapy may be followed by diminution of the murmurs associated with the valve disease, but this has not

Table 1 Suggested reasons for the decline of rheumatic fever in industrialised nations²

Reasons	Possible mechanism of benefit	Evidence
Improved standards of living	<ul style="list-style-type: none"> ● Less overcrowding ● Improved nutrition 	<ul style="list-style-type: none"> ● Declining incidence of RF before the antibiotic era
Greater access to health care and widespread use of antibiotics	<ul style="list-style-type: none"> ● Prompt treatment of symptomatic streptococcal infections ● Reduced occurrence of epidemics of streptococcal sore throat ● Prevention of recurrence of RF through secondary prophylaxis 	<ul style="list-style-type: none"> ● Studies examining the effect of improved health care availability in poor urban areas ● Fourfold decline in reported national mortality from RF after introduction of penicillin
Diminished streptococcal virulence and fewer “rheumatogenic” subtypes	<ul style="list-style-type: none"> ● Less rapid spread of streptococcal infections ● Reduced prevalence of specific “rheumatogenic” strains 	<ul style="list-style-type: none"> ● No direct evidence, diminishing incidence of RF in the face of unchanged prevalence of streptococcal infection

RF, rheumatic fever.

been confirmed by echocardiography. These patients have to be managed conventionally, with appropriate medical and surgical interventions as used to treat rheumatic or degenerative valve disease.

Appetite suppressants drugs and cardiac valve disease

Reports on the efficacy of the combination of fenfluramine and phentermine in the treatment of obesity appeared in 1992. Dexfenfluramine, the d-isomer of fenfluramine, was approved by the US Food and Drug Administration (FDA) in 1996. These drugs were very successful, and by 1997 approximately 14 million prescriptions had been written (although a concern was raised on their association with pulmonary hypertension). However, in July 1997, Connolly and colleagues reported a series of 24 patients who had taken the fenfluramine-phentermine combination for an average of 11 months, and found a high incidence of cardiac valve regurgitation; five patients in the study need valve surgery, with findings similar to those occurring in serotonin related carcinoid syndrome (although in these patients they were left sided).¹⁵ Immediately afterwards, a series of retrospective echocardiographic studies found that the prevalence of aortic or mitral regurgitations in patients treated with these drugs ranged from 20–30%, and as a result the drugs were withdrawn from the market.

Three reports published simultaneously in the *New England Journal of Medicine* confirmed the association between the cardiac valve disease and the drugs, although the reports differed in the estimate of risk magnitude.^{16–18} The prevalence of echocardiographic valvar regurgitation (FDA criteria) varied from 6.9–25%, depending on the study, the type of appetite suppressant drug, and the duration of treatment. The incidence of clinically detected cardiac valve disease was much lower (reflecting the insensitivity of clinical evaluation in diagnosing mild to moderate valve regurgitation). Other conclusions were that the probability of developing valve disease was related to longer times of exposure and higher doses.

The lesson in this case is similar to that learned with ergot alkaloid cardiac valve disease. Drugs that act via the serotonin pathways are potentially dangerous. Phentermine, which acts via the catecholamine pathway, has

escaped incrimination as a cause of valve damage when given alone. The main difference between what happened with the appetite suppressant drugs and the ergot alkaloid drugs was that in the former the valve damage occurred after only a few months of treatment, while in the latter the valvar involvement was described only after years of treatment.

Cardiac valve disease associated with the antiphospholipid syndrome

The antiphospholipid (aPL) syndrome is an entity characterised by vascular thrombosis with frequent heart involvement, particularly valvar lesions.¹⁹ The syndrome is caused by the appearance of circulating aPL antibodies, which are spontaneously acquired circulating immunoglobulins directed against negatively charged phospholipids. aPL antibodies were initially found in sera of patients with systemic lupus erythematosus. They have since been found occasionally in other connective tissue diseases, as well as in drug induced, malignant, and infectious disorders. In addition, they have been found in subjects without any underlying disorder.

aPL antibodies are associated with an intriguing effect on blood coagulation. In vitro they act as an anticoagulant that prolongs the whole blood clotting time, although no specific deficiency of the clotting factors is detectable. Despite its anticoagulant behaviour in vitro, the paradox comes from the clinical manifestations associated with the aPL phenomenon, as these patients present with a high incidence of arterial and venous thrombosis. The combination of a laboratory finding—that is, the presence of aPL antibodies—and of a clinical finding—that is, the presence of either arterial or venous occlusive events—has been termed the antiphospholipid syndrome.

aPL antibodies are associated with a wide variety of clinical manifestations, but the vast majority of them share in common the characteristic of being part of the hypercoagulopathic state. The most frequent features are thrombosis either in the venous or in the arterial bed as deep vein thrombosis, commonly multiple and bilateral, pulmonary embolism, secondary pulmonary chronic hypertension, stroke, transient ischemic attacks, multiple visceral arterial occlusions, and other large vessel occlusions—for example, of the subclavian artery. No portion of the vasculature is spared from thrombotic events.

Cardiac involvement is frequently seen under the broad umbrella of the aPL syndrome, and it can be present in many diverse ways.²⁰ Initially, aPL antibodies were significantly associated with the finding of valve lesions in lupus patients. Nevertheless, systemic lupus is a complex disease in which multiple inflammatory, thrombotic, and degenerative phenomena are involved. Thus, the best model to determine whether aPL antibodies and valve lesions are related is the primary antiphospholipid syndrome, namely, those patients with antibodies to phospholipids, thrombotic manifestations, but no other disease that may account for the antibodies. Subsequently,

Table 2 Hospital admissions for rheumatic heart disease.²

Country	Admissions as percentage of all cardiac admissions
Asia	
Bangladesh	34.0
Burma	30.0
India	16.5–50.6
Mongolia	30.0
Pakistan	23.0
Thailand	34.0
Africa	
Ethiopia	34.8
Ghana	20.6
Malawi	23.0
Nigeria	18.1–23.0
South Africa	25.0
Tanzania	9.7
Uganda	24.7
Zambia	18.2

valvar involvement has been demonstrated in patients with the primary aPL syndrome.²⁰ Lesions are found by means of Doppler echocardiography in 38% of patients, involving the mitral and the aortic valve; they are regurgitant, and in some cases the valvar regurgitation is so severe as to require surgery. The lesions appear as irregular, localised valve thickenings, not vegetative. The pathogenesis of these endocardial lesions is as yet unknown. Some investigators have found thrombi over the involved valves. In order to link the thrombotic occlusions of the vessel and the valve involvement in these patients, it could be hypothesised that the initial valve lesions are thrombi deposits that subsequently promote an unpecific anti-inflammatory response and ultimately become organised.

The isolated finding of aPL antibodies in the absence of clinical manifestations does not require treatment, but patients with thrombotic manifestations have to be fully anticoagulated. It is unknown whether the finding of valve heart disease should be treated, but the tendency is not to give specific therapy to asymptomatic subjects. Nevertheless, these patients should probably receive infective endocarditis prophylaxis.

1. **Veasy LG, Wiedmeier SE, Orsmond GS, et al.** Resurgence of acute rheumatic fever in the Intermountain area of the United States. *N Engl J Med* 1987;**316**:421–7.
 - The paper reports an outbreak of acute rheumatic fever that occurred in 74 children during a 18 month period (from January 1985 to June 1986) at one centre in Salt Lake City. The children were predominantly white and from middle class families with above average incomes and ready access to medical care. There was no apparent increase in the incidence of streptococcal disease or other explanation for the major increase in rheumatic fever. In the previous 10 year period the average incidence had been six cases per year.
2. **Narula J, Virmani R, Reddy KS, Tandon R, eds.** *Rheumatic fever*. Armed Forces Institute of Pathology, Washington: American Registry of Pathology, 1999.
 - This book is a comprehensive multidisciplinary review of the state of the art of rheumatic fever at the present time. The monograph comprises aspects such as history, epidemiology, microbiology of group A streptococci, clinical manifestations, the problem of the resurgence of rheumatic fever, treatment, and prevention (including the progress on the vaccine development).
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6. **Passik CS, Ackermann DM, Pluth JR, et al.** Temporal changes in the causes of aortic stenosis: a surgical pathologic study of 646 cases. *Mayo Clin Proc* 1987;**62**:119–23.
7. **Stewart BF, Siscovick D, Lind BK, et al.** Clinical factors associated with calcific aortic valve disease. *Cardiovascular Health Study. J Am Coll Cardiol* 1997;**29**:630–4.
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9. **Wilmshurst PT, Stevenson RN, Griffiths, et al.** A case-control investigation of the relation between hyperlipidaemia and calcific aortic valve stenosis. *Heart* 1997;**78**:475–9.
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12. **Acierno LJ.** Cardiac complications in acquired immunodeficiency syndrome (AIDS): a review. *J Am Coll Cardiol* 1989;**13**:1144–54.
 - This review emphasises that the most common endocardial lesion seen in AIDS is non-bacterial thrombotic bacterial endocarditis (so-called marantic endocarditis). This type of involvement is probably due to the long-term wasting characteristics of AIDS.
13. **Milei J, Grana D, Fernandez Alonso G, et al.** Cardiac involvement in acquired immunodeficiency syndrome—a review to push action. The committee for the study of cardiac involvement in AIDS. *Clin Cardiol* 1998;**21**:465–72.
14. **Redfield MM, Nicholson WJ, Edwards WD, et al.** Valve disease associated with ergot alkaloid use. Echocardiographic and pathologic correlations. *Ann Intern Med* 1992;**117**:50–2.
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15. **Connolly HM, Crary JL, McGoon MD, et al.** Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997;**337**:581–8.
 - Investigators at the Mayo Clinic describe 24 women in whom valvar heart disease developed after an average of 12 months of treatment with fenfluramine and phentermine. Eight women also had newly documented pulmonary hypertension. At the time of the report valve surgery was needed in five cases of the series. This paper was the first to arouse concern about this relation and prompted other studies that finally confirmed the association.
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18. **Weissman NJ, Tighe JF, Gottdiener JS, et al, for the Sustained-Release Dexfenfluramine Study Group.** An assessment of heart-valve abnormalities in obese patients taking dexfenfluramine, sustained-release dexfenfluramine, or placebo. *N Engl J Med* 1998;**339**:725–32.
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