Cardiol Young 2005; 15: 568–577

ISSN 1047-9511

Review

A new look at acute rheumatic mitral regurgitation

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Keywords: Rheumatic fever; mitral valve; echocardiography; cordal elongation; annular dilation

In developing countries, rheumatic heart disease remains the chief cause of acquired cardiac disease during the first five decades of life.[1] In industrial countries, rheumatic fever and its only sequel, rheumatic heart disease, have become relatively rare because of improved living conditions and effective programs of primary and secondary prevention with penicillin. Significant outbreaks of rheumatic fever, however, occurred in the United States of America during the last two decades of the 20th century,[2–13] and sporadic cases continue to be encountered across the nation.

A resurgence of rheumatic fever in Utah, which began in 1985,[2] has persisted to the present,[14] and has coincided in time with the development of echocardiography. Echocardiography, which is now firmly established as an integral part of the practice of cardiology, is the only new test in the last forty years that aids the clinician in the diagnosis and management of rheumatic fever and rheumatic heart disease. Echocardiography, coupled with Doppler interrogation, is ideally suited for the evaluation of rheumatic heart disease, and has given new insight into the pathogenesis of acute rheumatic carditis.

In endemic regions, cardiologists and cardiac surgeons have gained a new understanding of rheumatic mitral regurgitation.[15,16] This new concept, however, is not discussed in many current paediatric and medical textbooks, or in other authoritative publications.[17,18] Our goal in compiling this review is to present this newer understanding, and to describe how past clinical experience and autopsy findings, as well as recent studies of the function of the mitral valve during life and in the experimental setting, support this new concept. Combining past and present experience into a coherent, unified concept involves a "back to the future" scenario.

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Accepted for publication 27 June 2005

Pre-echocardiographic concept

A discussion of rheumatic fever in the most recently published textbooks varies little from what was published in textbooks thirty years ago. Both then and now, chapters begin the discussion of carditis, with a statement that rheumatic carditis is a pancarditis, in other words the disease involves the endocardium, the myocardium and the pericardium. While such a statement is not completely erroneous, it is simplistic, and lacks a specificity we currently demand in the description of any other form of cardiac disease.

The role of the pericardium

In reviewing the involvement of the three layers of the heart, the role of the pericardium merits only a brief discussion, since rheumatic pericarditis never occurs in the absence of significant mitral valvar involvement.[19] The full blown clinical picture of chest pain, friction rub, and ST-T wave changes on the electrocardiogram with or without radiographic cardiomegaly, is present in less than one-tenth of patients with rheumatic fever.[19] Cardiac tamponade is exceedingly rare. We could find only a single case report.[20] Unlike other forms of pericarditis,[21–23] rheumatic pericardial inflammation almost never results in constrictive pericarditis.

The role of the myocardium

Myocarditis was thought to be responsible for most of the symptoms, and certainly was held to be the cause

of heart failure and death during the acute episode of rheumatic carditis. This concept was endorsed by our most respected authorities, including T. Duckett Jones, Milton Markowitz, Gene Stollerman, Benedict Massell and Jesse Edwards. Although the current buzzword of "evidence-based" was never used in their consideration of acute rheumatic carditis, the evidence from their clinical experience and autopsy findings led to their conclusions. Clinically altered heart tones, elevated sleeping pulse rate, and cardiomegaly seen on a chest film, were considered to be due to myocardial inflammation and resultant chamber enlargement and ventricular dysfunction.[24,25]

Convincing evidence of myocardial involvement came from autopsy findings in children and young adults who died during an acute episode. The left atrium and left ventricle were uniformly massively dilated, which could not be explained by minimal deformity of the mitral valve.[26,27] Microscopic examination showed inflammatory cells along with the pathognomic Aschoff bodies in the myocardium.[28] Some investigators proposed that the Aschoff bodies were necrotic myocardial cells.[29]

Early immunological evidence also supported the concept of myocardial involvement. In 1964, cross-reactive antistreptococcal antibodies were found to bind the sarcolemma of the myocyte.[30] Additional immunological studies stemming from that early experience continued to support significant myocardial involvement, with a demonstration of cross-reactive antistreptococcal antibodies to myosin[31,32] and molecular mimicry between segments of group A M-protein and myosin[33,34] and tropomyosin.[35] Thus, there was strong evidence from a clinical standpoint, autopsy findings, and immunological data that the myocardium was significantly involved.

There was, however, strong clinical evidence 25 years ago, long before the widespread use of echocardiography, that childhood rheumatic carditis was essentially a valvar disease, and that the myocardium did not have a dominant role. Most notably, the right-sided chambers were not dilated as should have been encountered with a global myocarditis.[36,37] In addition, the clinical presentation of non-rheumatic myocarditis was distinctly different from rheumatic carditis. Heart failure without significant mitral regurgitation was the usual presentation, and tachyarrhythmias and ventricular ectopy were common.[38]

Additional evidence against the dominant role of myocarditis comes from the success of valvar replacement. In 1974, Strauss et al.[39] reported that four boys suffering from medically intractable heart failure from rheumatic carditis recovered following prosthetic replacement of the mitral valve. This was a remarkable surprise to everyone except, perhaps, the authors. Yet, this landmark event had relatively little impact in changing the thinking that myocarditis played a dominant role in rheumatic carditis. In 1979, Lewis et al.[40] using M-mode echocardiography, detected no evidence of myocardial dysfunction in an 18-year-old girl in intractable heart failure with marked aortic and mitral regurgitation. This early M-mode echocardiographic demonstration gave them courage to have the patient undergo double valvar replacement. Subsequent to the recovery of the patient, this group replaced the mitral valves in four additional patients suffering from intractable failure during acute episodes of rheumatic carditis. All recovered.

Currently, myocytic injury from whatever cause, be it ischaemia,[41,42] infection,[43] trauma,[44] toxic agents,[45] or cardiopulmonary bypass,[44] is confirmed clinically by echocardiographic demonstration of decreased ventricular function, and by the finding of elevated levels of troponin in the serum. Neither is present during acute rheumatic carditis.

M-mode evaluation, along with cross-sectional and Doppler echocardiographic studies, have also shown that impaired myocardial contractility is not encountered during the initial episode or episodes of rheumatic carditis.[15,46,47] Conversely, normal or increased left ventricular ejection fraction and percent shortening are typically found. Decreased impedence to left ventricular ejection from mitral regurgitation could affect these determinations, but after the surgical restoration of mitral valvar competence, left ventricular function remains normal. Decreased ventricular function is encountered only in patients with long-standing volume overload due to significant mitral regurgitation, and/or aortic regurgitation.[48–50]

As already discussed above, in contrast to other myocarditities, and despite reports of antibodies to myosin and tropomysin, rheumatic carditis is not associated with elevated levels of troponin in the serum . The initial report, and the largest clinical experience determining the levels of troponin in acute rheumatic carditis, comes from Kamblock et al. working in Tahiti.[51,52] Additional reports from the United States of America[53,54] and Turkey[55] confirm the Tahitian experience. This data provides further evidence that the primary site of rheumatic myocarditis is not the myocyte.

Cunningham[56] has demonstrated molecular mimicry between cardiac myosin and streptococcal M-proteins. In addition, she found that Lewis rats immunized with streptococcal M-protein or cardiac myosin develop valvar lesions that mimic rheumatic valvar disease.[56] Despite these findings, from a purely clinical standpoint it is difficult to understand how antibodies to cardiac myosin capable of causing cross-reactive valvar disease do not cause sufficient myocytic injury that can be recognized by

either altered ventricular function or elevated levels of troponin.

Role of the endocardium

Historically, there was clinical, autopsy, and immunological support for the endocardial component of rheumatic pancarditis. The endocardial component includes "valvitis", since the endocardium extends over the valvar leaflets. Autopsy findings supported this concept, since the leaflets were oedematous, contained extensive cellular infiltrates, and presented with fibrinous vegetations on the atrial side of the coapting surfaces of the mitral valve, and on the ventricular aspect of the aortic valvar leaflets. In addition, antibodies to group A streptococcus carbohydrate are elevated in patients with rheumatic mitral valvar disease.[57] These antibodies disappear when the diseased valve is replaced.[58]

The term endocarditic valvitis, however, is somewhat misleading, since the leaflets of the mitral and aortic valves are much more than mere extensions of the endocardium. In the past, all components of the mitral valve were incompletely considered. The changes that occur during an acute episode of rheumatic activity are quite specific, and involve much more than the endocardium of the leaflets, since the entire mitral valvar apparatus is involved. The mitral annular dilation seen with rheumatic carditis was thought to occur secondary to left ventricular dilation from mycarditis. The cordal elongation of the aortic leaflet of the mitral valve, when noted, was also thought to be secondary to myocarditis.[23]

Normal mitral valvar function

Understanding how all components of the mitral valvar apparatus contribute to normal function is necessary to understand how the valve becomes incompetent during the acute rheumatic episode or episodes, as well as the changes that occur after recovery. While the papillary muscles, the left atrium, the left ventricle, and the systemic vascular bed all contribute to the successful function of the mitral valve, we shall limit our discussion to the so-called "intrinsic" components of the mitral valvar apparatus, that is, the leaflets, the annulus, and the tendinous cords.

The two leaflets of the mitral valve are the largest and singularly the most important components of the total mitral valvar apparatus. They are what make the mitral valve a valve. All other components of the apparatus are designed to support the function of the leaflets. While the aortic and mural leaflets have a different gross appearance, individually they vary little in their gross structure.

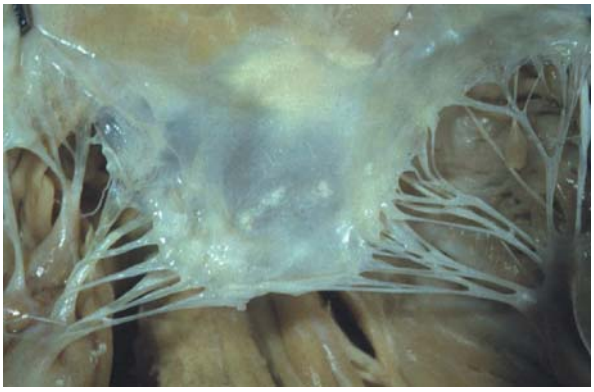

Figure 1.
The aortic leaflet of the mitral valve has a modified delta, or triangular, shape with a broad base attached at the annulus, and a somewhat rounded apex. The tendinous cords inserting in the apical portion of the leaflet are perceptively thinner than the so-called "secondary cords", which insert more centrally on the ventricular aspect of the leaflet. Photograph courtesy of Professor Robert H. Anderson.

The aortic leaflet has a shorter length of attachment to the more fibrous anterior component of the annulus when compared to the mural leaflet, but also has greater depth. It has a somewhat delta, or triangular, shape, with a broad base of attachment, and a rounded apex centrally (Fig. 1).[59]

The aortic leaflet, along with the ventricular septum, serves as the outflow tract of the left ventricle.[60,61] With this important function, it is subject to more stress, and appropriately is slightly thicker than the mural leaflet.

The mural leaflet is attached to the fibrous annulus at the parietal junction of the left atrium with the left ventricle. The mural leaflet has a larger length of attachment or circumference, but is narrower and slightly thinner than the aortic leaflet. It has a semicircular shape overall, but exhibits distinct separations along its length which extend from the apposing edge nearly to the annulus.[61] This gives the mural leaflet a scalloped appearance, with some going so far as to suggest that the scallops are distinct leaflets.[62,63] The chief function of the mural leaflet is to coapt against the aortic leaflet to create an effective seal, the so-called keystone effect. It is the scallops that permit the mural leaflet, with its longer annular attachment, to fulfill this function, functioning akin to the pleats of a skirt.[61]

The edges of both leaflets where their surfaces coapt, and at the points of insertion of the primary cords, a feature to be discussed, are thicker than the more central non-coapting surfaces of the leaflets (Fig. 1). This area, known as the "rough zone", extends around the entire mobile edges of both leaflets, and functions as the competent seal of the valve.

In the normal mitral valve, it is the annulus which defines the mitral valvar orifice, having a

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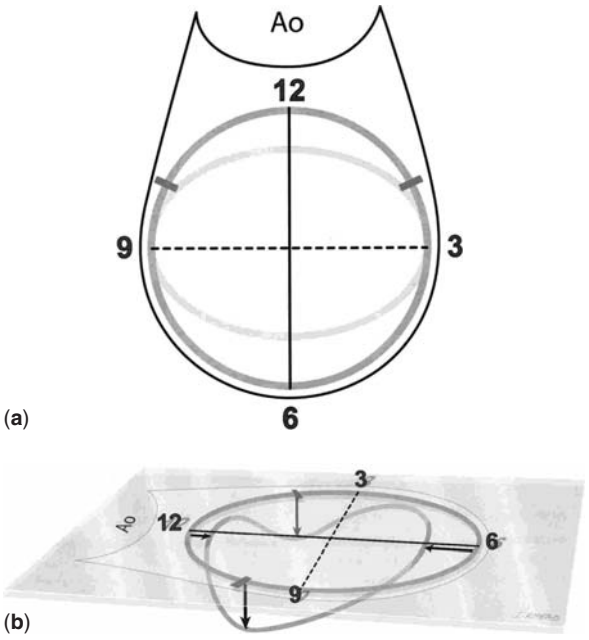

Figure 2.
*A diagram of the orifice of the mitral valve (**a**), with the mid-point of the attachment of the aortic leaflet attachment to the anterior annulus designated as 12:00, while the midpoint of the attachment of the mural leaflet to the posterior annulus is designated as 6:00. The nearly circular configuration of the annulus permits the same diameter in the 3:00 to 9:00 axis as in the 12:00 to 6:00 axis. The two ends of the solitary zone of apposition between the leaflets, the so-called "commissures", are roughly at 10:00 and 2:00 position. With systole, the diameter from 12:00 to 6:00 diameter (shaded) is shortened, while the axis from 3:00 to 9:00 is essentially unaltered. The diagram (**b**) provides a three-dimensional concept of how the annulus changes from a circular, flat position in diastole to an elliptical configuration in systole, thus bringing the mid-portion of the aortic and mural leaflets into closer proximity.*

larger diastolic and a smaller systolic diameter. The annulus serves as a combined anchor and hinge to support the motion of the leaflets. The structure of the anterior and posterior parts of the annulus differ markedly. The anterior annulus has a thick ridge of connective tissue that joins the non-coronary and left coronary leaflets of the aortic valve. This central band of connective tissue extends both to the right and left around the aortic root, and also around the aortic leaflet of the mitral valve. It is called the region of valvar continuity. The extensions from the central portion of this fibrous skeleton of the heart have a triangular appearance, and are appropriately called the right and left fibrous trigones. The fibrous trigones taper in thickness as they go around the aortic leaflet to join the thinner annulus of the mural leaflet.[60,61]

The posterior annulus occupies two-thirds of the overall valvar circumference, while the anterior annulus obviously occupies only one-third. Although anatomically the posterior annulus is typically called the fibrous annulus, a fibrous band is not as readily detected as with the anterior annulus.[60,61]

The annulus brings the leaflets closer together in systole to allow a large surface of the leaflets to coapt, insuring the keystone effect and valvar competence.[59,60] The movement of the annulus, which makes the orifice of the mitral valve smaller in systole, is not accomplished by a sphincter-like movement. Instead, the annulus changes from a flat planar axis in diastole to an ellipse in systole, giving the well-described saddle-shaped configuration to the mitral valve.[64–67] This is accomplished by the annulus in the region of the commissural cords being pulled during systole below the horizontal axis of the annulus along the central attachment of the leaflets. The total length, or circumference, of the annulus does not change, but the diameter decreases, permitting the leaflets to have a larger surface for coaptation. This spatial concept can be more readily understood by considering schematically the midpoint of the attachment of the aortic leaflet to the anterior annulus as 12:00, and the midpoint of the attachment of the posterior annulus to be 6:00 (Fig. 2a). In diastole, the mitral orifice is on a planar axis, and is nearly circular. With systole, the diameter of the axis from 12:00 to 6:00 is decreased, enabling coaptation of the leaflets. The diameter of the axis from 3:00 to 9:00 is essentially unchanged. This critical function occurs when the annulus assumes an elliptical configuration, as the parts of the annulus in the regions of the ends of the solitary zone of apposition between the leaflets, at 10:00 and 2:00, is pulled below the planar axis (Fig. 2b).

Tendinous cords

The arrangement of the tendinous cords is unique to an individual. The variation includes the number of cords that arise from the two papillary muscles, the site of insertion into the aortic and mural leaflets, the size and thickness of the individual cords, the number that insert into the thickened rough zone of the leaflet, and whether the insertions include just a single or multiple branches of the cord.[60] Basically the cords can be assigned to three groups by their site of insertion into the leaflet.[60,61] Those that insert into the thickened edge of the rough zone are called "primary" or "marginal" cords. Those that insert farther into the central portion of the body of the leaflet are termed "secondary" cords. Some secondary cords insert beyond the rough zone into the body of the leaflet without branching, and are called "strut" cords. The third group, the so-called "commissural" cords, usually arise as single cords from each of the papillary muscles, and send branches to both leaflets

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adjacent to the mitral annulus at the site of their most peripheral attachment.[60] These so-called commissural cords, therefore, support the ends of the solitary zone of apposition between the aortic and mural leaflets.

Cordal function varies between these three groups. The primary cords are responsible for bringing the leaflets down into the left ventricle so as to gain a large area of coaptation, and thus to insure the keystone effect.[60] Because the primary cords attach to the leaflets where they coapt, they are subject to less stress. Hence they are thinner than secondary cords (Fig. 1). Cutting a primary cord results in immediate mitral regurgitation, but not in loss of ventricular function.[68]

The secondary cords are necessary to maintain valvar and ventricular systolic interaction. They aid in shortening the ventricular myocardium to decrease the size of the left ventricular cavity. Cutting secondary cords does not result in mitral regurgitation, but does result in decreased ventricular function.[68]

The commissural cords behave similarly to the action of the primary cords in maintaining coaptation of the leaflets. Primary cords inserting along the edges of the scallops of the mural leaflet are also necessary to maintain valvar competence.[61] A qualifying comment concerning the term "commissure" is appropriate. When applied to the valvar leaflets, the term "commissure" defines the area of coaptation. In the mitral valve, therefore, there is but a solitary commissure, albeit that its two ends are usually defined as the "commissures". The commissural cords, however, are involved with the leaflets at their most peripheral attachments to the annulus. In addition to maintaining coaptation at the base of the leaflets, the commissural cords may also contribute to annular configuration.

Acute rheumatic carditis

What happens to the individual components of the mitral valve during acute rheumatic carditis? The most important component, the leaflets, is heavily involved. The coapting surfaces develop fibrinous vegetations on their atrial side. The body of the leaflets show cellular infiltrates, oedema, and neovascularization.[23] These impressive changes probably do not result in any valvar incompetence. Oedema of the leaflets should not cause loss of coaptation. Even the fibrinous vegetations apparently do not cause significant regurgitant flow. Nothing is seen on Doppler studies during the initial bout or bouts of carditis to indicate that the specific involvement of the leaflets results in mitral valvar incompetence. The extensive changes in the leaflets that follow the acute episode do set the table, so to speak, for what follows to establish chronic rheumatic heart disease. This is persistent mitral regurgitation from leaflet and cordal contraction, and mitral stenosis from thickening of the leaflets, and fusion of the cords and the ends of the zone of apposition between the leaflets.

The annulus dilates during acute rheumatic carditis, as described by Carey Coombs in 1924,[69] who stated "At this time the cusps are but little deformed but owing to the wide separation of the ring the valvular apparatus is apparently rendered inadequate." In the 1950s, initial efforts to decrease annular size involved suturing across the ends of the zone of apposition between the leaflets.[70,71] Prosthetic valves well above the expected size of the annulus in younger patients can be well accommodated if replacement is deemed necessary.[72] Although the cause of the annular dilation was always assumed to be myocarditis, this seems unlikely in the absence of myocytic injury and ventricular dysfunction. As the volume of mitral regurgitation increases, both the left atrium and left ventricle dilate, producing further annular dilation, and cordal and papillary muscular dysfunction.[48] Thus, the adage that mitral regurgitation begets mitral regurgitation.[73]

Marcus et al.[48] described well the pathogenesis of acute mitral regurgitation. They argued that the initial post-streptococcal injury causes annular dilation, leading to a decrease in effective coaptation of the leaflets. This loss of the large surface of coaptation results in increased tension on primary cords. The primary cords, structurally unsuited to excessive tension, elongate, causing the edge of the aortic leaflet to lose effective apposition with the mural leaflet, and resulting in prolapse of the apposing edge of the aortic leaflet into the left atrium. The loss of coaptation of the aortic leaflet results in a regurgitant orifice, with a posterolaterally directed jet of mitral regurgitation striking the left atrium at the site of McCallum's patch.[74]

Primary cordal stretching, and prolapse of the aortic leaflet of the mitral valve, was described by Carpentier over 20 years ago.[75] This remarkable French cardiovascular surgeon, well-known for correcting mitral annular dilation with a plastic ring which bears his name, and which is employed worldwide, added cordal shortening to correct rheumatic mitral regurgitation over two decades ago.[76] The combination of reducing annular size with a plastic ring, and plastic repair of cords and leaflets, is now standard for correction of stable rheumatic mitral regurgitation.[15,76–79] Prosthetic replacement is usually reserved for intractable failure during acute carditis, since repair may break down, requiring a second operative procedure. In the 21st Century, where established cardiovascular surgery is available, no patient should die from rheumatic mitral regurgitation or aortic regurgitation, be it acute or chronic.[80]

While we have stressed involvement of primary cords of the aortic leaflet of the mitral valve, it should be appreciated that infrequently cords of the mural leaflet may also be involved, and may even rupture during an acute episode.[81]

Recent studies of mitral valvar function

Numerous clinical and experimental studies of mitral valvar function conducted recently, without rheumatic mitral regurgitation in mind, support the new post-echocardiographic concept of the pathogenesis of the initial episode of childhood rheumatic carditis. In 1997, Obadia et al.,[68] using a working pig heart, found that primary cords of the aortic leaflet are important for mitral valvar competence, with the secondary cords being more involved with left ventricular function.

A highly detailed study of five excised porcine mitral valves mounted in a left heart simulator was reported by a collaborating group from Aarhus University, Denmark and the Georgia Institute of Technology, Atlanta.[82] In this study, the position of the papillary muscles was changed to alter cordal tension which, in turn, caused functional mitral regurgitation.

A recent report by Nazari et al. from Pavia University[83] summarized the effects of varying systolic stress distribution on the cords supporting the aortic leaflet of the mitral valve under normal and pathologic situations. This insightful theoretical analysis, similarly done without specific consideration of rheumatic carditis, supports the new post-echocardiographic concept of childhood rheumatic mitral regurgitation. Figure 3 is reproduced (with permission) from their article.

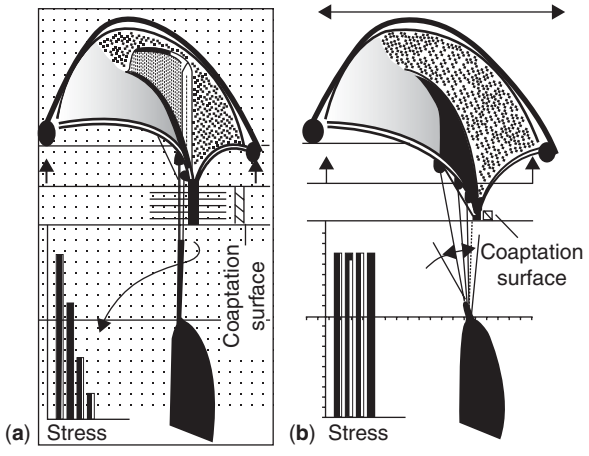

Figure 3.
This schematic illustrates how annular dilation results in loss of coaptation between the surfaces of the leaflets, which in turn causes an increased tension on the primary tendinous cords. Reproduced with permission from Nazari et al. J Cardiovasc Surg 2000; 41: 193–202.

Lomholt et al. at the Aarhus University in Denmark[84] reported an elegant experimental study in a porcine model using miniature C-arm pressure transducers to measure cordal tension in primary and secondary mitral cords. The miniature transducers were inserted into cut cords during cardiopulmonary bypass. When the animals became stable after removal from bypass, they were subjected to manoeuvres to raise and lower left ventricular pressure, thereby altering cordal tension. With partial aortic occlusion causing an increase in left ventricular pressure from 109 to 152 millimetres of mercury, cordal tension in the strut cords rose by 45 percent. Conversely, partial caval obstruction effecting a drop of left ventricular pressure from 100 to 90 millimetres of mercury, reduced cordal tension by approximately half. A strikingly similar study, albeit infrequently cited, was reported in 1963 by Salisbury et al.[85] Their study was done with 15 mongrel dogs, using essentially the same measurements of cordal tension subsequent to bypass with a small pressure transducer. Their study also showed that cordal tension was proportional to left ventricular pressure. In addition, they found that increased left ventricular volume also caused increased cordal tension.

While it is clearly evident that annular dilation is an early event leading to mitral regurgitation, we do not have a precise explanation for why it occurs. A possibility, not previously considered, is that injured commissural cords might stretch similarly to what occurs with primary cords. This could result in the annulus failing to assume an elliptical configuration. If the diameter of the annulus from 12:00 to 6:00 were not reduced, a smaller area of leaflet coaptation would result (Fig. 2a,b). With minimal injury, resolution of the acute episode could permit the cords and the annulus to return to normal or near normal, which could explain the frequent disappearance of the murmur of mitral regurgitation. We emphasize that such an initial event, while logical, remains theoretical, and will require studies for confirmation.

The new concept of the pathogenesis of childhood rheumatic mitral regurgitation admittedly is not the total answer, but does explain many aspects of acute rheumatic carditis which are infrequently or incompletely addressed. Molecular mimicry between components of group A streptococcus and components of human cardiac valvar tissue is an accepted concept explaining the "valvitis" of acute rheumatic carditis. Molecular mimicry, however, should involve both atrioventricular valves equally, which clearly is not the case. Significant tricuspid regurgitation virtually never occurs with the initial episode or episodes of rheumatic carditis, whereas mitral regurgitation is the benchmark of rheumatic carditis. The principal difference between the two valves is the tension to which they are

subject from their respective ventricles. Left ventricular pressure is roughly four times that of the right ventricle. Significant tricuspid regurgitation occurs in the setting of mitral valvar disease and secondary pulmonary hypertension.[86] Rheumatic tricuspid regurgitation, as with rheumatic mitral regurgitation, follows annular dilation[86] and surgical repair is technically the same, that is, annuloplasty.

Figures 4a, 4b and 4c demonstrate the wide spectrum of echocardiographic findings in childhood acute rheumatic mitral regurgitation, from gross prolapse of the apposing edge of the aortic leaflet (Fig. 4a), to the posterolateral jet of mitral regurgitation associated with a grade 3 murmur of mitral regurgitation (Fig. 4b), and to a holosystolic posterolateral jet that is not audible in a patient with Sydenham's chorea (Fig. 4c).

The posterolateral jet is typical of rheumatic mitral regurgitation in childhood. When large, this jet causes a lesion of thickened endocardium known as MacCallum's patch.[74] This lesion is seen only on postmortem examination or at open heart surgery. The lesion differs from other endocardial jet lesions in that cellular infiltrate is present in the subendocardial tissue. It is not known if smaller jets of mitral regurgitation also cause subendocardial cellular infiltrate. With chronic rheumatic mitral regurgitation, fusion of the leaflets and cords, and contracture, can result in more central jets and smaller patches of endocardial thickening.[87]

In a significant number of patients with "pure" chorea and isolated rheumatic polyarthritis, a holosystolic posterolaterally directed jet of mitral regurgitation that cannot be heard by auscultation can be detected with Doppler echocardiography (Fig. 4c). Some of these patients later develop murmurs of mitral regurgitation. In others who initially have a murmur of mitral regurgitation which disappears on follow-up, a posterolateral jet of mitral regurgitation may still be detected with Doppler echocardiography. This phenomenon is called "subclinical carditis". Its importance has not been established, and a worthwhile discussion of this somewhat controversial topic is beyond the scope of this presentation. The American Heart Association, with a justifiable concern that over-interpretation of echocardiographic findings could lead to iatrogenic disease, has recommended that mitral regurgitation must be heard to validate the presence of carditis.[17,88] Experience to date suggests their concern is not justified, and that the use of echocardiography is more likely to lead to a correct diagnosis than to an over-diagnosis of rheumatic heart disease.[89,90]

Institutions that cared for large numbers of cases of rheumatic fever during the first half of the last century had regimes of prolonged and strict bed rest. This practice was based largely on the empirical observation

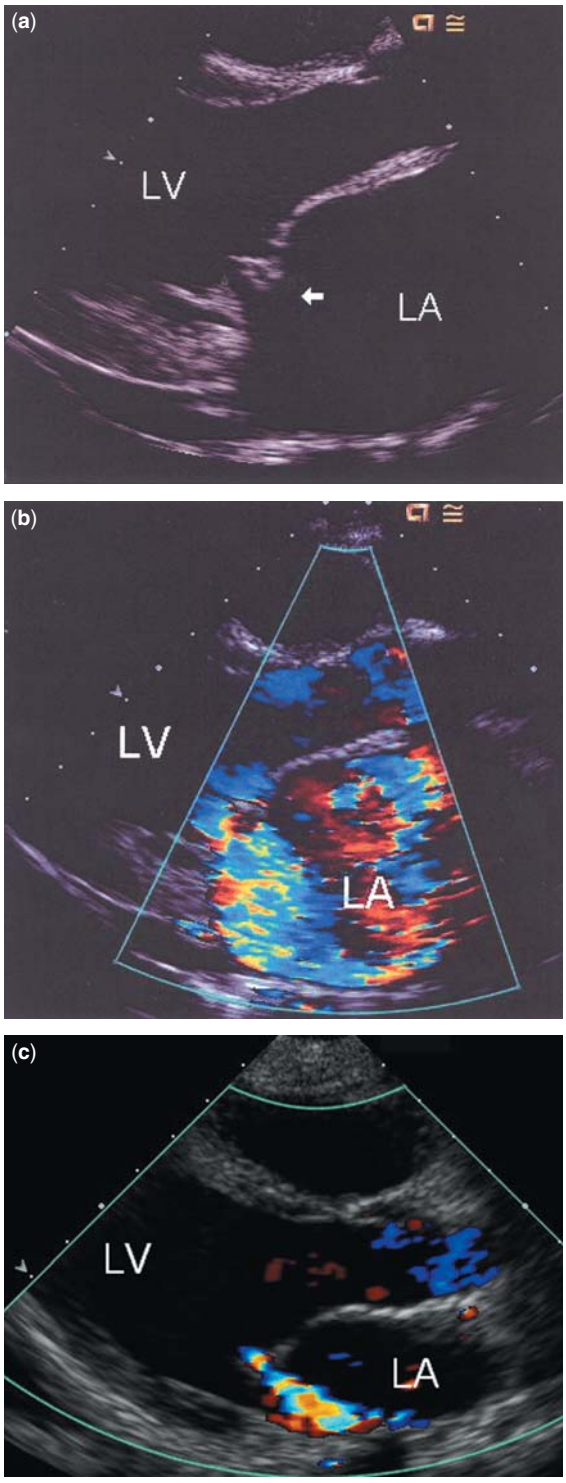

Figure 4.
*(**a**) shows prolapse of the apposing edge (arrow) of a thickened aortic leaflet as seen in a 12-year-old boy with a grade 3 murmur of mitral regurgitation. (**b**) shows a turbulent mosaic jet of mitral regurgitation directed posterolaterally as seen on color flow Doppler in a 10-year-old boy with a grade 3 murmur of mitral regurgitation, and a grade 2 mid-diastolic murmur, the so-called Carey Coombs murmur. (**c**) shows a posterolateral jet of mitral regurgitation detected in a 10-year-old girl with Syndenham's chorea, in whom no murmur could be heard.*

https://doi.org/10.1017/S104795110500171X Published online by Cambridge University Press

that patients improved with bed rest, sometimes dramatically. There were no randomized studies, except for a "control" study which showed patients cared for at home had more residual rheumatic heart disease than those who received institutional convalescent care.[91] At that time, myocarditis was considered to be the dominant component of rheumatic pancarditis, and the most effective way to decrease cardiac output was to put the patient on bed rest. As discussed, both recent and past experimental studies of mitral valvar function have shown that cordal tension is decreased with lower left ventricular pressure. Thus, the beneficial effect of bed rest in patients with acute carditis is more likely due to reduced tension of the primary cords of the aortic leaflet. Removing children from active play, and placing them on bed rest, is an effective way of decreasing cordal tension. While such studies have yet to be done, this newer understanding would suggest that afterload reducing agents may also be beneficial in this setting.

Children with polyarthritis tend to develop less severe rheumatic carditis. There are probably two reasons why this is true. Children with polyarthritis are inactive because of pain and are also more likely to seek medical care and be placed on bed rest. This observation also offers additional support of the new concept.

We stress that this new concept does not explain specifically how the annulus and cords are initially injured, nor does it explain how mitral regurgitation progresses to mitral stenosis. It does, however, give us reason to consider valvar structure and function in seeking a more complete explanation of both acute and chronic rheumatic heart disease.

Acknowledgements

Dr. Edward B. Clark and Dr. Harry R. Hill reviewed the manuscript and made editorial suggestions. Members of the University of Utah Post-Streptococcal Syndrome Study Team offered critical suggestions.

References

1. Stollerman GH. Rheumatic fever. Lancet 1997; 349: 935–942.
2. Veasy LG, Wiedemeier SE, Orsmond GS, et al. Resurgence of acute rheumatic fever in the intermountain area of the United States. N Engl J Med 1987; 316: 412–427.
3. Congeni B, Rizzo C, Congeni J, Srunavasan VV. Outbreak of acute rheumatic fever in northeast Ohio. J Pediatr 1987; 111: 176–179.
4. Hosier DM, Craenen JM, Teske DW, Wheller JJ. Resurgence of acute rheumatic fever. Am J Dis Child 1987; 141: 730–733.
5. Wald ER, Dashefsky B, Feidt C, Chiponis D, Byers C. Acute rheumatic fever in western Pennsylvania and the Tristate Area. Pediatrics 1987; 80: 371–374.
6. Burns DL, Ginsburg CM. Recrudescence of acute rheumatic fever in Dallas, Texas [Abstract 495]. Proceedings of the Society for Pediatric Research. Pediatr Res 1987; 21: 256A.
7. Papadimas T, Escamilla J, Garst P, et al. Acute rheumatic fever at a Navy training center – San Diego, California. Morb Mortal Wkly Rep 1988; 37: 101–104.
8. Sampson GL, Williams RG, House MA. Acute rheumatic fever among trainees, Ft. Leonard Wood, Missouri 1997–88. Morb Mortal Wkly Rep 1988; 37: 519–522.
9. Westlake RM, Graham TP, Edwards KM. An outbreak of acute rheumatic fever in Tennessee. Pediatr Infect Dis J 1990; 9: 97–100.
10. Leggiadro RJ, Birnbaum SE, Chase NA, Myers LK. A resurgence of acute rheumatic fever in a mid-South children's hospital. South Med J 1990; 83: 1418–1420.
11. Mason T, Fisher M, Kujala G. Acute rheumatic fever in West Virginia: not just a disease of children. Arch Intern Med 1991; 151: 133–136.
12. Hefelfinger DC. Resurgence of acute rheumatic fever in West Alabama. South Med J 1992; 85: 261–265.
13. Kavey RE, Kaplan EL. Resurgence of acute rheumatic fever [Letter]. Pediatrics 1989; 84: 585–586.
14. Tani LY, Veasy LG, Minich LL, Shaddy RE, Ruttenberg HD, Orsmond GS. Is rheumatic fever still a problem in the US [Abstract]. Pediatrics 1998; 102 (Suppl); 685.
15. Marcus RH, Sareli P, Pocock WA, et al. Functional anatomy of severe mitral regurgitation in active rheumatic carditis. Am J Cardiol 1989; 63: 577–584.
16. Kinsley RH, Pocock WA. Rheumatic fever and rheumatic heart disease. In: Barlow JB (ed.). Perspectives on the Mitral Valve. FA Davis and Company, Philadelphia, Pennsylvania, 1987, pp 227–259.
17. Dajani AS, Ayoub E, Burman FZ, et al. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease of the Council of Cardiovascular Disease in the Young of the American Heart Association. Guidelines for the diagnosis of rheumatic fever: Jones criteria 1992 update. JAMA 1992; 268: 2069–2073.
18. Cheitlin MD, Armstrong WF, Aurigemma A, et al. ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography: Summary Article. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2003; 108: 1–17.
19. Stollerman GH. Rheumatic Fever and Streptococcal Infection. Grune & Stratton, New York, 1975, pp 159.
20. Tan AT, Mah DK, Chia BL. Cardiac tamponade in acute rheumatic carditis. Ann Rheum Dis 1983; 42: 699–701.
21. Przybojewski JZ. Rheumatic constrictive pericarditis. A case report. S Afr Med J 1981; 59: 682–686.
22. Virmani R, Farb A, Berske A, Narula J. Pathology of acute rheumatic carditis. In: Narula J, Virmani R, Reddy KS, Tandon R (eds). Rheumatic Fever. Armed Forces Institute of Pathology, Washington, DC, 1999, p 233.
23. Edwards JE. An Atlas of Acquired Diseases of the Heart and Great Vessels. Vol 1. WB Saunders Company, Philadelphia, Pennsylvania, 1961, pp 4–93.
24. Stollerman GH. Rheumatic Fever and Streptococcal Infection. Grune and Stratton, New York, 1975, pp 162–163.
25. Ayoub EM. Acute rheumatic fever. In: Emmanouilides GC, Allen HD, Reimenschneider TA, Gutgessel HB (eds). Moss and Adams Heart Diseases in Infants, Children and Adolescents, 5th edn. Williams & Wilkins, Baltimore, 1995, p 1406.
26. Stollerman GH. Rheumatic Fever and Streptococcal Infection. Grune and Stratton, New York, 1975, p 130.
27. Netter FH, in collaboration with Edwards JE. The heart. In: Yonkman FF (ed.). The Ciba Collection of Medical Illustrations, 1978, Vol 5, Plate 4, p 169.

28. Stollerman GH. Rheumatic Fever and Streptococcal Infection. Grune & Stratton, New York, 1975, pp 124–129.
29. Murphy GE. The histopathology of rheumatic fever: a critical review. In: Thomas L (ed.). Rheumatic Fever. Minnesota Press, Minneapolis, 1952, pp 28–51.
30. Kaplan MH, Bolander R, Raketa L, Blair J. Presence of bound immunoglobins and complement in the myocardium in acute rheumatic fever. N Engl J Med 1964; 271: 637–645.
31. Zabriskie JB, Freimer EH. An immunologic relationship between the group A streptococcus and mammalian muscle. J Exp Med 1966; 124: 661–668.
32. Krisher K, Cunningham MW. Myosin: a link between streptococci and heart. Science 1985; 227: 413–415.
33. Dale JB, Beachy EH. Epitopes of streptococcal M-proteins shared with cardiac myosin. J Exp Med 1985; 162: 583–591.
34. Dell A, Antone SM, Gauntt CJ, Crossley CD, Clark WA, Cunningham MW. Autoimmune determinants of rheumatic carditis: localization of epitopes in cardiac myosin. Eur Heart J 1991; 12 (Suppl D): 158–162.
35. Manjula BN, Fischetti VA. Tropomysin-like seven residue periodicity in three immunologically distinct streptococcal M-proteins and its implications for the antiphagocytic property of the molecules. J Exp Med 1980; 151: 695–708.
36. Stollerman GH. Rheumatic Fever and Streptococcal Infection. Grune & Stratton, New York, 1975, p 130.
37. Edwards JE. An Atlas of Acquired Diseases of the Heart and Great Vessels, Vol 1. WB Saunders Company, Philadelphia, 1961, p 72.
38. Lewis AB. Myocarditis. In: Emmanouilides GC, Reimenschneider TA, Allen HD, Gutgessel HP (eds). Moss and Adams Heart Disease in Infants, Children and Adolescents, 5th edn. Williams & Wilkins, Baltimore, 1995, pp 1381–1390.
39. Strauss AW, Goldring D, Kessani J. Valve replacement in acute rheumatic heart disease. J Thor Cardiovasc Surg 1974; 67: 59–70.
40. Lewis BS, Gelt IL, Milo S, Gotsman MS. Echocardiography and valve replacement in the critically ill patient with rheumatic carditis. Ann Thorac Surg 1979; 27: 529–535.
41. Adams JE, Bodor GS, Davila-Roman VG, et al. Cardiac troponin I: a marker with high specificity for cardiac injury. Circulation 1993; 88: 101–106.
42. Apple FS, Falahati A, Paulsen PR, Miller EA, Sharkey SW. Improved detection of minor ischemic myocardial injury with measurement of serum cardiac troponin I. Clin Chem 1997; 43: 2047–2051.
43. Smith SC, Ladenson JH, Mason JW, Jaffe AS. Elevations of cardiac troponin I associated with myocarditis: experimental and clinical correlates. Circulation 1997; 95: 163–168.
44. Herrmann J, Volbracht L, Haude M, et al. Biochemical markers of ischemic and non-ischemic myocardial damage Med Clin 2001; 96: 144–156.
45. Lipshultz SE, Rifai N, Sallan SE, et al. Predictive value of cardiac troponin T in pediatric patients at risk for myocardial injury. Circulation 1997; 96: 2641–2648.
46. Essop MR, Wisenbaugh T, Sareli P. Evidence against a myocardial factor as the cause of left ventricular dilation in active rheumatic carditis. J Am Coll Cardiol 1993; 22: 826–829.
47. Vasan RS, Shrivistava S, Vijayakumar M, Narang R, Lister BC, Narula J. Echocardiographic evaluation of patients with acute rheumatic fever and rheumatic carditis. Circulation 1996; 94: 73–82.
48. Marcus RH, Sareli P, Pocock WA, Barlow JB. The spectrum of severe rheumatic valve disease in a developing country. Correlation among pathologic findings and hemodynamic sequelae. Ann Intern Med 1994; 120: 177–183.
49. Gentles TL, Colan SD, Wilson NJ, Biosa R, Neutze JM. Left ventricular mechanics during and after acute rheumatic fever: contractile dysfunction is closely related to valve regurgitation. J Am Coll Cardiol 2001; 37: 201–207.
50. Kontos GJ, Schiff H, Gersh B, Bove A. Left ventricular function in subacute and chronic mitral regurgitation effect on function early postoperatively. J Thorac Cardiovasc Surg 1989; 98: 163–169.
51. Kamblock JM, Payot L, Cao MM, et al. Does rheumatic myocarditis really exist? A study based on a systematic analysis with echocardiography and cardiac troponin I dosages [Abstract]. Circulation 2000; 102: II-788.
52. Kamblock JM, Payot L, Iung B, et al. Does rheumatic myocarditis really exist? Systematic study with echocardiography and cardiac troponin I blood levels. Eur Heart J 2003; 24: 855–862.
53. Gupta M, Lent RW, Kaplan EL, Zabriskie JB. Serum cardiac troponin I in acute rheumatic fever. Am J Cardiol 2002; 89: 779–782.
54. Williams RV, Minich LL, Shaddy RE, Veasy LG, Tani LY. Evidence for lack of myocardial injury in children with acute rheumatic carditis. Cardiol Young 2002; 12: 519–522.
55. Olehan D, Ayabakan C, Hallioglu O. Role of serum cardiac troponin T in the diagnosis of acute rheumatic fever and rheumatic carditis. Heart 2004; 90: 689–690.
56. Cunningham MW. Autoimmunity and molecular mimicry in the pathogenesis of post-streptococcal heart disease. Frontiers in Bioscience 2003; 8: S533–S543.
57. Dudding BA, Ayoub EM. Persistence of streptococcal group A antibody in patients with rheumatic valvular disease. J Exp Med 1968; 128: 1081–1098.
58. Ayoub EM, Taranta A, Bartley TD. Effect of valvular surgery on antibody to the streptococcal group A carbohydrate in rheumatic valvular disease. J Lib Clin Med 1985; 105: 114–119.
59. Edwards WD. Cardiac anatomy and examination of specimens. In: Emmanoulides GC, Reimenschneider TA, Allen HD, Gutgessel HP (eds). Moss and Adams Heart Disease in Infants, Children and Adolescents, 5th edn. Williams and Wilkins, Baltimore, MD, 1995, pp 82–83.
60. Antunes MJ. Functional anatomy of the mitral valve. In: Barlow JB (ed.). Perspectives on the Mitral Valve. F.A. Davis Company, Philadelphia, PA, 1987, pp 1–14.
61. Kanani M, Anderson RH. The anatomy of the mitral valve: a retrospective analysis of yesterday's future. J Heart Dis 2003; 12: 543–547.
62. Kumar N, Kumar M, Duran CMG. A revised terminology for recording surgical findings of the mitral valve. J Heart Valve Dis 1995; 4: 70–75.
63. Yacoub MH. Anatomy of the cordae and cusps. In: Kalmanson D (ed.). The Mitral Valve. A Pluridisciplinary Approach. Edward Arnold, London, 1976, pp 15–20.
64. Levine RA, Triulzi, Harrigan P, Weyman AE. The relationship of mitral annular shape to the diagnosis of mitral valve prolapse. Circulation 1987; 4: 756–767.
65. Salgo IS, Gorman III JH, Gorman RC, et al. Structural implications of mitral annular geometry and the saddle shape: a finite element analysis [Abstract]. Circulation 2000; 102 (18 Suppl II): II-631.
66. Jiminez HF, Sorensen DD, He Z, HE S, Yoganathan AP. Effects of a saddle shaped annulus on mitral valve function and chordal force distribution: An in vitro study. Ann Biomed Eng 2003; 31: 1171–1181.
67. Kaplan SR, Bashein G, Sheehan FH, et al. Three dimensional echocardiographic assessment of annular shape changes in the normal and regurgitant mitral valve. Am Heart J 2000; 139: 378–387.
68. Obadia JF, Casali C, Chassignolle JF, Janier M. Mitral subvalvular apparatus. Different functions of primary and secondary chordae. Circulation 1997; 96: 3124–3128.
69. Coombs CF. Physical signs. In: Coombs CF (ed.). Rheumatic Heart Disease. John Wright and Sons, Bristol, 1924, pp 182–191.
70. Lillehei CW, Gott VL, DeWall RA, Varco RL. The surgical treatment of stenotic or regurgitant lesions of the mitral and/or aortic valves by direct vision utilizing a pump oxygenator. J Thorac Surg 1958; 35: 154–191.

71. Merendino KA, Thomas GI, Jesseph JE, Herron PW, Winterscheid LC, Vetto RR. The open correction of mitral regurgitation and/or stenosis with special reference to regurgitation treated by posteromedial annuloplasty utilizing a pump-oxygenator. Ann Surg 1959; 150: 5–22.
72. Kinsley RH, Pocock WA. Rheumatic fever and rheumatic heart disease. In: Barlow JB (ed.). Perspectives on the Mitral Valve. F.A. Davis Company, Philadelphia, PA, 1987, p 236.
73. Edwards JE, Burchell HB. Pathologic anatomy of mitral insufficiency. Mayo Clin Proc 1958; 33: 497–509.
74. MacCallum WG. Rheumatic lesions of the left auricle of the heart. Bull Johns Hopkins Hospital 1924; 35: 341.
75. Carpentier A. Reconstructive surgery of rheumatic valvular disease in children under 12 years of age. In: Borman JB, Gotsman MS (eds). Rheumatic Valvular Disease in Children. Springer-Verlag, New York, 1980, pp 149–159.
76. Chauvaud S, Perier P, Touati G, et al. Long term results of valve repair in children with acquired mitral valve incompetence. Circulation 1986; 74: I104–I109.
77. Duran CG. Surgical management of elongated chordae of the mitral valve. J Cardiac Surg 1989; 4: 253–259.
78 Kumar AS, Rao PN, Saxena A. Results of mitral valve reconstruction in children with rheumatic heart disease. Ann Thorac Surg 1995; 60: 1044–1047.
79. Kalangos A, Beghetti M, Vala D, et al. Anterior mitral leaflet prolapse as a primary cause of pure rheumatic mitral insufficiency. Ann Thorac Surg 2000; 69: 755–761.
80. Barlow JB. Epilogue in Barlow JB, Perspectives on the Mitral Valve. FA Davis and Company, Philadelphia, PA, 1987, p 361.
81. Haizlip JA, DiRusso GB, Vernon DD, Tani LY. Flail posterior leaflet of the mitral valve in acute rheumatic carditis. Pediatr Cardiol 2004; 25: 165–166.
82. Nielsen SL, Nygaard H, Fontaine AA, et al. Chordal force distribution determines systolic mitral leaflet configuration and severity of functional mitral regurgitation. J Am Coll Cardiol 1999; 33: 843–853.
83. Nazari S, Carli F, Salvi S, et al. Patterns of systolic stress distribution on mitral valve aortic leaflet chordal apparatus: a structural mechanical theoretical analysis. J Cardiovasc Surg 2000; 41: 193–202.
84. Lomholt M, Nielsen SL, Hansen SB, Andersen NT, Hasenkam JM. Differential tension between secondary and primary mitral chordae in an acute in-vivo porcine model. J Heart Valve Dis 2002; 11: 337–345.
85. Salisbury PF, Cross CE, Reiben PA. Chordae tendineae tension. Am J Physiol 1963; 205: 385–392.
86. Ewy GA. Tricuspid valve disease. In: Alpert JS, Dalin JE, Rahimtoola SH (eds). Valvular Heart Disease. Lippincott Williams and Wilkins, Philadelphia, PA, 2000, p 379.
87. Virmani R, Farb A, Burke AP, Narula J. Pathology of acute rheumatic carditis. In: Narula J, Virmani R, Reddy KS, Tandon R (eds). Rheumatic Fever. American Registry of Pathology Armed Forces Institute of Pathology, Washington, DC, 1999, p 221.
88. Ferrieri P. Jones Criteria Working Group. Proceedings of the Jones Criteria Workshop. Circulation 2002; 106: 2521–2523.
89. Grover A, Dhawan A, Iyengar SD, Anand IS, Wahi PL, Ganguly NK. Epidemiology of rheumatic fever and rheumatic heart disease in a rural community in northern India. Bull WHO 1993; 71: 59–66.
90. Regmi DR, Pandey MR. Prevalence of rheumatic fever and rheumatic heart disease in school children of Kathmandu City. Ind Heart J 1997; 49: 518–520.
91. Taran LM. The value of convalescent care for rheumatic children. J Pediatr 1941; 18: 737–749.