SCIENTIFIC LETTER

Heart valve structure: a predisposing factor for rheumatic heart disease

S Nayar, P G Nayar, K M Cherian

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Rheumatic fever and its cardiac sequelae continue to be an enigma as to why some people are predisposed to cardiac involvement while others are not. That this is due in predisposed patients to an autoimmune reaction to untreated or partially treated group A streptococcal pharyngitis has been established. The component of the bacteria responsible for the antigen cross reactivity to the heart tissue has not been established. Cross reactivity was initially observed in extracts of the streptococcal cell wall. The M protein has been the most extensively studied component of the streptococcus.[1] The streptococcal cell wall has a high concentration of *N*-acetyl-glucosamine, which is also found in high concentrations in valvar tissue.[2]

The group A streptococcus capsule is composed of hyaluronic acid, which is also increased in valves having increased myxomatous tissue.[3] As hyaluronic acid is a common component we hypothesised that this may be responsible for the cross reactivity.

METHODS

We studied 134 mitral and aortic valves removed surgically for either stenosis or regurgitation or from double valve replacements. The valves were examined grossly for commissural fusion; thickening of leaflets; shortening, thickening and fusion of chordae tendineae; and presence of calcification. The presence of these features was taken as evidence of infection.

After gross examination, a sample of the whole length of the leaflet was taken from the leaflet avoiding calcified areas and was subjected to routine histopathological processing. The sections were stained with haematoxylin and eosin, elastic van Gieson (where collagen is stained reddish-brown and elastic fibres are stained black) and Alcian blue at pH 2.5 highlighting the hyaluronic acid content of the valves (stained bluish-green).

The sections were examined under 4 × 10, 10 × 10 and 40 × 10 magnifications. The relative amounts of fibrous, myxomatous and elastic tissues were noted. Microscopic evidence of infection such as inflammatory cells and neovascularisation was noted. The presence of gross or microscopic features was taken as evidence of infection.

The sections stained with Alcian blue were viewed under 4 × 10 magnification. The myxomatous component was assessed as 1+ when the leaflet had few strands of myxomatous tissue; 2+ when less than half of the length and breadth of the leaflet was myxomatous tissue; 3+ when more than half of the length and breadth of the leaflet was myxomatous tissue; and 4+ when almost the whole leaflet was myxomatous tissue.

When the leaflet had 1+ and 2+ levels of myxomatous tissue, it was graded as having no increase in myxomatous tissue, and 3 + and 4 + was graded as an increase in myxomatous tissue.

RESULTS

A total of 134 valves were studied (table 1). Of the 57 mitral valves studied 27 (47%) had an increase in myxomatous tissue. Of the 36 aortic valves studied, 21 valves were tricuspid and 15 were bicuspid. Myxomatous tissue was increased in 58% of tricuspid aortic valves and 67% of bicuspid aortic valves. Of the 16 × 2 valves studied after double valve replacement 88% had an increase in myxomatous tissue. All these valves showed evidence of infection in the form of commissural fusion, neovascularisation and mononuclear cell collection (on microscopic examination). Nine valves (6.7%) had an increase in myxomatous tissue without any evidence of infection.

Myxomatous tissue increased in 47% of mitral valves, of which 59% were from patients presenting when they were less than 40 years old. Myxomatous tissue increased in 58% of tricuspid aortic valves, of which 25% were from patients less than 40 years old. Myxomatous tissue increased in 67% of bicuspid aortic valves, of which 30% were from patients less than 40 years old. Myxomatous tissue increased in 88% of the valves removed during double valve replacement, of which 50% were from patients less than 40 years old.

DISCUSSION

We observed that a significant number of valves removed for either incompetence or stenosis secondary to rheumatic heart disease had an increase in myxomatous tissue. Floppy or myxomatous valves are known to present at a later age with degenerative disease in the fifth decade of life or at a younger age with regurgitation. Here, a significant number of patients

Table 1 Distribution of valves by patients' age with and without increases in myxomatous tissue (MT)

	Mitral valve (n = 57)		Aortic valve (n = 36) Tricuspid (n = 21)		Aortic valve (n = 36) Bicuspid (n = 15)		Double valve replacement (n = 16×2)		Floppy (n = 9) Mitral valve	Floppy (n = 9) Aortic valve
Increase in MT	No	Yes	No	Yes	No	Yes	No	Yes		
MT component	1+ to 2+	3+ to 4+	1+ to 2+	3+ to 4+	1+ to 2+	3+ to 4+	1+ to 2+	3+ to 4+	3+ to 4+	3+ to 4+
Number	30	27	9	12	5	10	2×2	14×2	6	3
Age at operation (years)										
>30	2	6	0	3	1	2	1	5	1	0
31–40	4	10	2	0	0	1	0	3	2	2
41–50	13	7	1	3	2	3	0	3	0	0
>50	11	4	6	6	2	4	1	3	3	1

with myxomatous heart valves presented in the fourth decade with rheumatic involvement suggesting that this component may predispose valves to rheumatic heart disease.

This is especially evident in the valves removed during double valve replacement, where 88% of valves had an increase in myxomatous tissue and of which 50% were from patients presenting at less than 40 years of age. Of the mitral valves with an increase in myxomatous tissue 59% were from patients presenting at less than 40 years of age.

Hyaluronic acid is a high molecular weight linear polysaccharide composed of repeating sequences of glucuronic acid and *N*-acetyl-glucosamine, which expands the spongiosa layer of myxomatous heart valves.

According to Stollerman *et al*,[4] mucoid or highly encapsulated strains of group A streptococci cause unusually severe infections and outbreaks of acute rheumatic fever. The hyaluronic acid capsular polysaccharide disrupts connections of epithelial cells, promotes invasion of deeper tissues and resists internalisation of the organism by epithelial cells or by skin keratinocytes. Studies by Moses *et al*[5] have shown that the major antiphagocytic determinants are the M protein and hyaluronic acid capsule. The hyaluronic acid capsular polysaccharide is a critical virulence determinant in group A streptococcus infection and hence we hypothesised that antibodies against the hyaluronic acid capsular polysaccharide may cross react with the hyaluronic acid in myxomatous heart valves. This may be one of the mechanisms by which myxomatous heart valves are predisposed to rheumatic heart disease.

Further experiments with sheep antibodies raised against purified hyaluronic acid and cross reacting with streptococcal capsule and valvar tissue are underway.

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Authors' affiliations

S Nayar, Department of Pathology, International Centre for Cardio Thoracic and Vascular Diseases, Mogappair, Chennai, India
P G Nayar, Department of Cardiology, International Centre for Cardio Thoracic and Vascular Diseases, Mogappair, Chennai, India
K M Cherian, Department of Cardiothoracic Surgery, International Centre for Cardio Thoracic and Vascular Diseases, Mogappair, Chennai, India

Correspondence to: Dr Sushma Nayar, International Centre for Cardio Thoracic and Vascular Diseases, Frontier Lifeline & Dr K M Cherian Heart Foundation, R 30 C Ambattur Industrial Estate Road, Mogappair, Chennai 600 101, India; divya_s35@hotmail.com

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