The aetiology and course of isolated severe aortic regurgitation: a clinical, pathological, and echocardiographic study

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SUMMARY Seventy two consecutive patients with severe isolated aortic regurgitation were evaluated by preoperative echocardiographic and angiographic assessment of the aortic root. Biopsy specimens of the aortic wall were taken at operation. Two major groups of patients were found: those with cusp derangement but normal aortic roots and those with normal cusps but dilated aortic roots. Of the 42 cases of abnormal cusps, 20 were rheumatic, 15 were infective, and six were bicuspid. One patient had a tear in an otherwise normal cusp. Of the 30 cases of abnormal roots but normal cusps, six had inflammatory changes (syphilis, Reiter's disease, giant cell aortitis) and 24 had root dilatation caused by non-inflammatory destruction of elastic laminae. Echocardiographic measurement of the aorta at the level of the top of the commissures predicted the findings at pathology. In 37 of 39 patients with cusp disease the measurement was <37 mm. In 27 of 33 patients with root disease the measurement was ≥ 37 mm. This difference was statistically significant. There was no difference in the sizes of the prosthesis used in each group, suggesting that it was the diameter of the junction of the aorta with the sinuses rather than the junction of the sinuses with the ventricle that was important in aortic regurgitation.

Clinical progression in patients with non-inflammatory aortic root disease is slower than in patients with infective disease but faster than in those with rheumatic cusp disease.

Isolated aortic regurgitation has many known causes yet in a high proportion of patients who require valve replacement the exact aetiological diagnosis is uncertain. Because of this some clinical reports of patients with isolated aortic regurgitation have not distinguished between aetiological groups that may have different rates of progression.^{1,2} In studies where aetiology was considered, it was unknown in 22-25% of the patients.^{3,4} We have undertaken a prospective study in which the clinical course, pre-operative echocardiograms of the aortic valve, and aortograms were correlated with studies of the cusps

removed at operation and with biopsy specimens of the aortic root.

Patients and methods

We studied 72 (15 women aged 19-72 and 57 men aged 22-73) consecutive patients who had aortic valve replacement for isolated aortic regurgitation. Forty six patients were of British origin and 26 were foreign, mainly from the Middle East. All had symptoms: nine were in New York Heart Association class I, 18 in class II, 26 in class III, 15 in class IV, and four patients were operated on as emergencies because of rapidly worsening symptoms at rest. Dyspnoea was present in 94% of the patients, angina in 35%, and syncope or near syncope in 7%. Eighteen patients or 25% of the total had evidence of active or treated infective endocarditis.

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In assessing the progress of symptoms in different subsets of this cohort of patients the concept of a "break-point" was used.⁴ This was the interval between the first appearance of symptoms and the time at which symptoms intensified to greater than New York Heart Association class II or required both digitalis and diuretics.

Preoperative electrocardiograms showed left ventricular hypertrophy in 85% of the study group and probable left ventricular hypertrophy in another 11%. The Romhilt-Estes criteria were used, and the mean (SD) score was 7.4 (2.4).⁵

M mode echocardiography was performed on all patients before operation.⁶ The transducer was placed over the fourth left intercostal space; angulation of the transducer medially and cephalad permitted visualisation of the aortic root. The widest dimension that still kept the free edge of the cusps in view was recorded. Ultrasound frequency was 2.25 MHz. Aortic dimensions were measured by callipers initially, and these were subsequently verified by digitising the tracings with the Numonics Computer System.

Ninety two per cent (66/72) of the patients underwent cardiac catheterisation including aortography. Of those who did not have a catheter study, three were under 40 years of age making additional coronary artery disease unlikely. In the other three patients urgent surgery was indicated and catheter evaluation was thought inappropriate. In no patient was there another cardiac diagnosis sufficient in itself to warrant surgical intervention.

There was no pressure gradient between the left ventricle and the aorta on pull back tracings in 49 patients. Minor peak-to-peak gradients of five to 25 mm Hg were noted in 14 patients. Three patients with peak-to-peak gradients of 26–35 mm Hg were included because on clinical grounds the diagnosis was severe aortic regurgitation rather than aortic stenosis.

At operation, patients were given Hancock porcine heterograft valves (45), Starr Edwards (Model 1126U) ball and cage prostheses (12), or fresh nutrient homografts (15).

Biopsy specimens were taken 1 cm above the commissures from the edge of the aortotomy site and averaged 10 × 4 mm in size. Haematoxylin and eosin and Weigert-van Gieson's elastic tissue stains were used. The cusps were photographed before histology. The cusp area was measured by digitising the photographs. Echocardiographic and pathological examination were independent of any knowledge of the clinical findings.

The size of the lower border of the aortic annulus in each patient was assessed by the type and size of the prosthesis implanted. Patients in whom a homo-

graft valve was inserted were excluded. Normal aortic valves were obtained from 35 necropsies on patients dying suddenly from non-cardiac causes and whose isolated left ventricular mass lay within the normal range for a subject with their total body mass. The aortic valve was fixed in the closed position by perfusion of the cross clamped aorta with formal saline at a hydrostatic pressure equivalent to 100 mm Hg.

Statistical analysis⁷ included one-way analysis of variance to compare groups of patients.

Results

NORMAL VALVES

In normal aortic valves the total (mean (SD)) cusp area was 838 (139) mm² and bore a linear relation to the cross sectional area of the aortic root at commissural level ($r = 0.69$).

REGURGITANT VALVES

There were two groups of abnormal valves: those with a normal aortic root in whom abnormal cusps were responsible for the aortic regurgitation and those with an abnormal aortic root and basically normal cusps altered only by the secondary changes resulting from regurgitation.

Cusp disease was responsible for aortic regurgitation in 42 patients (58.3%) (table). In twenty (27.7%) the leaflets were shrunk, thickened, and retracted with reduction in the distance from base to the free edge (fig 1). This is typical of chronic rheumatic disease. The mean (SD) total cusp area was 575 (96) mm², significantly less than normal valve cusps ($p < 0.001$). Microscopical examination confirmed that the fibrosis had obliterated all normal cusp structure.

Fifteen patients with infective endocarditis had well defined perforations in the central area of the cusp associated in three instances with cusp

Table Aetiology of aortic regurgitation in 72 cases

Aetiology	No
Cusp disease:	
Rheumatic	20
Infective	15
Bicuspid	6
Torn cusp	1
Total	42 (58.3%)
Root disease:	
Non-inflammatory	24
Inflammatory	6
Syphilis (3)	
Reiter's disease (1)	
Ankylosing spondylitis (1)	
Giant cell aortitis (1)	
Total	30 (41.7%)

Fig 1 Comparison of excised aortic cusps in rheumatic aortic incompetence (a) and aortic root disease (b). The cusps of rheumatic disease are smaller and thickened by fibrosis extending from the base to free edge. The cusps in root disease are larger and of normal thickness with only minimal fibrous thickening of the free edge.

aneurysms. Nine of the infections were on bicuspid valves and six on tricuspid valves.

Six patients had non-infected bicuspid valves in which the leaflets were either strikingly unequal in size (fig 2) or had one leaflet with a deep notch in the free edge. One patient had a bicuspid valve with superimposed rheumatic heart disease and one patient had a spontaneous tear of a normal cusp.

Disease of the aortic root was present in 30 patients (table). Six of these were found to have inflammatory infiltration, usually in focal areas, associated with destruction of the aortic media. With the exception of one patient whose biopsy specimens included large numbers of giant cells, the chronic inflammatory response was non-specific. Clinical information allowed the diagnosis of syphilis in three of these patients, ankylosing spondylitis in one, and Reiter's disease in another.

In contrast, the remaining 24 of these 30 patients had non-inflammatory aortic root disease. Five of these 24 patients had coexistent bicuspid valves. The histological picture was that of patchy disruption and destruction of smooth muscle and elastic tissue in the aortic media. The degree of medial destruction varied, but all showed deposition of connective tissue mucins in areas of elastic fibre destruction (figs 3a-c). There was no inflammatory infiltrate within the media. The mean (SD) total cusp area in the patients with a tricuspid aortic valve was 942 (95) mm². The total aortic cusp area was higher than in normal hearts (mean 942 vs 838 mm² $p < 0.025$). The cusps in these patients were thin, translucent, and pliable, and appeared normal in

every way (fig 1). The only structural abnormality was an area of thickening caused by linear fibrosis on the free edge of the cusp. Histological examination did not show destruction or myxoid degeneration of the fibrous centre of the cusps. At the free edge, there was a knobbed fibrous thickening (fig 4).

ECHOCARDIOGRAPHY

All patients demonstrated left ventricular volume overload and diastolic fluttering of the anterior mitral leaflet or the septal endocardium and in some there was premature closure of the mitral valve.

The mean (SD) diameter of the aortic root at the level of the free edge of the aortic cusps in those patients subsequently found to have abnormal cusps was 32.1 (5.1) mm (fig 5). In patients with histopathological evidence of root disease the mean (SD) diameter was significantly larger ($p < 0.001$) 42.3 (9.0) mm (fig 6). Despite the difference in aortic root size, the diameter of the lower aortic ring or annulus as judged from the size of the prosthetic valves implanted was not different in the two groups (25.8 mm vs 26.3 mm).

The pathological findings in individual patients were predicted by the preoperative echocardiographic assessment of the valve. Thirty nine patients had root diameters at the commissural level of < 37 mm. Of these, 37 (95%) were found at surgery to have normal aortic roots with the aortic regurgitation caused by cusp disease. Of those 33 patients with aortic root diameters ≥ 37 mm, 28 (85%) were later found to have disease of the aortic wall accounting for the regurgitation. This difference is highly significant ($p < 0.001$).

Fig 2 Bicuspid aortic valve in which one cusp is larger and of a different shape than the other.

Fig 3 Increasing degrees of aortic medial destruction caused by non-inflammatory disease. In the normal aorta (a) the media contain regularly arranged elastic laminae. In (b) there are focal areas in which the laminae have vanished leaving spaces containing fine collagen. In (c) the media are almost entirely replaced by fibrous tissue with only small islands of residual elastic laminae. By this stage the media are much reduced in width. A, adventitia; In, intima.

Fig 4 Histological section across the cusp in aortic root disease. The body of the cusp (arrows) is of normal thickness and structure. The free edge has a round mass of collagen superimposed on the underlying structure. There are no vessels in the valve (elastic van Gieson stain, original magnification $\times 20$).

When 37mm was used as the dividing line between normal and abnormal aortic roots, separation of the two groups is achieved with a sensitivity of 96.7%, a specificity of 88.1%, and a diagnostic accuracy of 91.6%.

The echocardiogram was also predictive of cusp pathology. In the patients with rheumatic disease the aortic leaflets were generally found to be thickened with heavy diastolic echoes (fig 5). The mitral valve apparatus was not found to be entirely normal on echocardiographic examination in any of these

patients, even though in no case would mitral valve surgery have been contemplated. In patients with abnormal aortic roots the presence of a double echo from the free edge of the cusps (fig 6) was matched by finding fibrous thickening of the cusp edge in the operation specimen.

Eccentricity of the aortic valve closure line was seen in seven cases all of which had bicuspid valves. Thirteen patients without eccentric closure lines also had bicuspid valves, however.

ANGIOGRAPHY

Angiographic examination confirmed the clinical impression of severe aortic regurgitation. The degree of regurgitation was estimated by conventional criteria: width of the regurgitant jet, degree of opacification of the left ventricle, and rapidity of clearance of the dye from the left ventricle.⁸

The aortic root where cusp disease was responsible for the regurgitation was normal in size and marked by a definite waist just above the sinuses of Valsalva (fig 7). In cases in which aortic root abnormality was advanced, there was complete effacement of the aortic waist (fig 8).

PROGRESSION OF AORTIC REGURGITATION

Assessment of rate of progression of symptoms according to aetiological diagnosis showed that the course of disease differed in the three largest groups (fig 9). The mean (SD) course from the onset of symptoms to the break point was long in those with

Fig 5 M mode echocardiogram of rheumatic aortic regurgitation. (a) The mitral valve shows diastolic flutter of the anterior cusp and the posterior cusp is abnormal, indicating mild rheumatic disease. (b) The aortic root is not enlarged and the cusps are thickened.

Fig 6 *M mode echocardiogram of aortic regurgitation caused by a dilated aortic root. The diameter of the aorta at commissural level is 4.3 cm. The free edges of the cusps produce a double echo (arrow).*

rheumatic disease (82.6 (68) months) and short in those with infective endocarditis, either controlled or uncontrolled (10.1 (19) months). In those with non-inflammatory aortic root disease there was an intermediate course (20.6 (24.3) months). These differences are highly significant ($p < 0.001$).

Discussion

An understanding of the pathophysiological mechanisms of aortic regurgitation requires a review of the normal anatomy and function of the valve. For such a purpose normal aortic valves were fixed in the closed position under a hydrostatic pressure equivalent to 100 mm Hg. This provided for distension of the sinuses of Valsalva to a degree approximating their position in life (fig 10). When thus examined, the aortic root was seen to consist of a sleeve of about 1.5 cm in length bounded by ring-like structures both above and below with a distended area, the sinuses, in between. The lower ring, which lies

below the cusps (fig 11) and forms the attachment of the aorta to the left ventricle, is made up in part by the myocardium of the upper interventricular septum and in part by the base of the anterior leaflet of the mitral valve. Its fibrous support structure can be dissected out as part of the so-called cardiac skeleton and is familiarly, but perhaps misleadingly, known as the aortic annulus. The upper border of the aortic sleeve forms another definite circular ring at the level of the attachment of the aortic commissures and forms a major part of the structural support for the cusps. This has been termed the supra-aortic ridge or sinotubular junction. The cusps are contained within the aortic sleeve and meet at the commissures which are attached to the supra-aortic ridge. Just above the sleeve with its enclosed cusps, the more familiar smooth muscle layers and elastic laminae of the wall of the tubular portion of the ascending aorta merge with the more collagenous connective tissue of the sleeve. The tissue of the aortic sleeve bulges outward in life more than the elastic

Fig 7 Aortic regurgitation caused by gross dilatation of the aortic root with normal leaflets.

containing aorta and forms the sinuses of Valsalva.

Examination of the closed aortic valve from above reveals that cusp support depends on two factors, the firm fixation of the cusps to the supra-aortic ridge at the commissures and the abutting of the ventricular surfaces of adjacent cusps. Examination of the ventricular face of the cusps shows a central nodule or corpus Arantii from which ridges extend to the fixed edges of the cusp where it merges with the wall of the aortic sleeve. This ridge forms the true line of closure or apposition of each cusp as it abuts its neighbour. Above the line of closure, a more filamentous area of each cusp (lunula) provides a measure of overlap with a similar portion of the abutting cusp. The free edge of each cusp at the outer edge of this filamentous area acts like a guy-rope supporting the cusp in diastole. In older patients, fenestrations are commonly noted in the lunulae; these have no functional importance since the communication is only between aortic sinuses above the line of closure. The linear relation

between aortic root diameter at the commissural level and the total cusp area agrees closely with other published data.⁹

The pathogenesis of the three large groups of aortic regurgitation in the present series can now be evaluated in light of the above anatomical description. Patients with infective endocarditis posed no conceptual problem since there was a hole in the body of the cusp in all our surgical cases. Patients with chronic rheumatic disease had shrunken, retracted, and thickened cusps and reduction in cusp area relative to a normal aortic root area caused regurgitation.

In the patients with non-inflammatory aortic root disease the cusps were structurally normal save for an area of thickening on the free edge thought to be secondary to rather than causative of the aortic regurgitation. The total aortic cusp area is greater than in normal hearts. There was, however, a constant relation between cusp area and aortic root size in normal hearts without aortic regurgitation and as

Fig 8 Aortic regurgitation caused by cusp disease. The normal architecture of the root including the waist marking the insertion of the upper border of the aortic ring into the root of the aorta is effaced.

Fig 9 Onset of symptoms, breakpoint increase in symptoms (> New York Heart Association class II or a requirement for both digitalis and diuretics), timing of surgery in patients with aortic regurgitation caused by rheumatic disease, aortic root dilatation, and infective endocarditis.

the diameter of the aortic root increases with age there is a concomitant increase in cusp area.⁹ This suggests that any increase in aortic root size is matched inevitably by some remodelling of the aortic cusps. Regurgitation develops when there is disproportionate or rapid dilatation of the root relative to the increase in cusp size. Symmetrical dilatation of the upper border of the aortic sleeve causes a central defect that cannot be closed by the cusps. One cusp often has a straight free edge forming a "bow string" across the aortic root (fig 12). If the dilatation is eccentric one cusp may lie at a different level to its abutting neighbour (fig 13).

No differences were noted in the size of the aortic ring at the level of the prosthetic valve suture line in

groups of patients with aortic regurgitation of differing aetiologies, and this reinforces the view that the ventricular aspect of the aortic ring is largely irrelevant to the causation of aortic regurgitation.

Fig 10 Normal aortic valve viewed from the aorta after fixation in the closed position by a pressure head of 100 mm Hg formal saline. The valve cusps are tightly apposed. The sinuses bulge outward and there is a distinct ridge (arrows) where the upper aortic valve ring joins the aorta. The commissures of the valve are attached to this ridge. Bar = 1 cm.

Fig 11 Long axis transection of the normal aortic root. The lower border of the aortic ring just below the cusps is formed in part by the muscle of the interventricular septum (IVS) and also by the base of the anterior cusp of the mitral valve (arrow). Ao, aorta; LA, left atrium.

Fig 12 Aortic valve in a case of aortic regurgitation caused by root dilatation. (Fixation as in fig 10.) The whole aortic root has dilated leaving a large central defect where the cusps fail to appose. The cusps have normal bodies but distinct rolled fibrous edges. Root diameter 4.5 cm. Bar = 1 cm.

On the contrary, the upper border of the aortic ring or annulus, which provides most of the support for the valve cusps at their commissures, is of vital importance and when its structural integrity is compromised important aortic regurgitation results.

In keeping with this view, Reeves *et al* reported a lack of correlation between echocardiographic measurements of supposed aortic root size and that indicated by the size of the prosthetic valve.¹⁰ This could have been predicted since the echo beam traverses the aorta at the level of the top of the commissures, whereas it is the lower portion of the aortic ring at the base of the cusps, not measured by echocardiography, to which the prosthesis is sutured. It is clearly vital to define the exact site of "aortic root" measurements.

The appearance of symptoms in aortic regurgitation depend in large measure upon the ability of the left ventricle to handle a diastolic volume load. In the short term the amount of regurgitant flow depends on the size of the regurgitant orifice, the duration of diastole, the gradient between aortic diastolic pressure and left ventricular end diastolic pressure, and the distensibility or compliance of the left ventricle. The conventional view appears to be that in the chronic state it is not the amount of regurgitation that changes, but rather the ventricle.¹¹⁻¹³ This may be true in patients with chronic rheumatic valvulitis, in which the progress of scarring and retraction of the cusps change very slowly and this allows time for the left ventricle to compensate. Only when the compensatory mechanisms fail do symptoms occur.

In patients with non-inflammatory root disease it

is not difficult to envisage an increase in the size of the regurgitant orifice as the root dilates and the upper aortic ring enlarges; the ventricle is therefore required to compensate not for a constant amount of regurgitation but for one which increases with time.

The present study accords closely with an analysis of the aetiology of 225 cases of pure aortic regurgitation coming to surgery over a 15 year period at the Mayo Clinic¹⁴ which also emphasises that aortic root dilatation is now a common cause of pure aortic regurgitation in Western populations. Several groups have described aortic root dilatation both in Marfan's syndrome and what are regarded as "formes frustes" without any other manifestation of Marfan's syndrome known as annulo-aortic ectasia; in all these reports aortic regurgitation was attributed to aortic root dilatation.¹⁵⁻¹⁷

In contrast others have described a condition in which regurgitation has been attributed to "floppy" aortic cusps.¹⁸⁻²⁰ It is postulated that myxoid degeneration of cusp tissue leads to enlargement of the cusp and prolapse toward the ventricle allowing regurgitation despite a normal aortic root. The condition is regarded as analogous to floppy mitral valves with which it has been described to co-exist.²¹ The present study and the larger series from the Mayo Clinic¹⁴ do not contain any such cases. The condition does exist (fig 14) and when it is present the cusps are soft, nodular, thickened, and with pronounced elongation of the lunular area despite an aortic root of normal size. Over a 10 year period only two cases have been seen at St George's Hospital; neither is reported in the present series.

Fig 13 Aortic valve in a case of aortic regurgitation caused by root dilatation. (Fixation as in fig 10.) The supra-aortic ridge associated with one sinus is lost and the root is dilated. The cusp related to the dilated sinus lies at a higher level than the other cusps. Bar = 1 cm.

Fig 14 Valve cusps from a case of aortic regurgitation caused by "floppy" aortic valve cusps. The cusps are nodular and thickened without an appreciable increase in surface area. Unlike the cusps in rheumatic disease these felt soft and pliable; the lunulae of the cusps are elongated. The dimensions of the aortic root were normal.

Histologically the cusp fibrosa is disrupted and contains an excess of acid connective tissue mucins.

One study of 55 cases of aortic regurgitation ascribed 13 cases to floppy cusps but it may be significant that the size of the aortic root was not measured.²⁰ A study from Italy found 12 (7.3%) floppy aortic valves in 177 cases of pure aortic regurgitation.²² There may either be a true geographical variation or different morphological definitions of what is called a "floppy" aortic valve. Before a separate primary abnormality of the cusps is diagnosed the aortic root which supplies structural support for the cusps must be seen to be normal in size and morphology. Patients with mitral valve prolapse without Marfan's syndrome do not usually have aortic root dilatation.²³

There may be a fundamental difference between

patients with isolated aortic regurgitation caused by aortic root dilatation and those with mitral regurgitation caused by floppy valves. The former problem is marked by disruption or dissolution of elastic tissue in the aortic root and the valve leaflets are normal. The primary defect in mitral valve prolapse is one of collagen rather than of elastic fibres.^{24 25}

Roberts *et al* have reported bicuspid valves and isolated aortic regurgitation in which the anatomical abnormalities and inequality in cusp size appear such that an additional abnormality of the aortic wall is not required to explain the regurgitation.²⁶ These patients are similar to six of our patients with bicuspid valves and normal histology of the aortic root. Echocardiographic study has demonstrated prolapse of the larger cusp in bicuspid aortic valves²¹ and while minor prolapse is common in patients with bicuspid valves severe prolapse is directly related to regurgitation.²⁷ The five other patients in our series who had bicuspid valves without other gross abnormality of the cusps had additional non-inflammatory aortic root disease. The number of patients in our series with both aortic root dilatation and bicuspid valves is so small that no firm conclusion should be drawn on whether this is simply a chance association or whether there is a genetic link between bicuspid aortic valves and aortic medial degeneration. The increased risk of dissecting aneurysms in the ascending aorta^{28 29} associated with bicuspid valves, however, does support the concept of concomitant aortic medial disease.

The important clinical message from our investigation is that isolated primary dilatation of the upper aortic ring is a common cause of aortic regurgitation and is of particular importance because it is likely to progress much more rapidly than rheumatic aortic regurgitation. With the decline in rheumatic disease in Western populations isolated aortic root dilatation will become relatively more common.

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