Pathological and clinical study of calcification of the mitral valve ring

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SYNOPSIS The pathology and clinical features of 258 cases of mitral ring calcification were reviewed. The overall incidence in patients over 50 years of age was 8.5%; it was more than twice as high in women (11.5%) as in men (4.5%) and rose sharply with age.

Cardiac failure and systolic murmurs were each noted in over half the patients. Hypertension was slightly commoner than in age- and sex-matched groups without ring calcification, although the difference was not statistically significant.

Small nodules of calcification were more frequent in men and heavy deposits in women. Distortion and atrial displacement of the posterior mitral cusp was present in 26% of the hearts with early ring calcification, in 56% of the hearts with moderate, and in almost all hearts with marked changes. Systolic murmurs had been heard in 73% of these cases. 'Caseation' of the calcified ring was seen in seven hearts and haemorrhagic valvulitis in three. Calcium had ulcerated through the cusp in 12 cases, with thrombotic and/or bacterial endocarditis in five. Aortic valve calcification was present in 36% of men and was quantitatively related to the severity of mitral ring calcification. In women the incidence was 30% and there was no corresponding quantitative relationship.

Microscopy showed nonspecific chronic inflammatory changes adjacent to calcium in about half the cases in both sexes, with foreign body type giant cells in 6%. Similar inflammatory changes in the valve cusp were almost twice as common in women as in men.

There was no evidence that previous endocarditis was responsible for mitral ring calcification, neither did parity influence its incidence. Severe coronary atherosclerosis was unrelated, but severe aortic atherosclerosis was commoner in patients with calcified mitral rings. The difference, in women, was statistically significant.

The higher incidence of severe degrees of ring calcification, complications, and valvular inflammation in women suggests a sex-determined difference in tissue response in the mitral area. Possible provoking factors apply to both sexes and both left side valves, and such difference would account for the relative frequency and sex incidence of mitral ring calcification.

Calcification of the mitral valve ring is one of the commonest cardiac abnormalities encountered in necropsies at general hospitals, yet it is not mentioned in standard British reference books of cardiology (Wood, 1968) or systematic pathology (Wright and Symmers, 1966) and even

Hudson's 'Cardiac pathology' (1965) gives only one line of text to this condition. It is therefore not surprising that in Britain mitral ring calcification is largely ignored or dismissed as of no clinical or pathological importance, although in the USA it is now becoming recognized as a clinically significant disease (*New England Journal of Medicine*, 1962; Friedberg, 1966; Hurst and Logue, 1966).

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Fig. 1 The relation of age and sex to the incidence of mitral ring calcification.

		Cases with Mitral Ring Calcification	Cases without Mitral Ring Calcification
Hypertensive	Men	10/72 (14%)	11/96 (12%)
	Women	34/165 (20%)	20/156 (13%) ($\chi^2 = 3.47$)
Severe aortic atherosclerosis	Men	30/76 (40%)	24/96 (25%) ($\chi^2 = 4.12$)
	Women	53/170 (31%)	30/162 (19%) ($\chi^2 = 7.085$)
Severe coronary atherosclerosis	Men	21/81 (25%)	23/96 (24%)
	Women	42/166 (25%)	29/159 (18%) ($\chi^2 = 4.86$)
Parity—0		29 (25%)	15 (13%)
1-3		67 (54%)	83 (75%)
over 3		28 (23%)	13 (12%)

Table I Possible pathogenic factors

Pathology	Incidence		
	Men	Women	Total
Early calcification	85 (4.6%)	173 (11.5%)	258 (8.5%)
Moderate calcification	48 (56.5%)	55 (32%)	103 (40%)
Marked calcification	22 (26%)	44 (25%)	66 (26%)
Caseation	15 (17.5%)	74 (43%)	89 (34%)
Ulceration through cusp	1	6	7
Thrombotic endocarditis	1	11	12
Bacterial endocarditis	0	4 ¹	4
Haemorrhagic valvulitis	0	3 ¹	3

Table II Pathological findings in mitral ring calcification

¹Bacterial infection of the distal part of a large thrombus.

Incidence, Age, and Sex

Macroscopic (ie, visible and palpable) calcification of the mitral valve ring was seen in 258 (8.5%) of 3,334 necropsies on patients over 50 years of age. It was over twice as common in females (11.5%) as in males (4.6%) and was strikingly related to aging. The incidence rose with age from 1.4% in men under 70 years to 17% in those over 90, and women showed an even sharper increase, from 3.2% to 43.5% (Fig. 1).

Clinical Features

Hypertension had been present in 19% of all cases (14% of the men and 20% of the women). This incidence was higher than in an age- and sex-matched group without mitral ring calcification, where 11.5% of men and 13% of women had been hypertensive (Table I), but the difference was not statistically significant even for the women.

The relation between cardiac failure and mitral ring calcification has been fully discussed in a previous study (Pomerance, 1965); 53% of patients were in failure but most also had other cardiac pathology and ring calcification was the sole abnormality in only 3 per cent.

Systolic murmurs had been noted in 55% of the cases, varying from soft localized apical to harsh precordial conducted to the axilla. This finding was more frequent in patients in whom distortion of the posterior mitral cusp was subsequently found. Murmurs had been heard in 73% of this group compared with only 23% of those with early or moderate degrees of mitral ring calcification without distortion.

Electrocardiographs were available in only 25 cases but 10 showed conduction abnormalities; one man had complete atrioventricular block and four men and five women, a bundle branch block.

Gross Pathology

The degree of calcification varied from a small localized nodule or spicule to massive involvement of the whole ring; 103 hearts (56.5% of the 85 men and 32% of the 173 women) had early calcification only with small foci of calcification under the posterior mitral cusp, usually at its junction with anterior cusp and septum or in the central part of the ring (Table II). In most of these cases the normal anatomical relationships of the cusp were not disturbed but in 26% part of the calcified mass formed a spur projecting into the left atrium with distortion of the overlying part of the cusp.

Fig. 2 *Opened left side of heart showing distortion and fixed atrial displacement of part of the posterior mitral cusp by a spur of calcification from a moderately calcified ring. (The patient had a mitral pansystolic murmur.)*

Fig. 3 *Posterior wall of left ventricle, bisected through the mitral cusp to show a caseous mass extending from the ring into the posterior cusp, which was expanded and immobilized by pultaceous material.*

Sixty-six hearts showed moderate degrees of mitral ring calcification, with more extensive deposits than in early cases but not extending along the whole valve ring. Atrial displacement and distortion of the posterior cusp was present in 56% of cases (Fig. 2).

The remaining 89 hearts (17.5% of the men and 43% of the women) had severe changes, with a rigid curved bar of calcium up to 2 cm diameter occupying the whole mitral ring zone. These cases almost invariably showed distortion and atrial displacement of the posterior cusp. In the few exceptions, spread of calcification had been predominantly in a downward direction and in two hearts the calcified bar had become surrounded by thick fibrous tissue, forming an apparently fleshy subvalvular shelf.

In seven cases the calcified rings were not uniformly solid, but showed extensive central caseation; in the only example in a man the pultaceous material extended into the posterior cusp forming an 'abscess' (Fig. 3). Microscopy showed no granulomas or other evidence of tuberculosis or fungal infection. Ulceration and extrusion of calcium through the overlapping cusp (Fig. 4) was also not uncommon, being present in one man and 11 women with severe ring calcification. Thrombotic endocarditis had

occurred in four of these cases, in two of which the thrombus was pedunculated and large enough partly to obstruct the mitral orifice (Fig. 5). Bacterial endocarditis was present in three women, one of whom died from embolic staphylococcal meningitis (Fig. 6). An acute haemorrhagic valvulitis (Fig. 7) without endocardial breakdown was seen in three women, and mitral stenosis of chronic rheumatic type in a further three. Eight patients of each sex showed minor non-specific postinflammatory scarring of the anterior mitral cusps.

Small deposits of calcium were present in the aortic cusps of 18% of the men and heavier ones in a further 18%. The proportion of women with aortic cusp calcification was lower—15% in each group. In men, severity of aortic calcification was related to that of mitral ring calcification (Table III) but no such relationship was present in the women.

MICROSCOPIC PATHOLOGY

Sections stained with haematoxylin and eosin and Weigert's elastic and Van Geison stains were examined from the first 100 examples studied. The blocks were taken to include a palpably calcified segment of ring with adjacent atrium and ventricle.

Fig. 4 Opened left atrium and mitral valve with severe ring calcification and a mass of calcium ulcerating through the medial commissure.

Fig. 5 Opened left side of heart showing severe mitral ring calcification with a large pedunculated thrombus originating from the overlying posterior cusp and hanging through and partly obstructing the orifice.

Fig. 6 Opened left side of heart showing a large mass of vegetations (staphylococcal) on a posterior mitral cusp distorted by ring calcification.

and attached mitral cusp. Single blocks were selected from cases with early or moderate calcification and two or more from those with severe or complicated calcification of the mitral ring.

The calcification appeared as large amorphous basophilic areas surrounded by a variable amount of fibrous tissue. Cartilage was present in two cases (Fig. 8) but no true bone formation was seen.

Inflammatory changes (Fig. 9) were frequent around the calcified masses. They varied from few dilated vascular channels with scanty lymphocytes and plasma cells to dense cellular infiltration, including numerous polymorphs and extending between the myocardial fibres of the posterior wall for several millimetres. Inflammatory changes were present in 53% of the 100 hearts sectioned, 55% of men and 52% of women. In 33 of the 53 cases these changes were not limited to the zone surrounding the valve ring, but also involved the overlying cusp. This finding was more common in the women (70% of the 41 cases with inflammatory changes) than in the men (33%).

Haemosiderin-containing macrophages were

Fig. 7 Part of opened left side of the heart showing a large haemorrhagic area involving most of the posterior cusp. Severe ring calcification present.

Fig. 8 Section through a calcified mitral ring showing an area of cartilage formation (haematoxylin and eosin, × 127).

Fig. 9 Section through calcified mitral ring and adjacent tissue showing fibrosis, capillary channels, and moderate lymphocytic infiltration around the calcification (haematoxylin and eosin, × 90).

frequently seen but recent haemorrhage was surprisingly rare. Other occasional findings included groups of foreign body type giant cells in six cases (Fig. 10), zones of pallsided fibroblasts (Fig. 11) in two cases (neither with rheumatoid disease), and a large number of tissue mast cells in one case.

POSSIBLE AETIOLOGICAL ASSOCIATIONS
Severe aortic atheroma was more frequent

Mitral Ring Calcification	Degree of Aortic Cusp Calcification	
	Minimal	Moderate or Marked
Men		
Early	10 (66%)	2 (14%)
Moderate	2 (14%)	4 (26%)
Marked	3 (20%)	9 (60%)
Total	15 (18%)	15 (18%)
Women		
Early	9 (33%)	6 (22%)
Moderate	7 (26%)	9 (33%)
Marked	11 (41%)	12 (45%)
Total	27 (15%)	27 (15%)

Table III Relationship between aorta and mitral ring calcification

Fig. 10 Photomicrograph of inflammatory changes adjacent to mitral ring calcification, showing a group of multinucleate giant cells (haematoxylin and eosin, $\times 135$).

cases with mitral ring calcification than in the age- and sex-matched groups without this abnormality. Of the men with ring calcification, 40% had marked aortic changes compared with 25% of those without. In women the corresponding figures were 31% and 19%, and this difference was statistically highly significant. There was no similar correlation with severe coronary atherosclerosis which had virtually the same incidence in men with and without mitral ring calcification and was only slightly more frequent in the women with ring calcification (Table I).

The higher incidence of mitral ring calcification in women suggests that hormonal factors may be concerned in pathogenesis; however, the only man known to have been on prolonged stilboesterol therapy did not have ring calcification, neither did the two women with unusually early termination of ovarian function (at 29 and 39 years). The increased cardiovascular stresses of pregnancy are clearly another possible factor, but although 23% of women with ring calcification had more than three children, compared with only 12% of those without calcification, the proportion of nulliparous women in each group was almost the same, 23% and 13% respectively. No information could be obtained about lactation history, which would have been of interest in view of the influence of

Fig. 11 Section through calcified mitral ring showing chronic inflammatory changes, multinucleate giant cells, and pallsided arrangement of fibroblasts (haematoxylin and eosin, $\times 140$).

lactation on cardiac calcification in experimental animals (Záhoř and Czabanová, 1964 and 1965).

Discussion

The presence of cardiovascular signs and symptoms has been recorded in earlier studies of mitral ring calcification. Systolic murmurs were noted in half (Ashworth, 1946) to all (Korn, De Sanchs, and Sell, 1962) patients in the smaller series, and in half to two thirds of the three larger groups (Fertman and Wolff, 1946; Geill, 1951; Simon and Liu, 1954). Indeed, mitral ring calcification is the commonest abnormality found in elderly patients with systolic murmurs (Pomerance, 1968). The present study has shown that these murmurs were usually associated with distortion and atrial displacement of the posterior mitral cusp by calcified spurs, and it seems likely that this deformity, coupled with restriction of normal ring contraction, results in incompetence. Mitral incompetence was the

clinical diagnosis in one third of the 59 patients (Simon and Liu, 1954) and in all of the 14 cases described by Korn *et al* (1962). In cases without apparent distortion of cusps possible explanations for systolic murmurs are vibration of the ring (Geill and Kiaer, 1952) or vortex formation around an obstruction (Bruns, 1959). The latter seems most probable in those cases with early localized calcification at the junction of the posterior cusp and intraventricular septum.

The role of mitral ring calcification in cardiac failure has already been considered in a previous paper (Pomerance, 1965). Although failure was present in over half the cases, ring calcification was the only cardiac abnormality in 3%. The question is also discussed in recent text-books of cardiology; Friedberg (1966) states that the frequency of clinical abnormalities in mitral ring calcification was due to associated rheumatic or ischaemic heart disease and not to calcium deposition, while Hurst and Logue (1966) state that ring calcification can produce cardiac failure which may be mistakenly diagnosed as rheumatic or ischaemic. Fertman and Wolff (1946) considered mitral ring calcification an indication of other significant cardiac disease but Geill (1951), from his survey of 230 cases, concluded that it was an independent disease process, unrelated to other cardiac abnormalities. The present author's experience confirms Geill's view and also the suggestion of Simon and Liu (1954) that the effect of ring calcification is further impairment of cardiac function in hearts already diseased.

Complete or bundle-branch block, present in 10 of the 25 electrocardiographs available in the present series, was also noted in earlier studies (Yater and Cornell, 1935; Ashworth, 1946; Rytand and Lipsitch, 1946; Grayson, 1948; Fertman and Wolff, 1946; Simon and Liu, 1954; Korn *et al*, 1962). This is not surprising since the bundle of His and its main branches are in the area adjacent to the membranous septum which is one of the earliest regions involved in ring calcification.

The pathology of mitral ring calcification has received comparatively little attention. Edwards (1961) includes an illustration of caseation in a calcified ring similar to most of the seven examples in the present survey. This finding seemed of no practical significance other than possibly misleading the inexperienced pathologist into a diagnosis of cardiac tuberculosis. The more commonly seen ulceration of solid calcium through the valve cusp was, however, associated with endocarditis, including two cases with large pedunculated thrombi and a third with emboli from staphylococcal vegetations. Guthrie and Fairgrieve (1963) also record fatal embolism from a myxoid thrombotic mass originating on an ulcerated calcified mitral ring.

There is equally little work on the microscopic changes associated with mitral ring calcification.

Korn *et al* (1962) noted chronic inflammatory cells and old and recent haemorrhage. This finding is to be anticipated around calcified masses in a repeatedly contracting organ, and it is therefore surprising that recent haemorrhage was not seen more often in the present study, although haemosiderin-filled macrophages were common. The finding of foreign-body type giant cells was similarly not unexpected; it seems likely that these reactions contribute to further extension of the calcification. The pallisading observed in two cases in the present series was of interest in view of the ring lesions described in rheumatoid disease (Cruikshank, 1958); however, neither patient had clinical rheumatoid arthritis. The dilated vessels and nonspecific chronic inflammatory cell infiltration present in over half the cases were also noted by Rosenthal and Feigin (1947) but the presence of similar inflammatory changes in the valve cusp does not appear to have been recorded previously. As neither thrombosis nor infection was observed except where calcium had penetrated the endocardium the inflammatory reaction is presumably of no clinical significance, but the finding is of interest when considering pathogenesis since it was over twice as frequent in females.

It is generally agreed that rheumatic or other endocarditis is not related to the development of mitral ring calcification although Lannigan (1966) considers *Brucella* infection a possible factor. The present study confirms the majority view: the incidence of rheumatoid disease, rheumatic or nonspecific post-inflammatory valve changes was no greater than usually found in this age group (Pomerance, 1965). Yater and Cornell (1935) suggested that calcification may be related to mechanical stress, and hypertension might therefore be a factor in ring calcification, but no such relationship was demonstrable in my series or in Ashworth's cases (1946). The advanced age of patients with mitral ring calcification points to a degenerative process, related to other forms of calcific cardiovascular disease, and correlation with aortic atherosclerosis was indeed present. However, this was statistically significant only in women and severe coronary atherosclerosis was no commoner in hearts with calcified mitral rings than in those without. Sell and Scully's demonstration (1965) of increasing valvular sudanophilic deposits and calcification with age offers some support for a degenerative hypothesis but does not satisfactorily account for development of mitral ring calcification independent of similar aortic valve disease in most cases, nor for the marked sex difference. Because senile osteoporosis is also commoner in women, Blankenhorn (1964) postulated some factor affecting body calcium distribution between bone and soft tissue which is more active in elderly females. The existence of such a factor would explain the sex incidence of ring calcifi-

cation but would still not account for the predominantly mitral localization. The greater incidence in women also points to pregnancy as a possible aetiological factor, particularly as breeding is associated with cardiovascular calcification in rats (Gillman and Hathorn, 1959); however no correlation between parity and ring calcification was present.

A possible explanation for both location and sex incidence was suggested by pathological findings in the present study. Not only was calcification more often severe, but complications—ulceration, endocarditis, and caseation—occurred almost exclusively in women, and the incidence of valvular chronic inflammatory cell infiltration was twice as high as in men. No comparable changes were present in a series of calcified aortic valves from patients of both sexes. This suggests that in women the mitral valve region may be prone to an exaggerated response to injury, a possibility reinforced by the increased incidence of mitral stenosis in women (Wood, 1968) following rheumatic fever. Whether the initial stimulus is trauma, such as might be expected at the junction of fibrous ring and contracting muscle, or calcification in lipoid infiltration (Sell and Scully, 1965) is speculative, but either would apply equally well to aortic and mitral valves and to both sexes. The additional factor of a differing response in females would account for both the location and sex incidence of calcification of the mitral ring.

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