Thrombotic Calcific Mitral Stenosis
Morphology of the Calcific Mitral Valve

By CHARLES F. WOOLEY, M.D., NOBUHISA BABA, M.D., JAMES W. KILMAN, M.D., and JOSEPH M. RYAN, M.D.

SUMMARY

We compared the morphology of the calcific stenotic mitral valve (CSMV) with noncalcific stenotic mitral valves (NCSMV) removed at surgery; control valves were obtained at autopsy. X-rays of the excised valves permitted localization and quantitation of calcification. A classification of CSMV applicable to noninvasive techniques based on this methodology is presented. Moderate to heavily CSMV had greater weight, volume, specific gravity, weight per area, with smaller orifice size when compared with NCSMV and controls. Leaflet mobility was obliterated in moderate to heavily CSMV, while most NCSMV had some degree of leaflet mobility.

Surface morphology was strikingly different in CSMV with 1) surface ulceration, due to erosion of the underlying calcific focus through valvular endothelium, 2) thrombosis in the areas of ulceration (associated with symptomatic arterial embolization in four patients), 3) whisker formation, filamentous stalks along the line of valve closure.

Calcification in the CSMV is viewed as an active, progressive process resulting in altered physical characteristics of the valve, progressive leaflet immobility and orifice narrowing, and eruptive surface changes with thrombus formation and arterial embolization arising from the CSMV itself. Clinical implications and a rationale for more precise classification of mitral stenosis on the basis of valvular calcification are presented.

Additional Indexing Words:
Mitrval valve disease Arterial embolization Mitral stenosis — natural course

CLINICAL AND SURGICAL EVALUATION of patients with rheumatic mitral stenosis led us to the impression that certain fundamental differences existed between the calcific stenotic mitral valve (CSMV) and noncalcific stenotic mitral valve (NCSMV). Since little information was available based on antemortem study, a prospective study of stenotic mitral valves removed at surgery was performed in order to assess the morphologic basis for these differences. It is the purpose of this paper to report on the morphologic differences between the CSMV and the NCSMV, and to comment on the potential clinical implications.

From the Department of Medicine, Department of Pathology, and Department of Surgery, The Ohio State University College of Medicine, Columbus, Ohio.

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Address for reprints: Charles F. Wooley, M.D., Division of Cardiology, Room 206, University Hospital, Columbus, Ohio 43210.

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Material and Methods

Stenotic mitral valves were removed in a uniform manner by one surgeon (J.K.). Inspection and description of the intact valves by the surgeon, and the excised valves by the pathologist, were recorded.

Surgically excised valve tissue was immediately fixed in a 2% phosphate-buffered (pH 7.4) gluteraldehyde solution for 24 hr at 4°C before examination. Control valves were obtained from young subjects, previously healthy, who suffered accidental or traumatic death. After fixation, excessive papillary muscle tissue was trimmed. Excessive wash solution was removed by filter paper blotting and drying with compressed air. Valves were weighed on a top loading balance (Mettler P 323, precision ± 1 mg). The intact valve was immersed in a beaker containing 50 cc of a 10% sucrose solution. Displaced fluid was removed with a 10 ml serological pipet to measure the valve volume.

The extent of calcification was determined by still radiographs in a Field Emission Faxitron X-ray unit at 35 KVP. Radiographs were taken in two planes, horizontal (parallel to the annulus) and perpendicular. Localization of calcification and numbers of the foci of calcification were determined from the radiographs; the longest and shortest diameters of each focus of calcification were recorded in both planes (table 1).

The following measurements were obtained from each valve: 1) the longest (D2) and shortest (D1) diameter of the entire valve tissue removed; 2) the fixed ostium by measurements of the longest (d1) and shortest (d2) diameter;
Calcification

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>N with calcium</th>
<th>Avg calcif (mm)</th>
<th>Commissure</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>One</td>
<td>Both</td>
</tr>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS, NCMV</td>
<td>6</td>
<td>1.3 x 1.6</td>
<td>1*</td>
<td>0</td>
</tr>
<tr>
<td>N = 13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS, CSMV</td>
<td>17</td>
<td>10.2 x 17.4</td>
<td>6†</td>
<td>6†</td>
</tr>
<tr>
<td>N = 17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*No extension to leaflet.
†No extension to leaflet - 3; extension to one leaflet - 2 (1-anterior, 1-posterior); extension to both leaflets - 1 (horseshoe type).
‡No extension - 2; extension to one leaflet - 2 (2-anterior); extension to both leaflets - 2 (1-ring; 1-horseshoe).
**No commissural involvement.
Table 2

Calcification—Mitral Stenosis

<table>
<thead>
<tr>
<th>One commissure</th>
<th>Weight (gm)</th>
<th>Volume (cm³)</th>
<th>Specific gravity</th>
<th>Fixed orifice (cm²)</th>
<th>Weight per valve area (g/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No extension to leaflet</td>
<td>2.51 mean</td>
<td>2.64</td>
<td>.97</td>
<td>3.65</td>
<td>.28</td>
</tr>
<tr>
<td>Extension to one leaflet</td>
<td>.24 SEM</td>
<td>.28</td>
<td>.03</td>
<td>.30</td>
<td>.03</td>
</tr>
<tr>
<td>Extension to both leaflets — continuity of process across commissure (horseshoe)</td>
<td>.99 mean (b)</td>
<td>3.53 (b)</td>
<td>1.12 (b)</td>
<td>.85 (a)</td>
<td>.50 (b))</td>
</tr>
<tr>
<td>No extension to leaflet</td>
<td>.30 SEM</td>
<td>.25</td>
<td>.02</td>
<td>.08</td>
<td>.04</td>
</tr>
<tr>
<td>Extension to both leaflets —</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuity of process across commissure — horseshoe</td>
<td>.64 mean (a,c)</td>
<td>5.81 (b, c)</td>
<td>1.18 (a, d)</td>
<td>.51 (a,e)</td>
<td>.69 (a,d)</td>
</tr>
<tr>
<td>Both commissures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No extension to leaflet</td>
<td>.49 SEM</td>
<td>.45</td>
<td>.01</td>
<td>.05</td>
<td></td>
</tr>
</tbody>
</table>

a and b comparison with mean values, control valves
a: P < 0.001
b: P < .005
c, d, and e comparison with mean values, group A
c: P < 0.001
d: P < .025
e: P < .05

The valve area (cm²) was comparable in the three groups by virtue of sampling technique. Volume (cm³) divided by area (cm²) yielded an estimate of average valve thickness: control, 2.7 mm; group A, 4.1 mm; group B, 5.9 mm.

MORPHOLOGY OF CALCIFIC MITRAL VALVE

Physical Characteristics

There was significant and progressive increase in weight from control (2.51 g) to group B (6.64 g) (table 3). A progressive increase in volume, specific gravity and weight per area occurred from control through group A and group B, with a corresponding decrease in fixed orifice size. Fixed orifice size was inversely related to the extent of calcification, and measured orifice areas in group B were appreciably smaller than those usually calculated at catheterization.

Mobility

Ten of the 13 group A valves retained a reasonable degree of leaflet mobility. Sixteen of 17 group B valves had no leaflet mobility demonstrable; the remaining valve had only slight leaflet mobility.

Surface Morphology

Gross valvular characteristics were best appreciated in the horizontal view of the atrial surface and the perpendicular view of a cut section (figs. 8 and 9).

Three impressive changes occurred in the calcific, stenotic valves; first, eruptive, ulcerative lesions on the valve surface (figs. 8, 10 and 11); secondly, thrombotic changes (figs. 8, 9 and 11); thirdly, whisker formation (figs. 12 and 13). Surface Ulceration was caused by eruption of the underlying calcific focus through the valvular endothelium in 23 of the 24 ulcerative lesions. Gross ulceration occurred in the valves with moderate and severe calcification (group B). The severely calcified valves in group B usually had more than one ulceration; in valves with minimal or absent calcification (group A) only one of 13 showed ulceration. Thrombosis. Gross surface thrombosis (associated with symptomatic arterial emboliza-
X-ray of a slightly calcified mitral valve (x1). Several small foci of calcification are noted in the anterior leaflet (on the top), in the chordae inserting into the line of closure (strut chordae), and the posterior leaflet (at the bottom).

A horizontal view of a severely calcified valve. One commissure (on the right) is the site of massive calcification. There is extension of heavy calcification along the line of closure of the anterior leaflet (top) and slight linear calcification also extends along the line of closure of the posterior leaflet (x1).

A horizontal view of severe calcification in one commissure (on the right) and anterior leaflet (on the top) along the line of closure. Notice the irregular and granular pattern of calcification (x2).

A lateral view of the same valve shown in figure 4. Massive calcification is noted in the valvular substance; there is no calcium in the chordae (x1).

A horizontal view of massive calcification involving both commissures and both leaflets. Notice the irregular and granular appearance of the calcific material (x1).

A lateral view of the same valve shown in figure 6. Massive calcification is limited to the valvular tissue and chordae are free of calcification. Notice relationship of calcification and valvular surface, with protrusion of calcific spicules above the endothelial surface at the top right of this illustration. Extensive surface ulceration was present on this valve (x1).

Discussion

The present study considers the effects of calcification on the physical characteristics, leaflet mobility, orifice size and surface changes of the CSMV.

Physical Characteristics

Physical characteristics of the calcific stenotic mitral valve were altered. CSMV had increased mass, density and weight per area, and decreased orifice size when compared with controls and with noncalcific stenotic mitral valves. Since progressive mitral valve calcification increases valvular mass, density and resistance to deformation, left atrial and right ventricular work must be performed against a valve with reduced orifice size, decreased compliance and mobility, and increased specific gravity. Similarly, the left ventricular contraction and relaxation process is impeded by a valvular complex of increased weight and density occupying a ventricle of normal or smaller than normal size. The precise hemodynamic burden of the calcific, stenotic mitral valve cannot be defined by a morphologic study alone, but it is apparent that the same hemodynamic factors cannot be used to characterize function of valves with strikingly different physical characteristics.

Mobility

Only leaflet mobility was considered in this study; mobility of the entire mitral complex within the ventricle was beyond the scope of this study. While some degree of leaflet mobility was present in 10 of 13 group A valves, no leaflet mobility could be demonstrated in 16 of 17 excised group B valves. Although calcification is not the only determinant of leaflet immobility, heavily calcified valves had immobile leaflets. A certain degree of leaflet mobility within the mitral complex may persist in the presence of uni- or bicommissural calcium. As the calcific process extended from the commissures into one or both leaflets, leaflet mobility was impaired, until the orifice was virtually immobile in the heavy, rigid mitral complex.
Edwards discussed calcification occurring secondarily in stenotic rheumatic valves and noted that when secondary calcification was present it usually involved one or both commissures. The extent of calcification in the cusps varied. In some valves there was "hardly any beyond the commissure; in others all of one or both leaflets may additionally be calcified." When both commissures were fused, there was a tendency for considerable fixation of the two leaflets; when the process did not involve the leaflets, some pliability remained, and he postulated that valve closure could occur as a result of pressure of the deformed basal part of the anterior cusp against the base of the posterior cusp.

Since many of the clinical signs of mitral stenosis are dependent on mitral leaflet or mitral complex mobility, extension of severe calcification into the leaflets would be expected to dampen the auscultatory
wooley, baba, kilman, ryan

figure 8

gross demonstration of severely calcified mitral valve, atrial view. there is massive thrombosis in the area of the anterolateral commissure (at the left). a markedly stenotic fixed ostium is seen in the center of the valve caused by advanced bicommissural fusion (x2).

figure 9

sagittal cut section of the same valve shown in figure 8. there is marked calcification in the anterior leaflet (on the right of this figure). thrombosis on the anterolateral commissure is seen in the middle of the specimen. thickening of the chordae is noted in both anterior (on the right) and posterior (on the left) leaflets. fusion of the chordae is more pronounced in the anterior leaflet. calcification does not extend into the chordal tissue (x2).

figure 10

close-up of the anterolateral commissure (on the left in this figure) of another severely calcified valve. note a yellowish calcific mass which is partially covered with a transparent thin layer of the endothelium in its periphery. the middle portion of the calcific mass is devoid of this endothelial cover and ulcerated (at the lower half in the middle of the figure). a portion of less affected posterior leaflet is seen in the upper portion of the illustration (x2).

figure 11

close-up of the middle portion of the anterior leaflet of the same valve shown in figure 10. there is a deep linear ulceration in the center of the illustration covered with a piece of thrombus. at the top of the figure eruption of the calcified mass is seen (x9).

figure 12

close-up view of surface projections and an ulcer. the ulcerated area is seen in the background (in the right upper corner of this figure). there are filamentous processes of various sizes in the foreground which extend from the endothelialized, non-ulcerated portion of the valvular surface (x9).

figure 13

close-up view of filamentous processes (whiskers) over the endothelial surface along the line of closure. no ulceration is associated with these processes. the top of this figure shows the line of closure of the opposing leaflets (x9).

hallmarks of mobility2 (i.e., the accentuated first heart sound, and its reciprocal, the mitral opening snap).3 wynn4 noted that the first heart sound was rarely snapping or palpable in the presence of gross calcification, and that an opening snap was less often heard and was rarely loud or clicking. a mitral systolic murmur was heard in 80% of his 60 patients with gross mitral calcification.

stafason5 analyzed ultrasound tracings in relation to hemodynamic and surgical findings in mitral stenosis. the maximal amplitude of the ultrasound cardiographic tracing was related 1) to anterior leaflet mobility (amplitude decreased with decreasing mobility of the leaflet) and 2) to the degree of calcification (the mean value of maximal amplitude decreased with increasing degree of calcification). the relation of the tracing amplitude to the anterior leaflet mobility and to the degree of calcification was statistically significant by variance analysis. duchak et al.6 emphasized the need for anterior and posterior mitral valve echograms, and demonstrated that in normal subjects posterior and anterior leaflets move in virtually opposite directions, while in patients with mitral stenosis both leaflets move in essentially the same direction but to a different degree.

chakorn and associates7 used reflected ultrasound to show the relation of mitral valve ring to cusp movement in normal subjects and patients with mitral valve disease. they showed that valve ring movement makes an important contribution to the apparent movement of the anterior cusp, especially when the cusp is more rigid in mitral valve disease and therefore moves very little relative to the ring. three cases with a 'thick' echo record (which represented fusion of ring and cusp) were found at operation to have heavily calcified valves.

the last observation relates well to our heavily calcified group b valves with absent leaflet mobility. mobility of the calcified leaflets may be totally obliterated at the same time that the angiograms or echograms show mitral complex motion which is related to annulus and cardiac motion. thus mobility in mitral stenosis possesses at least two aspects, mitral leaflet mobility, and mitral complex mobility.

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Orifice Size

Since the orifice areas were considerably smaller in valves with advanced calcification, it seems likely that gradual extension of the calcification contributed to progression of the degree of stenosis. This explanation seems more reasonable than invoking the concept of reactivation of the rheumatic process to explain the severity of the stenosis in the CSMV, and had been suggested earlier by Dubin et al. Mitral valve calcification may be viewed as an active, progressive process, both topographic and biologic, producing constriction, immobility and eruptive surface changes.

Surface Changes

Alterations in surface morphology occurred as a consequence of valvular calcification, since calcium erupted through surface epithelium to produce surface ulcerations. Our concept of this process is shown in schematic form in figure 14. Formation of thrombotic material with embolic potential occurred within the surface ulcers. Thus, the valvular surface, rather than the atrium, may be the source of arterial emboli in patients with CSMV. For a number of years, the “clean” left atrial appendage at mitral surgery in patients with arterial embolization has been a source
of puzzlement; the source of emboli in many of these patients may be the valve itself.

Edwards\textsuperscript{1} discussed surface changes in mitral stenosis and noted that "... patients with mitral stenosis are susceptible to thrombosis of the valvular tissue. Minor degrees are probably common, and in the process of organization a thrombus may contribute to additional changes of the valvular cusps. Massive thrombosis of the valve when present, is usually present at a commissure which has underlying calcification." He also described postmortem findings where calcification was associated with ulceration and vegetation, but did not discuss the concept of arterial embolization in this setting.

Comment

Our observations lead us to disagree with Wynn\textsuperscript{4} who concluded (primarily on the basis of clinical observations) that gross calcification of the mitral valve occurring as a complication of rheumatic heart disease has no striking connotations in either the clinical or hemodynamic sense except in relation to the increased incidence of mitral regurgitation. Our findings demonstrate that there are multiple morphologic differences between the CSMV and the noncalcific stenotic mitral valve with predictable clinical and hemodynamic consequences.

From the clinical viewpoint there appears to be a rational basis for classifying mitral stenosis on the basis of valvular calcification; further definition and understanding of the calcification process should be forthcoming if calcification is classified in a precise manner. Cinefluoroscopy, cineangiography and ultrasound are currently available techniques for detection, localization and quantification of valvular calcification. The moderate to heavily calcified stenotic mitral valve has a small fixed orifice, and is likely to have surface ulcerations with thrombotic material and potential for arterial embolization.

Patients with mitral stenosis should be classified in a more precise fashion, since there are multiple forms of mitral stenosis. The presence or absence of arrhythmia or pulmonary hypertension; the size, compliance and function of the left atrium; right and left ventricular geometry and performance; presence and location of valvular calcification; mobility of the mitral complex; are all specific bases for classification.

References

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