Mitral annular calcification as a cause of mitral valve gradients

Salman M. Muddassir, Gregg S. Pressman*

St. Francis Medical Center, Seton Hall University, Trenton, NJ, United States

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Abstract

Background: Mitral annular calcification (MAC) is common, particularly in the elderly. While thought to occasionally produce significant mitral regurgitation, it is considered a rare cause of mitral stenosis.

Methods: Echocardiogram reports from general cardiology outpatients were searched for phrases regarding severe MAC and, separately, for mitral stenosis. Rheumatic disease or other mitral valve (MV) pathology was excluded. Mean MV and aortic valve (AV) gradients were recorded. The presence or absence of anterior MAC was noted and a semi-quantitative assessment of anterior mitral leaflet (AML) mobility was made. Ten patients with annuloplasty rings served for comparison.

Results: Group A (22 patients with moderately/severely reduced AML mobility) had a mean MV gradient of 7 mm Hg (range 3–14) vs. 3 mm Hg (range 1–5) in group B (21 patients with normal/mildly reduced AML mobility), p < 0.0001. Annuloplasty patients had a mean MV gradient of 3 mm Hg, p < 0.001 vs. group A but similar to group B. Mean AV gradient was 27 mm Hg (range 4–48) in group A vs. 14 mm Hg in group B (range 3–40), p = 0.013. No patient had more than mild mitral regurgitation.

Conclusion: MAC producing a potentially important MV gradient is not rare in the general cardiology population. Reduced AML mobility appears to be necessary for a gradient > 5 mm Hg. Significant AV gradients are commonly associated, reflecting greater overall cardiac calcification. These patients can be easily identified by looking for reduced AML mobility as part of widespread cardiac calcification.

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1. Introduction

Mitral annular calcification (MAC) is a common finding on echocardiography, particularly in the elderly [1]. The etiology is unclear although it is associated with the same risk factors as atherosclerotic disease of which it may be a subclinical form [2]. In addition it appears to be related to abnormal calcium and phosphorus metabolism with a high incidence noted in end-stage renal disease [3].

Generally, this process is regarded as benign although it is thought to produce significant mitral regurgitation on occasion [4]. Mitral stenosis due to annular calcification is reported to be quite rare [5–13]. However, we have noted a number of patients undergoing routine echocardiography who have a significant resting gradient across the mitral valve (MV) with the only apparent etiology being MAC. We therefore evaluated a series of echocardiograms demonstrating severe MAC for features associated with a resting MV gradient.

2. Materials and methods

Outpatient echocardiogram reports were searched for key phrases regarding severe annular calcification and, separately, for mitral stenosis; patients with rheumatic disease or other identifiable mitral valve disease were excluded. All outpatient studies were performed in the setting of a private general cardiology practice between 1/1/03–10/1/05. Several inpatient studies were included as they came to our attention for purposes of substantiating our observations. Forty-three cases (40 outpatients and three inpatients) of severe posterior and/or anterior MAC were identified.

Age and sex of each subject were recorded along with the mean MV gradient by steerable CW Doppler. The
extent of aortic valve (AV) calcification was visually assessed (none, mild, moderate or severe) and the mean gradient across the aortic valve by steerable CW Doppler was recorded. A note was made of the presence or absence of the extension of calcification from the aortic root onto the anterior mitral leaflet and of any apical displacement of the “hinge point” of the anterior mitral leaflet by that calcification. Mitral regurgitation (MR) was graded semi-quantitatively (none, mild, moderate, severe) based on the area of the color flow jet vs. the area of the left atrium. Significant MR was defined as that which was at least moderate in severity.

The characteristics of the annular calcification evaluated included the extent of the posterior annulus involved (by thirds) and the height of the “bar” of calcium both anteriorly and posteriorly (measured on the parasternal long axis view). Anterior mitral leaflet (AML) mobility was evaluated in the parasternal long axis, apical 4 chamber and apical long axis views. The anticipated diastolic excursion of the leaflet was compared with that which was actually observed. Mobility was then scored semi-quantitatively: “moderately to severely reduced” in cases with less than half of the anticipated excursion, vs. “normal to mildly reduced” when excursion was at least half of that anticipated. The visual impression of moderately to severely reduced AML mobility was then confirmed by measuring a maximum MV orifice dimension of ≤10 mm on parasternal long axis images.

Patients were divided into two groups according to anterior mitral leaflet mobility. Group A (22 patients) had moderate or severe reduction of AML mobility and group B (21 patients) had normal or mildly reduced AML mobility. Group C consisted of 10 additional patients who had annuloplasty rings in place (evaluated for purposes of comparison). For both groups A and B presence or absence of dyspnea and presence or absence of creatinine ≥1.5 mg/dL were also recorded.

Informed consent was not deemed necessary as patients were not directly approached and no patient specific information was disclosed. This study was approved by the St. Francis Medical Center Institutional Review Board.

Fisher’s exact test was used for all contingency tables. The Mann–Whitney test was used to compare two groups when continuous variables were not normally distributed. Analysis of variance followed by a post hoc test (Dunn’s test) was used to make comparisons among groups A, B and C. All statistical maneuvers were performed with Prism® software (GraphPad Corp., San Diego CA).

3. Results

A total of 4270 patients underwent echocardiography in our outpatient lab over this time period. Of those, 3096 were age 65 or older. Forty patients were reported to have severe MAC, representing 0.9% of the total group and 1.3% of those 65 and over. All but three had severe posterior MAC. Nineteen subjects were identified who had reduced AML mobility due to annular calcification (group A included these as well as three additional inpatients). They represented 0.4% of the total number of patients to come through the lab and 0.6% of those 65 and over.

The mean MV gradient in group A was 7 mm Hg (range 3–14) vs. 3 mm Hg in group B (range 1–5), p<0.0001 (Fig. 1, Table 1). The mean MV gradient in group C was 3 mm Hg. An analysis of variance measures showed the mean MV gradient to be significantly greater in group A vs. group B (p<0.001) and in group A vs. group C (p<0.001) but not in group B vs. group C (p>0.05). The mean AV gradient in group A was 27 mm Hg (range 4–48) vs. 14 mm Hg in group B (range 3–40), p=0.013 (Table 1). There were no significant differences between the two groups in age, sex or dyspnea. Creatinine ≥1.5 tended to be more prevalent in group A, Odds Ratio 3.6, p=0.07.

Of the morphological aspects evaluated only AML mobility was associated with the mean MV gradient. Nearly all group A patients had calcification of the entire posterior annulus. Only three did not. Notably, one of these three had virtually no posterior MAC and yet had a mean MV gradient of 9 mm Hg. AML mobility was judged moderately reduced in this patient. Anterior “bar” length was very variable as was posterior “bar” length, and did not correlate with mitral valve gradient or AML mobility. In addition it was observed that the density of calcification in the various parts of the annulus was highly variable. It was subjectively greater in patients with limited AML mobility.

Nineteen patients had a resting gradient across the mitral valve of 5 mm Hg or more, representing 48% of patients in whom severe MAC was reported. All but two had moderate or severe reduction of AML mobility. These two both had a gradient of 5 mm Hg. There were also four patients with significantly reduced AML mobility but a gradient of less than 5 mm Hg. Two of these had a reduced ejection fraction. No patient with normal or mildly reduced AML mobility had a mean MV gradient of 10 mm on parasternal long axis images.

![Mean MV Gradient](image)

Fig. 1. Individual data points for groups A and B. Open boxes indicate mean values.
greater than 5 mm Hg. Finally, no patient had significant mitral regurgitation.

4. Discussion

Mitral annular calcification is commonly observed on echocardiograms, particularly in the elderly [1]. While this is usually an incidental finding it has occasionally been associated with significant mitral regurgitation [4]. As demonstrated in our cohort of unselected outpatients it can also produce a clinically relevant resting gradient across the mitral valve, with approximately 0.5% of our outpatients affected. This is more likely when the MAC is severe and especially when there is reduced anterior mitral leaflet mobility. Most such patients have widespread intracardiac calcification. In an occasional case severe mitral stenosis can be produced; two of our outpatients had a gradient exceeding 10 mm Hg and one went on to mitral valve replacement.

Our group A patients (those with reduced anterior leaflet mobility) characteristically had marked thickening and calcification of the interannular fibrosa extending down onto the AML and it was this calcification that appeared to limit its mobility in most cases. Often the “hinge point” of the anterior mitral leaflet was displaced onto the body of the leaflet by the calcification (Fig. 2). There were, however, a few patients where mobility appeared to be limited by chordal thickening and calcification. Calcification of various cardiac structures was widespread in group A patients, frequently involving the aortic valve and submitral apparatus as well as the annulus. Additionally the presence of heavy calcification extending from the aortic valve to the interannular fibrosa, onto the mitral valve, posterior annulus and even into the subvalvular apparatus, gave a distinctive “staircase” appearance in some patients (Fig. 3).

Reduced AML mobility appeared to be a necessary precondition to have a resting gradient greater than 5 mm Hg. When this was absent the gradient was always 5 mm Hg or less no matter how severe the posterior annular calcification (even including instances where the posterior mitral leaflet was encased in calcium and completely non-mobile). Thus, reduced AML mobility was more important in producing a significant MV gradient than was the actual severity of MAC. Though both leaflets have the same area, the annulus to tip length of the anterior mitral leaflet is far greater than that of the posterior leaflet [14]. Therefore, significant restriction of motion of this leaflet would be expected to have greater impact on overall valve opening than the more commonly observed restriction of posterior leaflet motion. This mechanism of mitral stenosis stands in contradistinction to rheumatic disease which most commonly reduces valve opening via fusion of the commissures. While some of our subjects had calcific deposits involving the commissures, this did not by itself significantly reduce mitral valve opening.

Severe mitral stenosis has been previously reported as a rare complication of annular calcification. In 1962 Korn et al. described 14 cases of massive calcification of the mitral annulus at autopsy of which 9 had significant stenosis (defined as a narrowed valve orifice admitting one finger or less) [13]. Several reports since then have confirmed heavy annular calcification as a cause of clinical mitral stenosis. [6,11,13,15] More recently, Soeki et al. used Doppler echocardiography to more generally evaluate effects of MAC on mitral valve area [14]. In 53 patients with MAC, not preselected for mitral stenosis, they documented a reduced mitral valve area compared with 30 normal controls. In keeping with the concept of the annulus as a sphincter [14–16], they invoked

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Group A</th>
<th>Group B</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age median (interquartile range)</td>
<td>77 (65–83)</td>
<td>78 (70–88)</td>
<td>0.36</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>15/7</td>
<td>11/10</td>
<td>0.36</td>
</tr>
<tr>
<td>Mean MV gradient mm Hg±standard deviation (95% confidence interval)</td>
<td>7±3 (5–8)</td>
<td>3±1 (2–3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean AV gradient mm Hg±standard deviation (95% confidence interval)</td>
<td>27±15 (21–34)</td>
<td>14±14 (8–21)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

### Table 1

![Fig. 2. Limited excursion of the MV in diastole. Note the calcification of the interannular fibrosa with apical displacement of the “hinge point” of the AML. The aortic valve is prosthetic.](image1)

![Fig. 3. Extensive cardiac calcification creating a “staircase” appearance in systole.](image2)
“absence or reduction of normal annular dilation during diastole” as the cause of the functional mitral stenosis. Our study, however, points to impaired AML mobility as the key determinant of a significant resting gradient across the mitral valve. In line with this concept, it is interesting to note that of four patients identified by Labovitz et al. as having mitral stenosis due to MAC, three had AML involvement [13].

Nearly all our patients with a significant MV gradient had severe posterior MAC. This would be expected as posterior annular calcification is more common than anterior [4,7]. However, there was one notable exception of a patient with severe anterior calcification who had virtually no posterior MAC. This patient had aortic valve calcification extending onto the AML and limiting its mobility, again supporting the concept of reduced AML mobility as the chief determinant of a significant MV gradient. Aortic valve calcification was frequent in our series, confirming previous observations associating MAC and calcific aortic valve disease [4,5,7,14]. In fact, it may be more appropriate to consider AML restriction the consequence of aortic root calcification extension rather than the result of MAC per se. However, it is important to note that there were cases of mitral stenosis due to MAC in the absence of significant aortic calcification. Thus severe calcific disease can affect both valves simultaneously or each individually.

Premature calcification of cardiac structures is well documented in end-stage renal disease [3,16,17]. Of our group A outpatients none was on dialysis (the only dialysis patient in this group was an inpatient), reflecting the fact that end-stage renal disease is uncommon in our outpatient population. This suggests that the finding of a resting gradient across the mitral valve is not limited to those with end-stage renal disease and will be encountered in other cardiology outpatients. Many subjects in both groups had a creatinine of at least 1.5 mg/dl. with a nonsignificant trend towards increased prevalence in group A. In a larger population sample this might have reached significance and suggests an association between cardiac calcification and mild or moderate renal insufficiency. It is to be expected that those with the worst renal failure, as reflected by the need for dialysis, will develop calcification leading to aortic and mitral valve gradients at an earlier age than patients with normal kidney function.

In addition to anatomic disease there are several physiologic factors that may affect the gradient across the mitral valve. These include heart rate and volumetric flow across the valve. Increases in either or both would be expected to increase any existing or latent mitral valve gradient. On the other hand increased left ventricular diastolic pressure might, under certain conditions, decrease the mitral valve gradient. The chief clinical manifestations of mitral stenosis relate to pulmonary congestion and an impaired ability to augment cardiac output under conditions of physiologic stress. Many of our patients had signs or symptoms of heart failure but there was no difference in the prevalence of dyspnea between groups A and B. The patients in both groups were elderly and often had multiple reasons for dyspnea. However, it appears likely that the MV gradient was a contributor in some.

It is of interest that four of our group A patients had an unexpectedly low gradient despite obvious severe restriction of anterior leaflet and overall mitral valve mobility. Two of these had a significant reduction of ejection fraction and likely had increased left ventricular filling pressure and perhaps decreased cardiac output. These factors might account for a decrease in the trans-mitral gradient. Diastolic dysfunction, in the absence of a reduced ejection fraction, might also contribute to a lowering of the MV gradient via an increase in left ventricular filling pressure.

Mitrail annular calcification has been previously associated with mitral regurgitation. While our chief intent in this study was to evaluate the effects of annular calcification on mean MV gradient it is interesting to note that none of our patients had significant (moderate or greater) MR. Much of the literature looking at MR in patients with MAC predates the current Doppler techniques used for semi-quantitation [5,7,12,13]. In addition, mixed populations were studied including patients with other disease processes that could have caused MR. Often physical exam or autopsy was used to document MR. Our outpatient records were carefully searched in an attempt to identify all patients with severe MAC reported on echocardiography who had no other mitral valve disease. The population as a whole represents an unselected group of general cardiology patients. It would thus appear that significant mitral regurgitation due to MAC is uncommon, at least in a general cardiology practice setting.

Several limitations should be noted. This study was retrospective and observational. The patients were identified by searching echocardiogram reports for terms indicating severe annular calcification and/or mitral stenosis. Though multiple search terms were used we were probably not able to identify all affected patients. In addition the grading of annular calcification is subjective and various readers may also have reported annular calcification with varying consistency. This might explain why so many of the patients identified had significant anterior annular calcification when posterior calcium deposits are more common. If our theory is correct that anterior calcification is more physiologically significant, mitral valve findings in these patients would have been more likely to be reported than in those with isolated posterior annular calcification and no significant mitral valve gradient.

In addition, the study was not blinded. It is meant to be hypothesis generating. Ideally, these findings would be confirmed in a prospective, blinded fashion.

In conclusion, severe mitral annular calcification can produce a significant resting gradient across the mitral valve. This process was seen in approximately 0.5% of unselected outpatient echocardiograms and will likely be encountered with increasing frequency as the population ages. In most patients the stenosis produced will be minor though occasional cases may be severe enough to warrant mitral
valve replacement [6]. However, in situations where the heart rate rises, the mitral valve gradient may increase enough to cause or contribute to symptoms of dyspnea and fatigue. This would be particularly true in cases of rapid atrial fibrillation. Here it is important to note that atrial fibrillation, like MAC, is predominantly a disease of the elderly whose incidence is rising. Physical exertion, anemia and severe systemic illness also increase trans-mitral flow and might thus precipitate symptoms in MAC patients. Severe diastolic dysfunction, whether associated with a reduced or preserved ejection fraction, is another setting where anatomic limitation of mitral valve opening might be clinically relevant. These patients already have elevated left ventricular filling pressure. Any gradient across the mitral valve would be additive in effect on left atrial pressure and pulmonary capillary pressure.

Therefore, mitral annular calcification should be routinely evaluated whenever echocardiography is performed. Attention should be paid to involvement of the interannular fibrosa and extension onto the anterior mitral leaflet especially when it limits leaflet mobility. In such cases MAC may produce a resting gradient across the mitral valve. In the setting of tachycardia, increased cardiac output or severe diastolic dysfunction such gradients may be clinically significant.

References