Association of Mitral Annular Calcification with Cardiovascular Risk Factors and Cardiac Structural Disease in Patients with Mitral Regurgitation

Mitral Yetersizliği Olan Hastalarda Mitral Anular Kalsifikasyon ile Kardiyovasküler Risk Faktörleri ve Kalbin Yapısal Hastalığı Arasındaki İlişki

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ABSTRACT Objective: Mitral annular calcification (MAC) is the degenerative calcification of the supportive ring of mitral valve. In previous studies, MAC has been shown to be associated with atherosclerosis, and be an independent predictor of cardiovascular disease. The purpose of this study was to evaluate the association of MAC with mitral regurgitation, cardiovascular risk factors and other cardiac structural disease. **Material and Methods:** We retrospectively reviewed 30 701 echocardiograms performed for various clinical indications between 2006 -2007. Four thousand four hundred and forty six patients with mitral valve regurgitation were evaluated for MAC and its relation with severity of mitral regurgitation, cardiovascular risk factors and other cardiac structural and functional abnormalities. **Results:** MAC was diagnosed in 534 (12.0%) of the 4446 patients with mitral regurgitation. MAC was mostly observed in patients with older age, female gender, hypertension, diabetes mellitus, left atrial enlargement, atrial fibrillation, mitral stenosis and aortic stenosis. Presence of MAC was associated both with the severity of mitral regurgitation and mitral stenosis. In logistic regression analysis, older age, female gender, hypertension, left ventricular hypertrophy, diastolic dysfunction, left atrial enlargement, tricuspid regurgitation, aortic stenosis and mitral stenosis were independent predictors of with MAC. Among these variables, left ventricular hypertrophy was found to be the most predictive parameter of MAC. **Conclusions:** In this study, MAC independently associated with cardivascular risk factors and structural disease. Therefore, MAC may be used as a predictor of cardiovascular risk and cardiac structural abnormalities in daily clinical practice.

Key Words: Mitral valve; risk factors; mitral valve insufficiency

ÖZET Amaç: Mitral anular kalsifikasyon (MAK); mitral kapak destekleyici halkasının dejeneratif kireçlenmesidir. Yapılan çalışmalar; MAK'un ateroskleroz ile ilişkili olduğunu ve kardiyovasküler hastalık için öngördürücü olabileceğini göstermişlerdir. Bu çalışmanın amacı; mitral yetersizlik, kardiyovasküler risk faktörleri ve kalbin diğer yapısal hastalıkları ile MAK arasındaki ilişkinin değerlendirilmesidir. **Gereç ve Yöntemler:** 2006-2007 yılları arasında çeşitli klinik endikasyonlar ile yapılan 30 701 ekokardiyogram retrospektif olarak değerlendirildi. Mitral yetersizliği olan 4446 hasta; MAK, mitral yetersizliğinin derecesi, kardiyovasküler risk faktörleri, kalbin diğer yapısal ve fonksiyonel anormallikleri açısından analiz edildi. **Bulgular:** Mitral yetersizliği olan 4446 hastanın 534'ünde (%12) MAK tespit edildi. MAK; yaşlı, kadın, hipertansif ve diyabetik hastalara ek olarak, sol atriyumu geniş, atriyal fibrilasyonu olan ve mitral ya da aort darlığı olan hastalarda daha sık olarak gözlendi. MAK'un varlığı hem mitral yetersizliğinin, hem de mitral darlığının derecesi ile ilişkili idi. Lojistik regresyon analizinde; ileri yaş, kadın cinsiyet, hipertansiyon, sol ventrikül hipertrofisi, sol atriyumda genişleme, aort darlığı ve mitral darlığı , MAK'un bağımsız öngördürücüleri olarak bulundu. Bu değişkenler içerisinde sol ventrikül hipertrofisi öngördürücülüğü en yüksek olan parametre idi. **Sonuç:** Bu çalışmada MAK, kardiyovasküler risk faktörleri ve yapısal hastalık ile bağımsız olarak ilişkili bulunmuştur. Bu sebeple, günlük klinik pratikte, MAK'un kardiyovasküler risk ve kalbin yapısal anormalliklerinin öngörülmesinde kullanılabileceği düşünülmektedir.

Anahtar Kelimeler: Mitral kapak; risk faktörleri; mitral kapak yetmezliği

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Mitral annular calcification (MAC) is a chronic degenerative process of the supportive ring of mitral valve. Calcification of the mitral and aortic anuli were shown to be associated with aging.[1,2] MAC is one of the most common cardiac abnormalities found in autopsy series.[3] Previous studies reported that MAC was a common finding with 6.1% of the subjects in routine echocardiographic examinations.[4] Additionally, many studies demonstrated that cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia and obesity are also similar risk factors for MAC.[5-8] Thus, valvular calcifications, like aortic sclerosis and aortic stenosis have been shown to be related to cardiovascular risk factors, subclinical cardiac disease, coronary heart disease.[9,10] Framingham Heart Study[1] showed that MAC is predictive for cardiovascular disease, cardiovascular and all-cause mortality. Observational studies suggested that MAC might be associated with mitral valvular dysfunction, rhythm and conduction disturbances and endocarditis.[11]

Besides relation with cardiovascular risk factors, MAC had been demonstrated as an important cause of mitral regurgitation (MR) associated with the severity of MAC.[12] However, some studies reported that MAC was not related neither with mitral stenosis nor MR severity.[4] The purpose of this study was to evaluate the association of MAC with mitral regurgitation, cardiovascular risk factors and other cardiac structural disease.

MATERIAL AND METHODS

STUDY PATIENTS

We retrospectively reviewed 30 701 echocardiograms performed for various clinical indications between 2006-2007 years in our cardiology clinic. Four thousand four hundred and fourty six patients with mitral regurgitation were evaluated for cardiovascular risk factors and related valvular diseases. There were 534 patients with MAC (mean age 74.41 ± 9.21) consisted of 146 male (27.4%, mean age 72.5 ± 9.8 year) and 388 female (72.6%, mean age 75.1 ± 8.8 year).

ECHOCARDIOGRAPHIC MEASUREMENTS

All the patients were examined on the left lateral decubitus position by M-mode, two-dimensional and Doppler echocardiography using avaible systems (GE, Vingmed Vivid3 Expert, Horten, Norway and Siemens Acuson Sequoia C256, Mountain View, CA, USA). Left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters, interventricular and posterior wall thickness, left atrial (LA) diameter, diastolic dysfunction were obtained from echocardiography reports. MAC was defined based on the interpretation of cardiologist.

An intense echo-producing structure located at the junction of the atrioventricular groove and posterior mitral valve leaflet on the parasternal long axis and apical 4 chamber views or an intense echo-dense structure located posterior to posterior mitral valve leaflet on the parasternal short axis view defined as MAC (Figure 1).[11] The annular calcification was semi-quantified as absent or present.

Valvular regurgitations were defined as mild to severe according to colour and continuous wave Doppler measurements. Valvular stenosis were graded mild to severe according to valve areas and pressure gradients on the valves.

STATISTICAL ANALYSIS

All statistical data processed by using Statistical Package for the Social Sciences 11.0 (SPSS 11.0, Chicago, IL,USA) program. The results were expressed as mean and standard deviation together with chi-square analysis was used for comparisons

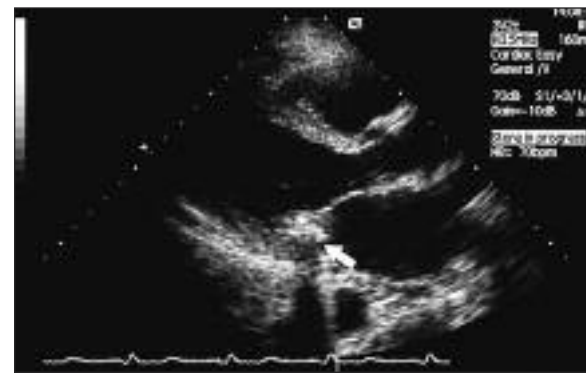

FIGURE 1: An example of mitral annular calcification.

of the groups. In the multivariate analysis, a logistic regression model was utilized to calculate the odds ratio and their 95% confidence interval to indicate strength of influence. The results were considered significant when the *p* value was less than 0.05.

RESULTS

MAC was diagnosed in 534 (12.0%) of the 4446 patients with MR. At the baseline examination, patients with MAC were older (74.42 ± 9.19 years) and more likely to be female (72.5%). Patients with MAC had also more obesity (p= 0.03), diabetes mellitus (p= 0.04) and hypertension (p= 0.001) as risk factors. Coexisting mitral stenosis was observed in 105 (19.7%) patients with MAC.

In univariate analysis, MAC was found to be significantly associated with enlarged left atrium, atrial fibrillation, left ventricular hypertrophy (LVH), diastolic dysfunction, mitral stenosis and aortic stenosis, aortic and tricuspid regurgitation and pulmonary hypertension (Table 1).

In correlation analysis, MAC was significantly related with older age (r= 0.260, p< 0.001). The associaton between MAC and LVH was statistically significant (r= 0.196, p< 0.001). Additionally, there was a positive significant correlation between MAC and diastolic dysfunction (r= 0.104, p< 0.001). We also found that there was a statistically significant correlation between LA enlargement (r= 0.087, p< 0.001) and MAC as well as the atrial fibrillation (r= 0.075, p< 0.001). We found an association between MAC and mitral regurgitation severity (r= 0.035, p= 0.021). Similarly, there was a significant correlation between presence of mitral stenosis and MAC (r= 0.075, p< 0.001) and relation between the degree of mitral stenosis and MAC (r= -0.057, p= 0.001). In correlation analysis, MAC was also significantly related with accompanying aortic stenosis (r= 0.225, p= 0.001) and severity of aortic stenosis (r= 0.061, p= 0.001) (Table 2).

In multivariate logistic regression analysis, we found that older age (OR: 12.6, CI: 6.38-23.21, p< 0.001), female gender (OR:2.16, CI: 1.617-

TABLE 1: Baseline characteristics of patients with and without MAC.

		MAC (+) n (%)	MAC (-) n (%)	
Age ≥ 60		503 (94.5 %)	2542 (65.2 %)	0.001
Gender	Female	387 (72.6 %)	146 (27.4 %)	0.001
	Male	2158 (55.4 %)	1740 (44.6 %)	
Diabetes mellitus		113 (25.7 %)	681 (21.4 %)	0.045
Hypertension		273 (62.2 %)	1552 (49.0 %)	0.001
Hyperlipidemia		137 (31.2 %)	977 (30.8%)	0.873
Heredity		58 (13.2 %)	484 (15.3 %)	0.256
Obesity		73 (16.6 %)	410 (12.9 %)	0.034
Left atrial enlargement		478 (89.7%)	3078 (79.0 %)	0.001
LVH		369 (%65.5)	1404 (%36)	0.001
Diastolic dysfunction		144 (%49.7)	626 (%35.2)	0.001
Atrial fibrillation		45 (11.7 %)	170 (5.9 %)	0.001
Mitral stenosis		105 (19.7 %)	467 (12.0 %)	0.001
Aortic stenosis		161 (30.3 %)	332 (8.5 %)	0.001
Aortic regurgitation		410 (76.9 %)	2384 (61.2 %)	0.001
Tricuspid regurgitation		505 (94.7 %)	3513 (90.1%)	0.001
Pulmonary hypertension		253 (50.4 %)	1416 (40.9 %)	0.001

LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter, LVH: left ventricular hypertrophy.

TABLE 2: Correlation analysis for MAC and cardiac structural abnormalities.

	r	p value
LVH	0.196	<0.001
Diastolic dysfunction	0.104	<0.001
LA enlargement	0.087	<0.001
Atrial fibrillation	0.075	<0.001
Severity of mitral regurgitation	0.035	0.021
Mitral stenosis	0.075	<0.001
Severity of mitral stenosis	0.057	0.001
Aortic stenosis	0.225	0.001
Aortic regurgitation	0.106	<0.001
Severity of aortic regurgitation	0.061	0.001
Tricuspid regurgitation	0.052	<0.001
Pulmonary hypertension	0.062	<0.001

LA: left atrium, LVH: left ventricular hypertrophy.

2.88, p= 0.001), hypertension (OR: 1.41, CI: 1.064-1.856, p= 0.017), LVH (OR: 80.8, CI:0.243-0.403, p< 0.0001), diastolic dysfunction (OR: 21.7, CI: 0.429-0.708, p< 0.0001), LA enlargement (OR: 1.66, CI:1.099-2.460, p= 0.016), atrial fibrillation (OR: 10.2, CI:0.36-0.78, p= 0.001) ,tricuspid regurgitation (OR: 11.34, CI: 0.342-0.753, p= 0.001), mitral stenosis (OR: 24.25, CI: 0.439-0.702, p< 0.001) and aortic stenosis (OR: 11.94, CI:0.315-0.727, p< 0.001) were predictive for the presence of MAC (Table 3). Among these variables, LVH was found to be the most predictive parameter with MAC.

DISCUSSION

MAC represents a chronic degenerative process in fibrous skeleton of the heart which is associated with atherosclerosis and cardiovascular risk factors. It is reported to be markedly related with age, hypertension, hyperlipidemia, diabetes mellitus and genetic disorders.[1] Fibrillar alteration of collagen ultrastructure is considered to be the primary pathological event causing calcification. After the triggering the lipid deposition, the small foci of calcification starts to develop at the junction of annulus, ventricle muscle fibers and within the annulus itself.[13] Before observational studies, MAC has been considered as an innocent change due to aging. In following years, MAC has shown to be a higher risk of cardiovascular disease, conduction disturbances and all cardiovascular death.[3]

Supporting the previous studies, our study results demonstrated that MAC was significantly associated with advanced age, female gender, hypertension, diabetes mellitus, LVH, diastolic dysfunction, pulmonary hypertension, LA enlargement, aortic stenosis, tricuspid regurgitation and mitral stenosis in a cohort of patients with mitral regurgitation.

This study showed a significant relationship between MAC and mitral stenosis unlike the study of Movahed, et al.[4] Because that study included a small number of mitral stenosis patients, assessment of the relation between MAC and mitral stenosis might be inaccurate. However, in our study 19.7% of the MAC patients had variable degree of mitral stenosis therefore we were able to demonstrate a marked relationship between MAC. We also found a significant correlation between MAC and the severity of mitral stenosis. Similarly, a significant correlation between MAC and severity of mitral regurgitation was determined. It is possible that calcified and thickened mitral valve leaflets may lead to insufficient closure causing MR.

TABLE 3: Multivariate logistic regression analysis for the association between MAC and various clinical characteristics and cardiac structural abnormalities.

	Odds Ratio (OR)	95%CI	P
Age >60 (years)	12.6	6.38-23.21	0.001
Gender (female)	2.16	1.617-2.88	0.001
HT	1.41	1.064-1.856	0.017
Atrial fibrillation	10.2	0.36-0.78	0.001
LA enlargement	1.66	1.099-2.460	0.016
LVH	80.8	0.243-0.403	0.0001
Diastolic dysfunction	21.79	0.429-0.708	0.0001
Mitral stenosis	24.25	0.439-0.702	0.001
Aortic stenosis	3.02	2.201-4.132	0.001
Tricuspid regurgitation	7.89	0.380-0.842	0.005

HT: hypertension, LA: left atrium, LVH: left ventricular hypertrophy.

MAC might play a role in the pathogenesis of aortic stenosis or in another perpective increased left ventricular pressures in aortic stenosis may cause enhanced calcification on mitral valve. Additionally, LVH was found to be the most associated parameter with MAC in our study. This result also suggest the hypothesis that MAC occuring as an outcome of increased valvular stress. Fulkerson et al.[13] reported that chronic increase in left ventricular pressures as in hypertension or in aortic stenosis led to accelaration of degenerative process. The present study showed a significant relationship with diastolic dysfunction and MAC. The cardiac strctural abnormalities like LVH and aortic stenosis may cause diastolic dysfunction and explain the accompanying diastolic dysfunction. In our study, we also found an independent relation between MAC and aortic stenosis. Moreover LVH was the most predictive parameter fort he presence of MAC in patients with MR.

We showed significant relationship between MAC and LA enlargement. We suggest that enlarged LA may be as a result of both mitral stenosis and MR. There was an independent association with tricuspid regurgitation. The association between MAC and tricuspid regurgitation might be due to MR, mitral stenosis or diastolic dysfunction. Our study also revealed an independent relationship between MAC and aortic regurgitation. It appears to be caused by degenerated integrity of aortic valve due to excess calcification. We found a siginificant correlation between MAC and the severity of aortic regurgitation. In conclusion, this was a large scale retrospective study demostrating an independent relationship between MAC and cardiac risk factors. MAC was also an independent relation with cardiac structural changes such as LVH, LA enlargement, severity of mitral regurgitation, mitral stenosis, aortic stenosis and tricuspid regurgitation in patients with MR. We suggest that MAC may be used as a predictor of cardiovascular risk and cardiac structural abnormalities in daily clinical practice.

STUDY LIMITATIONS

Since this was a retrospective study, all cardiac functional and structural abnormalities recorded from echocardiography reports. There was no data regarding to the grading and diagnosis of MAC.

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