JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 17, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.08.872

REVIEW TOPIC OF THE WEEK

Mitral Annulus Calcification

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ABSTRACT

Mitral annulus calcification (MAC) is a chronic, degenerative process in the fibrous base of the mitral valve. Although MAC was initially thought to be an age-related degenerative process, there is accumulating evidence that other mechanisms, such as atherosclerosis and abnormal calcium-phosphorus metabolism, also contribute to the development of MAC. Despite its frequency, the clinical relevance of MAC is grossly underappreciated. Indeed, MAC is associated with an increased incidence of cardiovascular disease, mitral valve disease, arrhythmias, and mortality. MAC also influences the outcomes of cardiac surgery and interventions, and its clinical relevance may well increase substantially in the forthcoming era of transcatheter mitral valve replacement. In this paper, we review the available published data to provide a consistent, clinically relevant description of MAC on the basis of contemporary imaging. We describe the pathophysiological mechanisms contributing to the formation of MAC and the clinical implications of this disease entity.
(J Am Coll Cardiol 2015;66:1934–41) © 2015 by the American College of Cardiology Foundation.

Mitral annulus calcification (MAC) is a chronic, degenerative process of the fibrous support structure of the mitral valve (1,2). The reported prevalence of MAC is between 8% and 15%, but it significantly increases with age and in patients with multiple cardiovascular risk factors or chronic kidney disease (CKD) (3–7). Although calcification of the mitral annulus was initially thought to be an age-related process, there is accumulating evidence that it is a tightly regulated, active process, with features similar to both medial and atherosclerotic cardiovascular calcification (8). Its clinical relevance comes from MAC's association with an increased rate of mortality and cardiovascular disease (CVD) (9). MAC has also been found to increase the incidence of mitral valve disease and arrhythmias and to influence the outcome of cardiac surgery (2,10,11). We reviewed the available published data to seek: 1) a consistent, clinically relevant definition of MAC on the basis of contemporary imaging; 2) a firm understanding of its pathogenesis and associations; and 3) the clinical implications of this disease entity.

DEFINITION AND DIAGNOSIS

The mitral annulus separates the left atrium from the left ventricle (LV). It has a complex saddle shape that is divided into anterior and posterior portions. The anterior annulus spans the left and right fibrous trigones and is anatomically coupled to the aortic annulus. The posterior annulus encompasses the remainder of the annular perimeter and is composed of a discontinuous rim of fibrous tissue periodically interrupted by fat (12). MAC is defined as a chronic degenerative process in the fibrous base of the mitral valve (1,2,13). In 1910, Dewitzky recognized noninflammatory calcific disease of the mitral annulus

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Manuscript received June 30, 2015; revised manuscript received August 22, 2015, accepted August 25, 2015.

fibrosus as an entity, presented a detailed pathological description of 36 cases, and likened the lesion to a similar process in the aortic valve described by Mönckeberg in 1904 (1). Large historical autopsy studies found MAC in approximately 10% of patients (3,14). MAC more commonly affects the posterior annulus than the anterior annulus (15,16).

Occasionally, a chest x-ray might reveal calcific demarcation of the mitral annulus. MAC is usually seen as a C-, J-, U- or O-shape, with the open part lying at the site of the aortic outflow tract (2). Lateral projection usually better demonstrates mitral calcification because the overlying spine and main left lower lobe arteries in the posteroanterior view may mask its visualization. Fluoroscopy during coronary angiography can also show mitral calcification, but is not an accurate modality for assessment of the extent of MAC.

Previously, echocardiography was considered to be the best method to demonstrate MAC (17). MAC can be recognized by M-mode echocardiography as an echo-dense band beneath the posterior mitral leaflet, with motion paralleling that of the free ventricular wall (2). The 2-dimensional technique more clearly demonstrates the localization of MAC to the angle between the LV posterior wall and the posterior mitral leaflet (18). MAC is usually visualized as an echo-dense, shelf-like structure with an irregular, lumpy appearance involving the mitral valve annulus, with associated acoustic shadowing. In a subanalysis of the Framingham Heart Study, MAC was assessed by M-mode echocardiography and defined as an echo-dense band visualized throughout systole and diastole, distinguishable from the posterior mitral valve leaflet, and located anterior and parallel to the posterior LV wall (9). In the Cardiovascular Health Study, MAC was defined by an intense echocardiograph-producing structure located at the junction of the atrioventricular groove and posterior mitral leaflet (19). Severity was qualitatively determined in parasternal short-axis view at the level of the mitral annulus as mild (focal, limited increase in echodensity of the mitral annulus), moderate (marked echodensity involving one-third to one-half of the ring circumference), or severe (marked echodensity involving more than one-half of the circumference of the ring or with intrusion into the LV inflow tract). Maximal MAC thickness measured from the anterior to the posterior edge at its greatest width is also used to assess MAC severity, with a value >4 mm defining severe MAC (20).

It has been suggested that echocardiography is probably not an ideal method for detection of valvular calcification because of its relatively low specificity in distinguishing between calcification and dense collagen (5). Electron-beam computed tomography (CT) and multislice (spiral) CT are effective, noninvasive techniques for cardiac, coronary, and aortic calcification imaging (4,21). Cardiac CT is a useful tool to predict the extent and location of MAC (22) and to quantify MAC objectively in order to assess the severity and associations of this entity (23). Allison et al. (4) assessed CT scans of 1,242 subjects without known coronary artery disease (CAD) (4). MAC was defined as calcification located at the junction between the left atrium and LV. Quantification of MAC with sufficient reproducibility can also be performed using the Agatston method with calculation of calcification in every level of the mitral annulus (23). Examples of the various diagnostic modalities in a patient with MAC are presented in **Figure 1**.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
CAD = coronary artery disease
CKD = chronic kidney disease
CT = computed tomography
CVD = cardiovascular disease
LV = left ventricle/ventricular
MAC = mitral annulus calcification
MR = mitral regurgitation
MVP = mitral valve prolapse

PATHOGENESIS AND ASSOCIATIONS

The pathophysiological mechanisms contributing to the formation of MAC are not fully understood. Previous autopsy histological and clinicopathological studies have shed light on the pathogenesis of MAC. Large, contemporary imaging studies that examined the association between MAC and other disease entities, such as atherosclerosis and CKD, have further enhanced our knowledge and enabled a better understanding of this process and its clinical importance (**Central Illustration**). Although MAC was first considered a passive, degenerative, age-related process (1,13), accumulating evidence now points toward a tightly regulated process with features similar to both medial and atherosclerotic cardiovascular calcification (8). A comprehensive description of the pathogenesis and associations of MAC can be found in the Online Appendix.

A DEGENERATIVE, AGE-RELATED PROCESS. Sell et al. (13) described calcification of the mitral annulus as a chronic, age-related, degenerative, noninflammatory process in the fibrous support structure of the mitral valve. Kanjanauthai et al. (5) evaluated 6,814 CT scans of participants enrolled in MESA (Multi-Ethnic Study of Atherosclerosis). The overall prevalence of MAC was 9%, and multivariable analysis found increased age to be independently associated with MAC in all ethnicities.

ATHEROSCLEROSIS. On the basis of pathological features seen in specimens from more than 300 patients with MAC (e.g., finding foam cells in early mitral annular lesions) and the strong association