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EDITORIAL COMMENT

Diastology: Don't Throw Out the MAC*

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Mitral annular calcification (MAC) is a chronic degenerative process involving calcification of the fibrous base of the mitral valve, with a reported prevalence of 10% (1). Initially thought to be solely a degenerative process, recent studies have demonstrated similarities between MAC and atherosclerosis, both pathologically and with respect to predisposing factors, such as diabetes, hyperlipidemia, and smoking, suggesting a common pathophysiological process (2). States of abnormal calcium and phosphorous handling, such as chronic kidney disease (3) and increased mitral valve shear stress (4), such as hypertension, can also promote calcium accumulation in the mitral annulus. Given these risk factors, patients with MAC are at high risk of concomitant diastolic dysfunction, and a reliable method of noninvasively estimating left ventricular filling pressure (LVFP) in patients with MAC would be of great value.

This last decade (2000s) has been coined the "decade of diastology" (5), with an overall movement toward more specific measures of LVFP, such as the ratio of early mitral inflow-to-mitral annular velocity (E/e′) and away from less specific measures, such as the ratio of early-to-late mitral inflow velocities (E/A), which is affected in varying ways by left ventricular (LV) stiffness, relaxation and left atrial pressure (6). However, the use of E/e′ in the setting of MAC is problematic (7,8). Calcification of the mitral annulus may increase mitral inflow velocities (E) by decreasing mitral annular area while restricting annular movement and decreasing mitral annular velocity (e′). As a result, current guidelines for assessing diastolic function are not applied to patients with significant MAC (6). Methods to circumvent these limitations have been proposed, such as measuring tissue velocity at extra-annular sites free of calcium (8); however, there have been no prospective studies to validate these methods.

SEE PAGE 1411

In this issue of *iJACC*, Abudiab et al. (9) address this clinical conundrum through a simple, prospective study using a cohort of 50 patients with various degrees of MAC. The authors performed complete Doppler echocardiography on each patient and correlated different Doppler parameters with LVFP measured by right or left heart catheterization (9). The authors then applied classification and regression tree (CART) analysis to develop an algorithm for predicting LVFP, which they subsequently validated in a cohort of 21 patients with MAC. The key findings were that E/e′ does not correlate well with LVFP regardless of the sample location used and that the best correlation was with the conventional E/A ratio ($r = 0.66$; $p < 0.001$). This "come back" of the E/A ratio for estimating LVFP may come as a surprise but is actually in keeping with our current understanding of Doppler assessment of diastolic function.

The commonly cited limitation of the E/A ratio is its U-shaped relationship with LV diastolic function and its inability to differentiate pseudonormal filling from normal patients in whom early diastolic filling is also increased. Given the demographic profile of patients with MAC, applying the E/A ratio to patients with at least mild MAC likely excludes most normal patients at one end of the "U" and improves the correlation between the E/A ratio and LVFP. However, although the E/A ratio outperformed the other parameters tested, the correlation was modest, with a correlation coefficient of 0.66, suggesting that only approximately 44% of the variability in LVFP can be explained by the E/A ratio. Indeed, the E/A ratio performed well in subjects with values approaching the restrictive range of >1.8, with a specificity of 100% for LVFP of >12 mm Hg, but the greatest challenge was in

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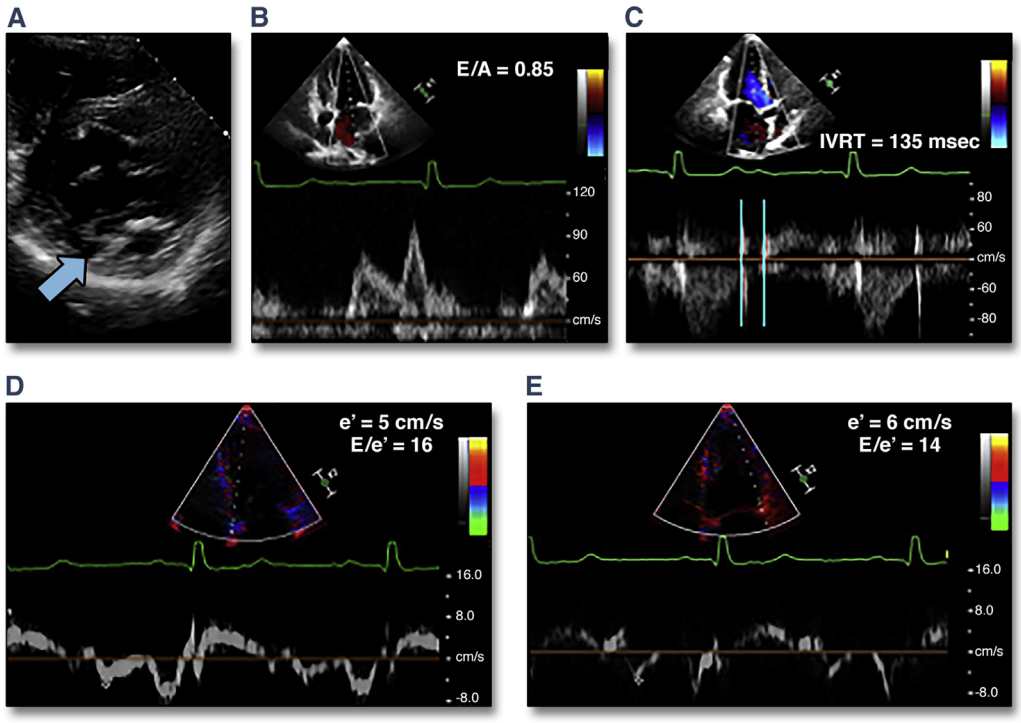
FIGURE 1 Application of Proposed Algorithm



This 71-year-old woman with moderate MAC, seen on short axis **(A, blue arrow)**, has an intermediate E/A ratio of 0.85 **(B)** and an IVRT of ≥80 ms (135 ms) **(C)**, indicating normal LVFP according to the proposed algorithm by Abudiab et al. (9). Tissue Doppler imaging of the inferoseptal **(D)** and anterolateral **(E)** mitral annulus reveals an average E/e′ of ≥14, which would have suggested elevated LVFP by standard criteria, but is unreliable in the setting of MAC. IVRT = isovolumic relaxation time; LVFP = left ventricular filling pressure; MAC = mitral annular calcification.

patients with intermediate E/A ratios (>0.8), where the specificity was only 62%.

Isovolumic relaxation time (IVRT), the time interval between aortic valve closure and mitral valve opening, is known to correlate directly with LV relaxation but is also affected by left atrial pressure, such that, in those with cardiac disease, its duration shortens as LVFP increases (6). Using CART analysis, the authors developed an algorithm where patients with E/A ratios below 0.8 or above 1.8 were classified as having normal or elevated LVFP, respectively, whereas for those with intermediate E/A ratios (0.8 to 1.8), a short IVRT (<80 ms) indicated elevated LVFP. This algorithm performed well, with a sensitivity of 100% and specificity of 90% for predicting elevated LVFP in the validation cohort. Prior studies that examined IVRT as an estimate of LVFP in mitral valve disease also used the time interval between E and e′ ($T_{E-e'}$) to correct for LV relaxation (10); however, in a population of patients with MAC, the importance of correcting for LV relaxation may be less important. This study suggests that IVRT alone can be useful in predicting LVFP in patients with intermediate E/A ratios.

This study highlights the importance of accurately grading the extent of MAC. In patients with mild MAC, there was good correlation between LVFP and anteroseptal E/e′ ($r = 0.81$; $p < 0.001$) and a modest correlation with standard inferoseptal and anterolateral E/e′ ($r = 0.6$ and 0.67, respectively; $p < 0.001$). This highlights MAC's posterior predilection and suggests that standard measurements of LVFP may be reasonable in patients with mild MAC; however, further study in this group is required. Thus, a standardized method of grading and localizing MAC would help clinicians decide which measurements of diastolic function to use. Echocardiography is limited by its relative inability to distinguish calcification from dense collagen. Methods for quantifying MAC using noncontrast computed tomography (CT) with good interobserver and intraobserver variability have

been developed (11). Although CT is well suited for quantifying MAC, given its high spatial resolution and calcium's high x-ray attenuation, it is not always feasible. Given the fact that echocardiography is the principal imaging modality for assessing mitral valve disease and noninvasively assessing LVFP, standardized echocardiographic methods for grading MAC correlated with CT are needed.

The proposed algorithm by Abudiab et al. (9) is simple to apply and has the potential to significantly affect how diastolic function is reported in patients with MAC (**Figure 1**). However, IVRT is not routinely measured in clinical practice and is affected by heart rate and arterial pressure. Atrial fibrillation, common among patients with MAC, would also limit the algorithm's applicability. Furthermore, whether mild MAC behaves similarly to moderate or severe MAC is unclear and needs further study.

As the population ages, the prevalence of MAC is increasing and, up until now, the classic teaching has been that current parameters for measuring LVFP do not apply in these patients. Invariably, patients with MAC present with undifferentiated shortness of breath, and the ability to utilize a simple algorithm to assess for elevated LVFP would be clinically useful. The algorithm proposed by Abudiab et al. (9) is promising, and its utility in patients with other mitral valve conditions, such as mitral valve repair or replacement, will be interesting. Thus, in the field of diastology, do not be too quick to throw out the MAC!

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