Editorial

Subclinical left ventricular systolic dysfunction in chronic mitral regurgitation and its potential impact on management: quo vadis?

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Mitral regurgitation (MR) is the second commonest valvular lesion prevalent in the community at large and its detection increases exponentially with advancing age.¹ Primarily, MR is of two types: intrinsic valvular disease or organic MR and the functional MR (FMR). The latter is essentially a left ventricular (LV) disease, primarily ischaemic, with secondary and functional involvement of the mitral valve apparatus. The issue of managing FMR is far more complex and out of pre-view of the present discussion. It is the organic MR, and more so when it is asymptomatic, that the need and timing of intervention requires attention. Decision-making process requires knowledge about aetiology, mechanism of valve incompetence, and severity of MR. In the western world, major cause of MR is degenerative while in the developing countries, rheumatic heart disease continues to be an important aetiology along with mitral valve degeneration in older subjects. No large-scale data on the natural history of asymptomatic rheumatic MR are available, although such data are reported on degenerative MR.^{2–4} We do not know if what is true for degenerative MR applies to rheumatic MR as well. Degenerative MR is progressive while rheumatic MR severity may remain static for a long period due to relatively fixed valve.⁴ Also, sudden cardiac death in degenerative MR is a known unfortunate event related to the degree of LV dysfunction, severity of MR, and the type of valve involvement.⁵ All symptomatic organic MR patients require repair or replacement, unless, co-morbidities are the confounders. Hence, it is the asymptomatic patients with significant organic MR and some symptomatic patients with confounding co-morbidities who are the focus of attention with regard to necessity and timing of surgical intervention. Morphology of the mitral valve is an important issue as far as feasibility and success of mitral valve repair is concerned and hence, there may be and should be different parameters for guiding therapy in rheumatic MR which is usually not reparable.

In chronic MR, stroke volume has to increase to maintain forward cardiac output if a significant regurgitant volume is present. Regurgitant volume along with its other components like regurgitant fraction, regurgitant flow rate, and regurgitant orifice are a define severity of MR and have prognostic significance in FMR, but not necessarily in organic MR.⁶ Severe organic MR alone may not be an indication for repair and on the other hand, moderate MR may need intervention if symptomatic with sufficient haemodynamic consequences. Increased stroke volume is achieved with progressive dilatation and geometric alteration of the LV. In compensated phase of MR, increased preload with reduced or normal after load and maintained intrinsic contractility attempt to preserve ejection fraction (EF). However, in chronic MR, progressive LV remodelling, with increasing wall stresses due to dilatation, can ultimately lead to irreversible changes in the myocardium, resulting in the development of LV contractile dysfunction.⁷ In this phase, the contractile dysfunction impairs ejection and LV volumes will start to increase further in order to maintain the required stroke volume. Fall in EF and LV dilatation beyond a certain point are easy ways of deciding the need for intervention and have been used for a long time.^{8–10} According to the ACC/AHA and the European guidelines, asymptomatic MR patients with an LV end-systolic diameter (ESD) ≥ 4.5 cm (≥ 4 cm more recently) and an EF $\leq 60\%$ benefit from valve surgery to protect ventricular function. However, if ESD ≥ 4.5 cm and EF $\leq 60\%$ is used as a cut-off point, there still is a high incidence of heart failure and poor survival after surgery. Thus, the measurement of ESD and EF is less than optimal measures of subclinical ventricular dysfunction in asymptomatic patients. The issue at hand for the clinician is to determine, whether or not, the patient with MR is entering the phase of early LV muscle dysfunction, a phase when correction of MR must be undertaken to prevent permanent myocardial damage. The major function of the myocardium is to develop force. Obviously, EF has no force term in its expression although indirectly end-systolic volume may be the product of force generated. Ejection

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fraction is especially fallible in patients with MR because, it is load sensitive and both afterload and preload are altered in patients with MR. Increased preload and reduced afterload act in tandem to increase EF beyond what would be expected from intrinsic inotropic state. Thus, patients with substantial LV dysfunction may still have a normal EF. To overcome this deficiency, the clinical use of EF in MR patients, a greater limit for normal has been set. Although, in most subjects the lower limit of normal for EF is 0.55, MR patients with EF <0.60 have been noted to have an impaired prognosis.¹¹ The EF is further compromised because it is often estimated rather than measured precisely, making it unclear whether the distinction between an EF of 0.60 and 0.55 is accurate. What the clinician would like to know is whether contractility, the innate ability of the myocardium to generate force, has begun to decline. As estimation of intrinsic contractility or LV elastance requires conductance catheter-based invasive studies to get end-systolic pressure-volume or stress-volume curves, surrogate, more sensitive yet non-invasively derived markers of early systolic dysfunction need to be defined which can guide therapy in patients with MR. This is based upon the premise that surgical repair or replacement of the mitral valve before or at the onset of LV systolic dysfunction provides better long-term results. Symptoms, on the other hand, are due to disturbed diastolic function which follows or accompanies systolic dysfunction and may occur late in the course of disease when compensation fails. The use of parameters like development of pulmonary hypertension and onset of atrial fibrillation as indication for surgery are manifestation of diastolic dysfunction. About two thirds of the patients who require surgery are determined as such based on the development of symptoms, one third on LV criteria and to a minor degree on pulmonary hypertension or atrial fibrillation alone.

Many methods have been proposed to detect subclinical LV dysfunction in chronic MR. These include contractile reserve by stress echocardiography,¹² integrated back-scatter and cyclic variation in back-scatter to gauge alteration in myocardial characteristics,¹³ tissue Doppler velocities and Doppler-derived strain parameters (Figures 1–4),¹⁴ two-dimensional strain by acoustic speckle tracking^{15,16} (Figures 5–6), torsion characteristics¹⁷ (Figure 7), and measurement of B-type natriuretic peptide (BNP).¹⁸ The ideal measure of contractility would be a parameter independent of afterload and preload, sensitive to changes in inotropy insensitive to LV size, and easy to apply. Unfortunately, no such measure has been validated. More difficult shall be to prove the utility of these parameters in predicting outcome in reasonably large studies. In the past two decades, an important field that has emerged as complementary to ultrasonic imaging is that of elasticity imaging. The term encompasses a variety of techniques that can depict a mechanical response or property of tissues. Myocardial deformation (strain), and the speed at which this deformation takes place (strain rate) reflect systolic function and are the result of the intrinsic contractility (force development) of the myocardium acting to overcome loading conditions and thus ejecting the required blood volume into the circulation. Strain parameters have been used to detect

subclinical systolic LV dysfunction in numerous clinical situations and shown to provide incremental information.¹⁹ Strain correlates more with stroke volume and EF and strain rate with intrinsic contractility.²⁰

In this issue, Gunjan et al. have used combined tissue Doppler and Doppler-derived strain and strain rate parameters in rheumatic MR and correlated these with standard LV function parameters and found a good correlation between geometric function measures and non-geometric strain measures.²¹ In an attempt to improve the assessment of early changes in contractility in these patients, myocardial velocities at basal septal and lateral segments were assessed and found to be lower in patients with MR, more so in those with evident LV systolic dysfunction. Peak regional systolic

Figure 1 Peak systolic tissue velocity (Sm) of 7 cm/sec at basal septal level in a 27-year female patient with severe mitral regurgitation. Peak systolic tissue velocity is not only load-dependent but also age-dependent making instantaneous decisions difficult but may be used in follow-up studies. Normal early diastolic velocity, however, indicates normal left ventricular function.

Figure 2 Myocardial Doppler-derived longitudinal strain in the same patient as in Figure 1 in the entire inter-ventricular septum in apical 4CV. Average peak systolic strain is –25% indicating possibly normal or supra-normal left ventricular ejection function. However, note that strain is more towards apex than at the base which suggests using global strain than only basal strain to define left ventricular function.

Figure 3 Same patient as in Figure 3 showing myocardial Doppler-derived peak strain rate of -3 sec^{-1} basal lateral wall. This is typically twice of normal indicating that this patient has well compensated mitral regurgitation with enhanced contractile function.

Figure 4 A 40-year-old male with rheumatic mitral regurgitation showing peak systolic strain rate of -1.2 sec^{-1} at basal lateral wall suggesting reduced contractility.

Figure 5 The same patient as in Figure 1. Mean global longitudinal strain of -27% by acoustic speckle tracking indicates enhanced contractile function due to increased preload with reduced or normal after load due to severe mitral regurgitation.

Figure 6 The patient as in Figure 1. Mid-LV ventricular radial strain of $+55\%$ by acoustic speckle tracking showing that radial strain is twice of longitudinal strain.

Figure 7 Twist by acoustic speckle tracking in the same patient as in Figure 1. Note markedly enhanced twist of 43° indicating enhanced ejection function.

velocities in MR have a biphasic response. These increase with increasing stroke volume and decrease with onset of systolic dysfunction. Hence, despite their ability to detect LV systolic dysfunction, these velocities do not predict subclinical dysfunction.²² These could also be affected by the rheumatic affliction of mitral valve apparatus due to fibrosis and calcification which has not been emphasised by the authors. To characterise myocardial deformation, three fixed volume, or spatial region, were used for the strain and strain rate calculation from Doppler-derived myocardial velocity gradients and strain parameters were found to be lower in MR subjects and still lower in those with manifest LV systolic dysfunction. However, this article does not show incremental value of tissue Doppler or strain measures over conventional parameters for assessing need and timing of surgery and nor does it provide validation by follow-up and utility of any of these strain parameters to see if asymptomatic status changes to

symptomatic one. The authors have not defined what can be construed as subclinical dysfunction by deformation parameters in group II patients who apparently have normal LV systolic function by conventional geometric parameters, although they do show a small decrease in longitudinal strain and strain rate in these subjects compared to normal controls (which could be due to bigger LV). However, there are major drawbacks even in this conclusion. Tissue Doppler and strain values have been obtained only at three specific points. Longitudinal strain was obtained at basal septal and lateral segments and radial strain at mid-posterior wall segment only. These segments by no means represent the global LV function and there are usually marked heterogeneity in deformation in diseased states due to marked non-linear elasticity although spatially homogeneous distribution of strain can be found in normal subjects by tissue Doppler techniques but not necessarily by non-Doppler methods again indicating a fatal technical flaw. Regional mechanical properties are likely to be variable depending upon the histology. Parameters, such as velocity of vibration, displacement, strain, strain rate, velocity of wave propagation and elastic modulus, have all been demonstrated feasible in their estimation by tissue Doppler and have resulted in the accurate depiction of stiffer tissue as found in patients with rheumatic MR, however, spatial non-uniformity dictates estimation of global strain and strain rate and not study of one or more representative segments as performed in this report. Longitudinal and radial strain decrease with increasing LV end-diastolic size and hence, deformation must be corrected for altered geometry before it can provide meaningful clinical data.²² An increase in size, without any change in stroke volume or contractility leads to a decrease in regional deformation. This finding is of importance when interpreting deformation values in patient groups like MR. A decrease in deformation indices does not necessarily mean that intrinsic myocardial function is decreased. Correcting deformation parameters for changes in geometry could be a sensitive way of detecting early changes in contractile function which was not performed by the authors. In absence of volumetric data, it can be presumed that the MR patients with lower regional strain and strain rates have greater LV end-diastolic size. There is another intriguing observation in their study. Longitudinal and radial strain in normal subjects (group I) are much lower than that reported in the literature.^{23,24} In fact, in this study, longitudinal and radial strain in group I (normal controls) are half of what is reported in normal subjects in the other studies^{23,24} and so is the radial strain rate. These cast serious doubts on the validity of data and also on the methodology. Another important mechanistic viewpoint is that in the initial stages of LV systolic dysfunction, a decrease in longitudinal strain is associated with increased radial strain. Such a phenomenon has not been shown in this study, indicating that the change in deformation indices in MR may be load-related rather than reflective of contractility. Also, tissue Doppler strain values are uni-dimensional and hence inferior to 2D or 3D strain by acoustic speckle tracking. Left ventricular function is characterised by contraction in the longitudinal, radial, and circumferential planes. Tissue Doppler imaging

technique is limited by angle-dependency such that only deformation along the ultrasound beam can be derived from velocities, while myocardium deforms simultaneously in three dimensions. Angle-dependence of Doppler-derived strain also produces large intra-observer and inter-observer variability, limiting its use in clinical practice as test-retest variability is high. Sadly, this aspect has not been reported by the authors.

The issue of detecting subclinical LV systolic dysfunction in asymptomatic MR and its importance is still unsettled. Recently, torsion and twist have been reported in patients with MR to further elucidate LV contractile function.²⁵ Torsion also shows a biphasic curve in MR patients. It gradually increases as severity of MR changes from mild to moderate and then again falls in severe MR. In patients with severe MR, having even normal torsion or twist may suggest LV systolic dysfunction. Similar data have been reported with regard to early diastolic strain rates.²⁶ Deformation indices decrease with increasing afterload and increase with increasing preload²⁷ and hence evaluation of subclinical LV systolic dysfunction in MR by tissue Doppler velocities and deformation indices remains complex and further long-term studies are required to obtain robust data on the issue.

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