The mitral valve is an actively adapting tissue: new imaging evidence

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With the mitral valve (MV) leaflet bases arising from the mitral annulus (MA) and the leaflet body and tips connected via the chordae and papillary muscles (PM) to the left ventricular (LV) wall, the anterior and posterior MV leaflets are hoisted like sails. The precise systolic spatial and temporal three-dimensional (3D) interplay of all these structures ensures optimal MV leaflet coaptation within the LV cavity just at the level of the MA, while preventing leaflet displacement into the left atrium (LA; prolapse) or the LV outflow tract (systolic anterior motion, SAM). Any change in form or function that leads to an imbalance of this interplay can result in mechanical leaflet stretch, and if leaflet redundancy is exhausted, to a relative tissue to MA area deficit and therefore mitral regurgitation (MR).

Gradually evolving changes that do not unsettle this balance, such as fetal to adulthood growth, seem to allow the MV leaflets to adapt, grow and match the needs of the enlarging LV and MA (× 20 area increase).3 The low prevalence of MR during normal cardiac growth highlights the effectiveness of MV adaptation and its finely tuned regulation as it maintains sufficient and physiological leaflet tissue to cover the MA area at an optimal ~2:1 ratio.4 Overshooting adaptation would result in too large MV leaflets with the potential for leaflet prolapse or SAM; insufficient adaptation would result in too small and therefore malcoapting leaflets and MR.

Motivated by the clinical observation that not all patients with comparable LV dysfunction and dilatation have significant MR, raising the question of whether this is related to potential leaflet adaptation, Chaput et al.6 assessed MV area in patients with dilated ischaemic and non-ischaemic cardiomyopathy (CMP). Using advanced imaging software (Omni4D, Mark Handschumacher) in combination with 3D transthoracic Echo, MV open leaflet area was found on average to be ~35% larger compared with normal subjects. Less MR corresponded to sufficient leaflet growth in relation to leaflet tethering and MA size, expressed by the closed leaflet area separating the LV and LA which reflects the degree of tethering.5 Additional human MV adaptation data have been reported by Saito et al. utilizing 3D transoesophageal echo (~30% MV leaflet area increase),5 and now the study by Debonnaire et al. in the current issue of the European Heart Journal - Cardiovascular Imaging6: based on 3D transoesophageal echo, the authors report ~44% larger MVs in patients with dilated ischaemic and non-ischaemic CMP versus normal patients with larger MV leaflets resulting in less MR. These currently available MV adaptation data are comparable in direction, but it is worth noting that because of software differences, Debonnaire et al.6 and Saito et al.5 were measuring MV leaflet area in systole and when stretched, whereas other studies measured total leaflet area in the open, relatively unstretched diastolic configuration.4,7

MV adaptation is adequate to match cardiac growth and enables significant MV leaflet growth in LV dysfunction, but nevertheless in cardiac disease it is often unable to prevent significant MR, as also observed in clinical practice and the studies above6,5 and Debonnaire et al. Moreover, there is evidence that post-myocardial infarction MV adaptation could be counterproductive, leading to stiff and fibrotic MV leaflets additionally impairing coaptation.8–10 Debonnaire et al. found that 83% of patients with ≥ moderate MR had ischaemic CMP as underlying MR aetiology despite LV function, dimensions, and volumes comparable with patients with moderate MR,7 Beaudoin et al., on the other hand, evaluated patients with compensated, chronic aortic regurgitation (AR) and a dilated, non-ischaemic LV.7 In line with prior results, MV leaflet area growth was ~31% compared with normal, and as clinically oftentimes observed, there was very little MR despite significant LV dilatation and leaflet tethering, indicating sufficient and effective MV adaptation.2

Experimental animal data have confirmed that MV adaptation occurs over time in ischaemic CMP and similar MV leaflet growth and adaptation have also been demonstrated in other animal studies.12,13 To now further explore MV adaptation on a tissue, cellular and regulatory pathway level requires an experimental model to study MV area and tissue changes as the main factors of tethering force, ischaemic environment, and turbulent MR flow are varied independently:14 isolated MV leaflet tethering over 2 months lead to significant MV area and leaflet thickness increase, with evidence for endothelial-mesenchymal-transformation (EMT). In this reactivated embryonic growth process, normally quiescent endothelial cells become activated and express α-smooth muscle actin, enter the MV interstitium and start to produce extracellular matrix such as collagen.14

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Human and experimental findings without doubt support a dynamic cellular MV tissue environment that actively adapts to superimposed stresses and likely aims to restore leaflet tissue homeostasis and valve function. Mechanical stretch seems centrally involved in MV leaflet adaptation, but we are only at the beginning of understanding and exploring its triggers, regulatory pathways, cellular mechanisms, and modulating factors and its varied response in different cardiac diseases. Further investigations into how and why MV adaptation is effective in physiologic cardiac growth and pathologic LV dilatation in chronic AR, but not in secondary, especially ischaemic, MR are now warranted. The aim is to identify potentially modifiable regulatory pathways, and the ultimate goal is to find therapies that will modulate MV leaflet adaptation towards optimal tissue growth while maintaining physiologic tissue characteristics.

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**References**