Mitral Annular Disjunction in Heritable Thoracic Aortic Disease: Insights From the Montalcino Aortic Consortium

BACKGROUND: Mitral annular disjunction (MAD), posterior displacement of the mitral valve leaflet hinge point, predisposes to arrhythmias or sudden cardiac death. We evaluated the burden of MAD, mitral valve prolapse (MVP), and mitral regurgitation (MR) by heritable thoracic aortic disease gene in a cross-sectional analysis of 2014-2023 data in the Montalcino Aortic Consortium registry.

METHODS AND RESULTS: MAD was determined by direct measurement of echocardiographic images. MR and MVP were defined according to current clinical guidelines. Associations were evaluated using $\chi 2$ or Fisher exact tests. MR and MVP were enriched in Montalcino Aortic Consortium participants (672) with pathogenic variants (PV) in transforming growth factor-β pathway genes. The combination of MR and MVP was associated with mitral surgery and arrhythmias. In the subgroup with available images, MAD was enriched in SMAD3 PV compared with other transforming growth factor-β PV (prevalence ratio 1.8 [1.1-2.8], P <0.02). Severe disjunction (>10 mm) was only observed in the transforming growth factor-β subgroup and was further enriched in participants with SMAD3 PV (prevalence ratio 3.1 [1.1-8.6]). MVP (prevalence ratio 5.2 [3.0-9.0]) and MR (PR 2.7 [1.8-3.9]) were increased in participants with MAD, but MAD was not independently associated with adverse cardiac or aortic events.

CONCLUSIONS: Pathological mitral valve phenotypes are more prevalent in individuals with PV in transforming growth factor-β pathway genes, particularly SMAD3. MR and MVP but not MAD are associated with adverse aortic and cardiac events. Because congenital mitral disease may be the primary presenting feature of SMAD3 PV, genetic testing for heritable thoracic aortic disease should be considered for such individuals, especially if they also have a family history of heritable thoracic aortic disease.