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Invited editorial

Aortic regurgitation in athletes: Pieces of the puzzle we have so far omitted

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The prevalence of valvular heart disease (VHD) rises with age, reaching 11.7% in individuals older than 75 years.[1] In young individuals, VHD is usually related to the presence of a congenital valve abnormality, as bicuspid aortic valve (BAV) or mitral valve prolapse. This is also the case for athletes, where in the presence of these abnormalities few restrictions exist in eligibility for competitive sports participation, even if a strict follow-up would be desirable. BAV is the most common congenital valve abnormality (1%) found in the general population and in athletes. BAV is more prevalent in males and it can lead to aortic regurgitation (AR), aortic stenosis and/or aortic root dilation. At present, no definitive studies have proved that intensive sports participation could worsen the progression of BAV and limited data are available on athletes.

Longitudinal data from a population of 210 athletes with BAV[2] showed that there is a progressive significant enlargement of the left ventricle (LV) over time; nevertheless, LV dimensions remained within normal ranges of the physiological heart remodeling induced by regular exercise. The authors concluded that the presence of BAV does not represent an additional risk for LV dilation and dysfunction, at least in the presence of mild aortic valve dysfunction.[2] Since in the presence of moderate to severe or severe AR, athletes are usually disqualified or discouraged from competitive sports participation, no data are available to date on the progression of LV dilatation. Marfan syndrome (MFS), an autosomal dominant connective tissue disorder exerted by FBN-1 gene mutation, is another possible cause of AR in young individuals. In MFS patients, the mechanism of AR is usually the result of aortic root dilation, which develops and progresses gradually from an early age, but at present no robust predictors of rapid aortic root dilation exist, even if proximal aorta longitudinal strain holds promise.[3] In the 2017 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines,[3] indication for surgery in severe chronic AR relies on the presence of symptoms and/or aortic root dilation and/or LV dysfunction, as a decline in LV ejection fraction $\leq$50% or LV enlargement identified by LV end-diastolic diameter $>$70 mm or LV end-systolic (LVESD) diameter $>$50 mm. LVESD should be indexed and a cut-off of 25 mm/m^2 seems more appropriate in patients with small body surface area (BSA) or in women.[4] More recently, Yang et al.[5] demonstrated that index LVESD is an important variable to identify asymptomatic surgical candidates in the presence of severe AR, because five-year survival started to deteriorate when LVESD reached the cut-off value of $>$20 mm/m^2. Independently of patient age, sex and small BSA, referring to this newly proposed cut-off value will favor early surgery for AR in a significant proportion of patients. The best way to resolve this issue will be to stratify patients based on index LVESD $>$ 20 mm/m^2 in a randomized controlled trial, being aware that patients undergoing early surgery will be in better pre-operative conditions than the control group – for now, the debate remains.

In this issue of the journal, Antonopoulos et al.[6] raised an important issue because the athlete's heart is characterized by LV dilation, which is more pronounced in endurance athletes; therefore, in the presence of more than moderate AR, an accurate distinction between physiological exercise-induced remodeling and pathological LV dilation can be challenging. The authors commented on the pivotal role of multi-modality imaging to correctly identify those athletes who fall within the grey zone between those two conditions. Transthoracic echocardiography is the cornerstone of non-invasive imaging modalities to follow-up athletes with BAV or AR in tricuspid aortic valve, because it allows a detailed definition of

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aortic valve morphology and AR mechanism, AR quantification, associated aortic dilation and hemodynamic impact on LV. Reference values of LV dimension in athletes exist in adults[7] and adolescents,[8] and both are very useful to outline an excessive LV dilation, but more than the absolute value it is important to highlight the temporal changes in LVESD and its z-score growth velocity to determine the correct timing for surgery.[9] In addition to these parameters, a newer echocardiographic marker is global longitudinal strain (GLS), a measure of LV long-axis systolic function, which is more sensitive in identifying a dysfunction, even in the presence of normal LV ejection fraction. GLS can predict the future need for surgery and overall mortality in asymptomatic patients with AR, and a worsening in LV GLS was significantly associated with long-term mortality.[10] Antonopoulos et al.[6] highlighted the growing role of cardiac magnetic resonance (CMR), which offers several advantages. First of all, CMR allows a direct quantification of AR if echocardiographic quantification of AR proves difficult, and can reclassify AR severity in up to one third of the cases. Moreover, CMR can further and deeper clarify aortic valve morphology, properly discerning a BAV or a tricuspid aortic valve, which has important prognostic and therapeutic implications. CMR can identify the exact mechanism of AR and the hemodynamic impact on LV with the quantification of LV volumes and function and the aortic root dilation. An accurate diagnosis with the quantification of these parameters is pivotal to evaluate sports eligibility and in guiding decision-making in top-level athletes. In contrast with echocardiography, CMR with the use of gadolinium allows tissue characterization and, in particular, the identification of fibrosis, which is a cause of sports ineligibility if associated with major ventricular arrhythmias, leading to cardiac sudden death. Antonopoulos et al.[6] reported that 10% of AR patients present interstitial fibrosis at CMR independently of AR severity, and this could potentially lead to exercise-induced arrhythmias. Therefore, multimodality imaging studies are not enough to identify those athletes who will benefit the most from early surgery in the case of severe AR, but a functional exam as stress test or exercise echocardiography is required to reveal symptoms and/or the presence of arrhythmias during effort. Maximal cardiopulmonary exercise testing could also be promising in asymptomatic athletes with AR to evaluate exercise tolerance, peak oxygen consumption and peak exercise oxygen pulse,[11] which holds promise as a predictor of cardiovascular mortality and could help in differentiating athletes that fall within the grey zone between physiological and pathological remodeling.

Last but not least, the recent insights of new molecular mechanisms underlying the development of AR, mainly related to the presence of BAV, highlighted the emerging critical role of phenotypic expression, cellular and molecular mechanisms and pathways in determining the natural history and consecutive clinical management of AR patients.[12] Unveiling genetics, epigenetics and molecular pathways together with environmental factors will be a fundamental advance in developing a personalized therapeutic approach. Translational research provides major advances in the scientific knowledge translating data from bench to bedside, and hopefully it will provide new biomarkers with diagnostic and prognostic implications also in AR.

We speculate to go beyond the valve morphology or quantification as the only parameters for disqualification from competitive sports participation or as recommendation to surgical intervention. A modern strategy would consider not only the clinical features but also state-of-the-art imaging, molecular, cellular and genetic profiles, particularly in athletes with AR.

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