Rev Port Cardiol. 2020;39(7):389–390

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

EDITORIAL COMMENT

A new predictive marker of ventricular remodeling associated with aortic stenosis

Um novo marcador preditivo da remodelagem ventricular associado a estenose aórtica

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Available online 15 July 2020

In their paper on microRNAs (miRs) and ventricular remodeling in aortic stenosis (AS) published in this issue of the *Journal*,[1] which studied circulating biomarkers of extracellular matrix (ECM) turnover from myocardial biopsies, Santos-Faria et al. investigated the association between left ventricular (LV) miR levels and LV mass, reverse remodeling and ECM alterations.

AS, in which the aortic valve progressively narrows, causes LV pressure overload that, in its early asymptomatic stages, triggers a compensatory hypertrophic response aimed at maintaining cardiac muscle performance. However, over the course of time, as a consequence of cardiomyocyte death and myocardial fibrosis, this process decompensates and patients progress to heart failure, which is associated with substantial morbidity and mortality.[2] AS should thus be considered a disease of both the valve and the myocardium.[3] Assessment of the pathophysiological effects on the myocardium associated with AS relies mainly on histological assays of heart samples. Small biopsy or autopsy studies have demonstrated that, besides cardiomyocyte hypertrophy, LV remodeling also encompasses changes in ECM proteins, in which the matrix structure is degraded and disrupted.[4] This is regulated by various factors, including the renin-angiotensin-aldosterone system (RAAS), transforming growth factor beta, apoptosis signal-regulating kinase 1, and tissue inhibitor of metalloproteinase.[5] However, in vivo studies using biopsies are limited and demanding given the small size of the samples, and fibrosis is assessed based on the quantity of collagen deposition, reflected in collagen volume fraction.[6]

Patient symptoms and outcome in AS are determined by the severity of valve stenosis. Despite progress in recent years, no therapies are available to prevent worsening of the disease. The only treatment at the clinician's disposal for severe AS with LV decompensation is aortic valve replacement (AVR). A recent study showed that surgical AVR improved the physical and mental health status of octogenarians with severe AS. This improvement was evident at three months and consistent at six and 12 months.[7]

It is therefore of the utmost importance to identify markers of early LV decompensation in order to determine the correct timing for AVR, as well as features that can be used to track myocardial health over time, which will provide better knowledge of the mechanisms underlying LV decompensation in AS. Histological studies and noninvasive imaging techniques have been used as a prognostic tool by correlating myocardial fibrosis stage with AS and heart failure progress and severity. Identification of markers of ventricular remodeling in AS therefore has considerable clinical potential.

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https://doi.org/10.1016/j.repc.2020.06.006
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MiRs are a class of small noncoding RNAs, about 22 nucleotides in length, that regulate post-transcriptional gene expression. It has been widely reported that miRs modulate various biological processes implicated in cardiovascular disorders including hypertrophy, ischemia, arrhythmias, pulmonary hypertension and valvular disease.[8–10] Importantly, several studies have associated miR profile with human diseases, making these molecules powerful diagnostic and prognostic tools. Changes in miR profile have been associated with myocardial fibrosis by targeting proteins involved in different aspects of ECM remodeling.

The study by Santos-Faria et al.[1] shows that miR expression is different in cardiac biopsies obtained from AS and non-AS patients, which may have implications for ventricular remodeling responses to pressure overload before and after AVR. The authors show that miR-101-3p is increased in AS compared to controls, which is associated with higher plasma angiotensin II (Ang II) receptor and angiotensin-converting enzyme levels, ascribing to this miR a role in the regulation of the RAAS. Strikingly, a positive correlation with LV mass regression after surgery suggests that higher levels of miR-101-3p may be an indicator of a more favorable response to AVR. Moreover, although no statistically significant differences were found between AS patients and controls, miR-4268 levels in AS correlated positively with LV mass regression and were associated with higher plasma Ang II receptor levels. Given the antihypertrophic and antifibrotic properties of this receptor, it is conceivable that the Ang II receptor is involved in the regression of hypertrophy after surgery.

Overall, these results associate miR-101-3p and miR-4268 with a hypertrophic response in AS, making these miRs predictive markers of LV myocardial remodeling after AVR. Importantly, their role in regulating the RAAS paves the way toward the development of new pharmacological strategies targeting the RAAS.

Conflicts of interest

The author has no conflicts of interest to declare.

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