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Editorial

Inflammation in aortic stenosis: Shaping the biomarkers network

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Degenerative calcific aortic stenosis (AS) is the most common valve disease in Western countries [1]. Less than twenty years ago, the groundbreaking approach of transcatheter aortic valve replacement (TAVR) has revolutionized the management of AS, offering a valid therapeutic option also for patients considered at high risk for aortic surgical replacement [2, 3]. Despite successful therapeutic interventions in AS, the basic pathophysiological mechanisms governing aortic valve degeneration are still not completely understood. Consequently, biomarkers for AS prognosis and risk stratification are lacking and have recently become matter of intense research.

AS and vascular atherosclerosis share, at least in part, pathogenic mechanisms and risk factors. Similarly to atherosclerosis, chronic inflammation of the valve has been recognized in AS [4]. Although a robust literature on biomarkers and inflammation is available for atherosclerosis, a considerably lower number of studies have investigated the role of inflammatory biomarkers and other circulating molecules in AS pathophysiology.

Left ventricular hypertrophy (LVH) is an independent risk factor for cardiovascular events in AS [5]. Variability of LVH degree observed in AS is only partially explained by the severity of AS, and a role for inflammatory cytokines and other growth factors has been advocated to explain such LVH variability [6]. Few studies have specifically addressed the potential role of cytokines and growth factors as prognostic indicators of cardiac remodeling in AS.

In the current issue of *International Journal of Cardiology*, Kim and colleagues [7] present an extensive analysis of circulating inflammatory markers in patients with AS undergoing TAVR. The authors measured serum levels of several cytokines and other active molecules in an ample cohort of subjects with AS, providing their association with demographic, echocardiographic and LV remodeling-related parameters after TAVR. Despite a large proportion of patients with AS exhibited normal LV ejection fraction (LVEF) at baseline, the majority of the population presented with abnormal global longitudinal strain (GLS), diastolic dysfunction (elevated mitral E/e′ ratio) and increased LV mass index (LVMI). Interestingly, analysis of cytokines and growth factors in the AS population revealed a different pattern of association between circulating molecules, the increase in LVMI and decrease in GLS. The strongest hit associated with higher baseline LVMI was the hepatocyte growth factor (HGF). Despite higher serum levels of HGF were also associated with low values of GLS, the levels of vascular endothelial growth factor (VEGF)-D resulted strongly associated to GLS reduction. Notably, despite several others classes of cytokines were variably associated with LVMI and GLS variations, the strongest association was found with two "canonical" growth factors well known to profoundly impact on cardiomyocyte response to stress [8].

Moving forward, the authors evaluated LV structural and functional parameters by echocardiography in patients with AS one year after TAVR. Although most patients exhibited a reduction in mean and peak transaortic gradient and an increase in aortic valve area after TAVR, reduction in LVMI was observed in only one third of the patients, whereas approximately 50% of them showed improvement in GLS, suggesting that changes in LV structure, as the regression of LVH, necessitate more time to occur after TAVR [9]. Identification of biomarkers providing prognostic information of ventricular recovery after TAVR might significantly impact on the management of this disease. In the attempt to pinpoint cytokines that can serve to this purpose, the authors found that high circulatory levels of HGF were associated with less reduction of LVMI and less improvement of GLS after TAVR, whereas high serum levels of fibroblast growth factor (FGF) and epidermal growth factor (EGF) positively correlated with LVMI reduction.

This study extends the knowledge about biomarkers in AS, and raises several questions. Although the investigators measured a conspicuous number of cytokines, by design, this study left out some molecules that, based on the pathophysiology of AS, might explain part of the observed variability. For example, circulating products of extracellular matrix (ECM) remodeling or growth factors and cytokines involved in mineral metabolism might also be expression of the "chronic

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inflammatory state" occurring in AS and their role as biomarkers should be also carefully assessed [6].

The strong association of LVMI and GLS dynamics in AS (either before and after TAVR) with HGF, suggests a role for this molecule in the AS-dependent cardiac remodeling. Although HGF has been involved in cardiomyocyte hypertrophy [8], no studies have provided mechanistic evidence of its role in AS pathophysiology. However, the fact that HGF levels correlate with the degree of LVH in AS might reflect its role in the general response to pressure overload, lacking specificity for AS. Along the same line, the fact that high circulating levels of HGF identify patients with worse LV remodeling and less responsiveness to TAVR might be related to the lack of LVH regression observed in about 30% of these patients. It would have been of interest to further stratify AS subjects with absence of regression of LVH after TAVR on the basis of HGF circulatory levels to have a better sense of the role of this growth factor in the response to unloading therapy in AS. More mechanistic studies to test this hypothesis will be needed in the future.

Another important observation that arises from this investigation is the sex-dependency of LVMI and GLS in AS. The authors found that male sex correlated with both the above-mentioned indexes of LV remodeling and function. Unfortunately, no differential sex-specific pattern of cytokines has been put in relation with this observation. Given the peculiar differences in LV remodeling in response to pressure overload between men and women [10], the identification of sex-specific circulatory biomarkers to track the progression of AS and predict its prognosis after TAVR might represent an exciting area of investigation. *Ad hoc* studies with the enrollment of ample cohorts of men and women with AS undergoing to TAVR will be necessary to specifically answer this question.

In conclusion, the study of Kim et al. [7] provides an ample catalogue of circulating inflammatory cytokines associated with LV function in AS and functional recovery after TAVR, shaping the inflammatory network in AS as potential source of clinically valuable biomarkers.

Conflict of interest

None declared.

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