Calcific aortic stenosis represents the most frequent valvular heart disease and one of the major cause of morbidity and mortality in the elderly. Aortic stenosis results from active biological events, characterized by lipid infiltration, inflammation, neoangiogenesis, endothelial dysfunction and bone deposition. The reduced mobility of aortic valve leaflets produces a fixed obstruction at the outflow, with a consequent remodelling of the left ventricle. The degree of left ventricle hypertrophy and fibrosis results in different degree of diastolic dysfunction and heart failure. Thus, the response of the left ventricle to the pressure overload guides the clinical status and the prognosis of patients with aortic stenosis. After aortic valve replacement hypertrophy and fibrosis partially regress, however the maladaptive LV remodelling strongly impacts the prognosis even after surgery. This review outlines the importance in the evaluation of the left ventricle in patients with severe aortic stenosis, exploring the pathophysiology of the transition from adaptive to maladaptive remodelling.

Key words: Aortic stenosis, Elderly, Diastolic dysfunction, Myocardial fibrosis, Left ventricular hypertrophy

AORTIC STENOSIS: EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Aortic stenosis (AS) represents the most prevalent valve heart disease in Western countries. In the elderly, severe AS is a major cause of morbidity and mortality, including sudden death, and its prevalence rises to 3% in patients over age of 80 years. In developed countries, the degenerative aetiopathy is the most frequent (82%), followed by rheumatic (11%) and congenital (5%). Nevertheless, it is important to emphasize that calcification of aortic valve (AV) is not only a consequence of aging, but several pro-atherosclerotic factors may account for this degenerative process, such as arterial hypertension, hypercholesterolemia, smoking, etc. Therefore, in the initial phase of the disease, the degeneration of AV leaflets is a part of a diffuse atherosclerotic process. Afterwards, a series of active biological events, such as lipid infiltration, inflammation, neoangiogenesis, endothelial dysfunction and bone deposition lead to a progressive AV calcification. Hemodynamic stress and the consequent endothelial damage with lipid infiltration are probably the first events in the AV calcification process. Microscopic observations in early stenotic valve show the presence of chronic inflammatory cells, lipids, disorganized collagen fibres, proteins of extracellular bone matrix, and bone minerals. Increased levels of oxidized low-density lipoproteins promote inflammatory response and mineralization activity, inducing the transition of valvular fibroblasts to an osteoblastic phenotype. Recent evidence suggests that low-grade inflammation, promoted by dysregulation of visceral adiposity, has an important role in the AV atherosclerotic process. In this regard, we have recently demonstrated that increased echocardiographic thickness of epicardial adipose tissue, the visceral fat depot of the heart, is correlated with the presence of severe AS and is directly correlated with the secreted levels of inflammatory mediators.
Epicardial adipose tissue, being a source of both inflammatory mediators and catecholamines may also have an important role in cardiac dysfunction and heart failure (HF) progression.

### THE LEFT VENTRICLE REMODELLING IN AORTIC STENOSIS

The presence of AS induces an abnormal and protract pressure overload upon the left ventricle, that results in systolic and diastolic dysfunction. These abnormalities exacerbate the well known adverse myocardial remodelling occurring with age. In the early phase of AS the main compensatory mechanisms are represented by concentric left ventricular hypertrophy (LV) and elevation of end-diastolic pressure. The protracted pressure overload induces changes in the myocardial extracellular matrix leading to progressive myocardial fibrosis and decreasing LV compliance. Thus, the initial adaptive remodelling becomes maladaptive with increased LV hypertrophy, myocardial fibrosis, heart failure, and worsening prognosis. However, the degree of LV hypertrophy appears to be more closely associated to age, male sex, diabetes and obesity rather than severity of AS. It is important to underline that in the elderly the presence of comorbidities, such as diabetes, hypertension, increased arterial stiffness, can influence cardiac overload and worse left ventricular response to AS. Myocyte apoptosis and fibrosis are supposed to mark the transition from hypertrophy to heart failure with the consequent onset of symptoms. Interestingly, the degree of myocardial fibrosis secondary to AS seems to condition the presence and the progression of LV systolic dysfunction. Studies exploring the effects of longstanding pressure overload secondary to hypertensive heart disease and AS suggest that fibrosis is increased in patients with reduced LV ejection fraction. Fibrosis occurs after myocyte apoptosis, and areas of fibrosis are observed to co-localize with areas of myocyte loss. Of note, the presence of mid-wall fibrosis is associated with a significant increase in mortality. It is reasonable to hypothesize that fibrosis is associated to adverse prognosis not only because it increases LV stiffness but also because it is associated to an increased risk of cardiac arrhythmias. Furthermore, the magnitude and chronicity of the increased LV filling pressure are associated with an increase in left atrial size, which has been shown to predict postoperative symptomatic improvement and subsequent prognosis in AS patients.

### THE LEFT VENTRICLE: BIOMARKERS OF DECOMPENSATION

The progressive LV decompensation in AS is driven primarily by two processes: myocyte death and myocardial fibrosis. Therefore, biomarkers of LV stress/damage could be helpful in the identification of those patients with more advanced disease. The increased LV wall stress determines an elevation of the circulating levels of brain natriuretic peptide (BNP) and the related N-terminal fragment of proBNP (NT-proBNP) which are widely used in the diagnosis and management of heart failure. In particular, several studies in AS patients demonstrated that BNP levels increase along with the transition from LV hypertrophy to heart failure, thus suggesting an important role for natriuretic peptides in the evaluation of patients with severe AS and equivocal symptoms. Myocardial ischemia due to inadequate microcirculation promotes myocardial loss. Myocyte death is believed to one of the key factors driving LV decompensation in AS, thus high-sensitivity troponin T is indicated as a valuable marker of myocardial damage. Some studies suggested that troponin levels are correlated with LV mass, myocardial fibrosis, severity of AS, and are predictive of adverse outcome. Furthermore, neurohormonal activation represents a putative additional mechanism of cell death and may offer important prognostic indications in heart failure. It is widely established that the presence and the extent of fibrosis are absolutely relevant in the transition from hypertrophy to heart failure. Unfortunately, biomarkers of fibrosis have not an established role in AS patients. Recently, Galectin-3, a member of the lectin family and important mediator of myocardial fibrosis, emerged as a potentially useful prognostic marker in patients with heart failure.

### EVALUATION OF SYMPTOMS

Echocardiography is the key tool for the diagnosis and evaluation of AV disease and clinical decision-making is based on echocardiographic evaluation of AS severity. Once the diagnosis of severe AS is achieved, a careful evaluation of symptoms becomes mandatory. Guidelines clearly establish that the onset of symptoms represents the indication to valve replacement, although, especially in elderly patients, there is often a reluctance to recommend valve replacement due to the supposed high surgical risk. The prognosis of AS dramatically changes with the onset of symptoms such as angina, syncope and dyspnoea. However, clinical manifestation is frequently insidious at the onset and can be
highly variable among patients with similar degrees of valve stenosis. In many patients, the first and subtle symptom is represented by a reduced exercise tolerance and consequently symptoms evaluation is particularly challenging because in this population the daily life activity is strongly conditioned by the presence of comorbidities.

Exercise testing may add important information in 'supposed' asymptomatic patients allowing to recognize exercise-related symptoms due to AS and unmask the reduced exercise capacity. In particular, in old sedentary patients, exercise-induced angina, early excessive dyspnea, dizziness or syncpe are compatible with symptoms of AS. It is important to underline that the risk of exercise testing is low in asymptomatic patients with AS as reported in numerous prospective and retrospective studies. Exercise testing should not be performed in symptomatic patients with AS when the aortic mean pressure gradient ≥ 40 mmHg, due to high risk of complications, comprising syncpe, ventricular tachycardia, and death.

**LEFT VENTRICULAR REMODELLING AFTER SURGERY**

AV replacement (AVR) is followed by immediate hemodynamic improvement due to afterload reduction and improved active myocardial relaxation. However the regression of hypertrophy and the amelioration of diastolic function require more time. The hypertrophy regression is more precocious and a marked reduction in LV mass usually occurs within 18 months from AVR. However, some authors described that a regression of muscular tissue was observed after surgery while fibrous tissue remained unchanged. Consequently, after surgery, there is a relative increase in fibrous content and some authors described a deterioration of LV diastolic function early after AVR. In accordance, it has been described a development of moderate to severe diastolic dysfunction late after AVR, despite a reduction in the LV mass index. A late and progressive reduction of LV fibrosis has been described after some years from surgery. Of note, the fibrosis regression is predominantly related to the reduction of interstitial fibrosis, while the replacement fibrosis seems to remain unchanged. Overall, presence of higher grades of myocardial fibrosis increases the risk of congestive heart failure and death while patients with mild diastolic dysfunction have a better prognosis after AVR.

As regard the systolic function, a rapid recovery has been described after both surgical and percutaneous AVR. Speckle-tracking echocardiography demonstrated improvements in LV systolic function 6 months after AVR. Of interest, there is a significant better recovery of circumferential and radial strain with respect to the longitudinal. Longitudinal strain is particularly affected by the presence of fibrosis, thus its impaired recovery after AVR may reflect the presence of higher degree of fibrosis. Several clinical factors can influence the extent and the duration of LV pressure overload and consequently to the persistence of hypertrophy and diastolic dysfunction. Indeed in patients with patient-prosthesis mismatch and hypertension after AVR, an attenuated LV remodelling has been described.

**CONCLUSIONS**

Aortic stenosis, the most diffuse valve disease in the elderly, is a disease of the valve and the myocardium. After an initial phase of adaptive remodelling, a maladaptive LV remodelling occurs in the advanced stages of the disease. Progressive myocyte death and myocardial fibrosis result in the transition from hypertrophy to heart failure. Markers of left ventricular (LV) decompensation, such as BNP and troponins, may help in the identification of patients who may benefit from early surgery. Preoperative myocardial remodelling conditions survival after surgery and continues after surgery.

**References**

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