Calcific aortic stenosis: novel insights in pathophysiology, diagnosis and management

Stenosi aortica calcifica: nuovi approfondimenti in fisiopatologia, diagnosi e gestione

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Calcific aortic stenosis (AS) is a common heart disorder in the elderly and the most prevalent valvular heart disease in the Western world representing one of the main causes of cardiovascular morbidity and mortality 1. It is important to strengthen that the severity of AS in elderly patients is worsened by the coexistence of several structural and functional cardiac alterations leading to a rapid deterioration of the hemodynamic status 2-4. AS was previously considered a passive, degenerative disorder of aging, but recent evidences have demonstrated that active biological events lead to a progressive degeneration of aortic valve (AV) leaflets mainly regulated by lipids and inflammation 5. It is now established that atherogenesis and inflammation generate biologically active calcification of AV leading to bone deposition 6 7.

ROLE OF LIPIDS IN THE PATHOGENESIS OF AS

In hypercholesterolemic mice, it has been demonstrated an enhanced oxidative state in the AV endothelium associated to increased levels of...
Ox-LDL inflammatory cell infiltrates, containing mast cells, macrophage and T lymphocytes. Accordingly, human stenotic AV contains oxidized LDLS, T-cells and macrophages. At this regard, in vitro studies show that oxidized LDLS strongly promote mineralization when assessed in isolated AV interstitial cells. The clinical association between LDLS and AS has been recently evaluated in 6942 patients of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium. In this study, genetic elevation in LDL-C, but not in HDL-C or triglycerides, was associated with increased prevalence of AV calcium and incident AS at a follow-up of 15 years. Yet, the role of HDL in AS remains controversial, but because of their antiatherogenic and anti-inflammatory properties, a protective role in AS pathogenesis and progression would be expected. In this regard, an high total cholesterol/HDL ratio and low serum HDL-cholesterol levels have been found to be associated with a rapid rate of AS progression. Although the amount of valvular HDL is reduced in human stenotic AV, recent evidences suggest that also HDL might promote AS. In fact, in explanted stenotic human AV, apolipoprotein A1 of HDL has been found close to calcific nodules and contributes to the production of amyloid proteins which promote the transition of isolated valvular interstitial cells (VICs) toward an osteoblast phenotype.

**Role of Exercise for Prevention of AV Degeneration**

Regular physical exercise training plays an important role in primary and secondary prevention of atherosclerotic cardiovascular diseases. Exercise improves endothelial function, attenuates oxidative stress, restores cardiac and vascular beta-adrenergic receptor system and has a significant impact on blood lipids and lipoprotein profiles. All these factors are known to be involved in AV degeneration and in AS development. This represented the rationale to test exercise training to prevent the progression of AV disease. In LDLR deficient mice, an experimental animal model which is largely used to mimic human atherosclerosis, a regular exercise training program prevented the development of AV sclerosis. Interestingly, in this study, the cellular and molecular mechanisms by which exercise counteracted the processes of AV degeneration were: i) preservation of the integrity of valvular endothelium; ii) attenuation of oxidative stress and reduction in ox-LDL; iii) attenuation of proosteogenic signaling pathways.

**AS and Altered Bone Turnover: The Role of Lipids**

It is widely accepted that bone deposition within the AV is inversely correlated with bone mineralization. This phenomenon has been observed in osteoporosis, in patients with chronic kidney disease (CKD) and in less frequent bone disorders such as Paget's disease. The relationship between ectopic calcification and reduced bone mineral density is commonly defined as “bone paradox.” This phenomenon has been largely demonstrated for vascular calcification and several evidences indicate that it could be also involved in the progression of AS. In a recent experimental study conducted in apoE-/- mice, a murine model of atherosclerosis, an association between AV calcification, arterial calcification and bone mineral loss has been demonstrated. These results add new insights in the pathogenesis of calcific AS, indicating that inflammation and atherosclerosis could represent both the initiating process and the link between valvular calcification and altered bone metabolism. Interestingly, the described association between atherosclerosis, inflammation and ectopic calcification/bone demineralization seems to be enhanced in the presence of CKD. Hjortnaes et al. described increased osteogenic activity in the femurs and greater arterial and aortic valve osteogenic signal intensity in apoE-/- mice with CKD when compared to animals with normal renal function. These findings are in line with the clinical evidence of bone demineralization and arterial calcifications in patients with CKD.

**Role of Lipids in the Activation of Molecular Pathways Involved in AV Calcification**

**a) The Lipoprotein-associated phospholipase A2/LDL/lyso phosphatidylcholine axis**

We have previously emphasized the role of ox-LDL in the pathogenesis of AS. Interestingly, ox-LDL are converted into lyso phosphatidylcholine (LPC) by the lipoprotein associated phospholi-
Pase A2 (Lp-PLA2) that is upregulated in calcified AV. In vitro studies indicate that LPC is a strong promoter of mineralization in isolated aortic VICS through a cyclic adenosine monophosphate (cAMP)/protein kinase A pathway. Lp-PLA2 is produced within the AV by macrophages and/or is transported in the aortic valve by LDL, particularly by small, dense LDL. Lipoprotein (a) represents a vector for oxidized phospholipids transport into the AV and its plasma levels have been found to be associated with increased risk of AS.

b) Renin-angiotensin system activation in AS
Activation of the renin-angiotensin system (RAS) is also implicated in AS pathogenesis and RAS inhibition slowers AS progression. In explanted human stenotic AV, angiotensin-converting enzyme (ACE) is expressed and colocalized with angiotensin II. Notably, ACE can be transported in the aortic valve by LDL, thus promoting local production of angiotensin II and triggering the process of tissue fibrosis which represents an hallmark of AV remodeling.

c) Wnt/Lrp5 signaling pathway
The upregulation of the Wnt/lipoprotein receptor-related protein 5 (Lrp5) signaling pathway is considered a relevant molecular phenomenon that can trigger calcification. Lipids and other cardiovascular risk factors induce oxidative stress in the AV endothelium which in turn activates the secretion of cytokines and growth factors activating cell signaling. Wnt3 secretion from valvular endothelium and the activation of Wnt canonical pathway through the Lrp5 are largely dependent on the abnormal oxidative stress environment promoted by atherosclerosis. Lrp5 is a member of the family of structurally closely related cell surface LDLRs (receptors involved in the LDL metabolism) that have diverse biological functions in different organs, tissues and cell types. In the AV, Wnt is secreted from endothelial cells into the subendothelial space and binds to his receptor on the myofibroblast extracellular membrane forming the complex Lrp5/Wnt3/Frizzled, which triggers the phenotypic transition of these cells toward osteoblasts.

d) Osteoprotegerin (OPG)/RANKL/RANK
OPG/RANKL/RANK pathway is considered to be involved in vascular and AV calcification. In addition, opposite regulation of this pathway in bone and vasculature may explain, at least in part, the calcification paradox. It has been demonstrated that the osteoblastic transition of AV myofibroblasts may be promoted by RANKL, produced by lymphocytes and macrophages. In calcified AV, RANKL expression is highly increased while OPG expression is not detectable with the net result of a decrease of the calcification inhibition potentially associated with OPG. Furthermore, in cultured AV myofibroblasts, exogenous RANKL accelerates the transition toward an osteogenic phenotype. Comprehensively, these data point to common molecular pathways that characterize vascular and valvular atherosclerosis as well as bone resorption.

POTENTIAL ROLE OF EPICARDIAL ADIPOSE TISSUE IN THE PATHOGENESIS OF AS

Epicardial adipose tissue is the visceral fat depot of the heart and in physiologic conditions exerts several protective functions for the myocardium. However, it has been also demonstrated that cardiac visceral fat may play an unfavourable activity through secretion of numerous pro-inflammatory factors that are correlated with the presence and the extent of several cardiac disorders. In this regard, we have recently demonstrated that echocardiographic thickness of epicardial adipose tissue is correlated with the presence of severe AS. Moreover, further studies from our group have suggested that cardiac visceral fat represents a source of catecholamines, thus potentially contributing to the adrenergic overdrive occurring in AS-related heart decompensation and cardiac adrenergic dysfunction.

DIAGNOSIS

Typical symptoms of AS are angina, syncope, and heart failure. However, clinical manifestation is frequently insidious at the onset and can be highly variable among patients with similar degrees of valve stenosis. Many patients note a subtle decrease in exercise tolerance as the first symptom of AS. This element is crucial in the evaluation of AS severity in the elderly because the limitation of the daily life activity due to comorbidity and disability would hardly elicit the symptoms in these patients with the consequence that AS tends to be asymptomatic for a long time. The onset of symptoms represents an
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**Indication to Surgical Replacement.** Echocardiography has become the key tool for the diagnosis and evaluation of aortic valve disease, and is the primary non-invasive imaging method for aortic valve stenosis assessment. Clinical decision-making is based on echocardiographic evaluation of aortic stenosis (AS) severity. The primary haemodynamic parameters recommended for clinical evaluation of AS severity are: AS jet velocity, mean transaortic gradient and valve area by continuity equation. Severe AS is usually defined by a mean gradient > 40 mmHg, aortic valve area (AVA) < 1 cm² and peak aortic jet velocity > 4.0 m/sec. However, discrepancies are frequently observed between the mean gradient and the valve area in the single patient. For this reason it has been imperative an underclassification of the general severe AS pattern, in terms of transvalvular flow rate and pressure gradient. In severe AS with an AVA < 1 cm², four flow gradient AS categories can be identified: Normal flow/Low gradient (NF/LG), Normal flow/High gradient (NF/HG), Low flow/High gradient (LF/HG) and Low flow/Low gradient (LF/LG). LF is defined through the Stoke Volume index (SVI) (Normal value > 35 ml/m²) and LG as a mean transaortic pressure gradient < 40 mmHg.

Exercise testing may add important informations in asymptomatic patients allowing to recognize normal exercise limitations from abnormal symptoms due to AS, even though patients with symptoms evoked by exercise testing should be considered symptomatic. In particular in old sedentary patients, exercise-induced angina, early excessive dyspnea, dizziness or syncope 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 velocity is ≥4.0 m/sec or mean pressure gradient ≥40 mm Hg, due to high risk of complications, comprising syncope, ventricular tachycardia, and death.

**Management**

For patients with low to moderate, international guidelines recommend medical therapy with the use of drugs which can reduce cardiac workload and sympathetic overactivity and restore cardiac adrenergic impairment related to HF, such as beta-blockers. In this regard, targeting cardiac beta-adrenergic receptor system has been demonstrated a valid strategy for treatment of HF of different etiologies, including AS and of other diseases that recognize autonomic dysfunction as an important patogenetic mechanism. In patients with AS related heart failure in sinus rhythm, left atrial enlargement and high thromboembolic risk, the use of anticoagulants could be taken in account. Patients with a pattern of “normal flow low gradient” represent 31-38% of patients with severe AS. They have a preserved longitudinal myocardial function and a less severe degree of AS. The prognosis in these patients seems to be relatively better then the others categories. Patients with “normal flow high gradient” represent the 39-72% of patients with severe AS. The longitudinal function is still preserved but the exposition to the disease seems to be longer. The cardiac event-free survival rate is reduced. Patients with a model of “low flow high gradient” represent the 8% of patients. It is characherized by a low SVI despite a preserved LVEF due to the compromission of the LV longitudinal function. It is the result of a concentric remodelling of LV that ensures a normal LVEF, thus underestimating the extent of myocardial impairment. The transvalvular gradient is high but lower than expected because of intrinsic myocardial disfunction and significant LV remodelling. The outcome in this patients is similar to patients with NF/HG. It is important to underline that AS outcome is strongly conditioned by the coexistence of coronary artery disease which in turn shows a worse behaviour in elderly patients with cardiac valvulopathy.

Patients with a pattern of “low flow low gradient” have a low transaortic volume flow rate due to LV systolic dysfunction with a low LV ejection fraction (LVEF). In general 7% of symptomatic patients and 15-35% of asymptomatic patients have this pattern. So actually when LV systolic dysfunction co-exists with severe AS, the AS velocity and gradient may be low, despite a small valve area. However, LVEF can be paradoxically preserved. In this case the small and hypertrophied LV ejects a small SV so that, even when severe stenosis is present, the AS velocity and mean gradient may be lower than expected for a given valve area.

Indication for AVR should be limited to patients in whom symptoms can clearly be attributed to AS. When asymptomatic, individual risk stratification
can support the identification of patients who may benefit from early surgery. In these patients, evaluation of circulating catecholamines, which are expression of adrenergic activity, may be useful for prognostic stratification togheter with other well recognized circulating biomarkers. Exercise echocardiography may be important in revealing patients with limited valve compliance and/or exhausted LV contractile reserve. In adults with severe symptomatic AS, AVR is the only effective treatment considered with a Class I recommendation by ACCF/AHA and ESC guidelines. Current AVR options include mechanical, bioprosthetic, and in specific situations homograft and autograft techniques. Each has its advantages and drawbacks, but the trend in some centers in the recent era has been toward tissue valve replacement in a majority of patients because of improved durability and the lack of requirement for anticoagulation therapy.

Minimally invasive AVR through a ministernotomy has been developed as an alternative approach to conventional full sternotomy AVR. The technique was developed to reduce surgical trauma and studies have demonstrated favourable postoperative outcomes compared with full sternotomy AVR. Mortality and morbidity outcomes of mini-AVR are equivalent to conventional AVR. Mini-AVR is associated with decreased ventilator time, blood product use, early discharge, and reduced total hospital cost. In contemporary clinical practice, mini-AVR is safe and cost-effective. Current data from the Society of Thoracic Surgeons (STS) registry documents a mortality that is under 3% for all patients undergoing AVR. As with any procedure, operative mortality is strongly correlated with the severity of the disease and comorbidity. However, despite substantial contemporary experience with successful AVR in elderly patients, multiple series have documented that 30% to 40% of patients with severe AS do not undergo surgery owing to advanced age. In summary, a substantial percentage of patients with AS are judged to be inoperable for surgery based primarily on the physician’s or surgeon’s determination of operative risk and survivability without an adequate multidimensional geriatric assessment. Although some patients may be found to be inoperable for technical and surgical reasons, most inoperable patients are felt to be too ill from associated comorbid conditions. When considered inoperable, patients may undergo alternative procedures. Balloon aortic valvuloplasty has been considered to be a less invasive and safe alternative to AVR for a long time, particularly in high surgical risk patients with multiple medical comorbidities. Although balloon aortic valvuloplasty results in immediate hemodynamic improvement with a significant decrease in transvalvular gradients resulting in larger valve area, it does not result in sustained clinical improvement because of high recurrence rates of restenosis or recoil of the aortic valve usually occurs within 6 months. Balloon aortic valvuloplasty, therefore, should not be used as a substitute for AVR in patients who are candidates for surgical AVR. Even as a palliative treatment, balloon aortic valvuloplasty data suggest that there is much uncertainty regarding improved longevity or quality of life after the procedure with a mean duration of symptom improvement of only 1 year. Although balloon aortic valvuloplasty as a stand-alone treatment is not recommended, it may still be used in contemporary practice as a bridge to subsequent AVR (both Class IIb, Level of Evidence C recommendation). In the current era of TAVR, there has been increased interest in balloon aortic valvuloplasty. In this setting, balloon aortic valvuloplasty may be used to assess whether there is initial clinical improvement, in which case, then the patient may be a candidate for transcatheter aortic valve replacement (TAVR).

TAVR

**Background and History**

Given the increased mortality and morbidity of AVR for high-risk patients and the poor long-term results of balloon aortic valvuloplasty, there has been interest in the development of a percutaneously delivered aortic heart valve. The concepts of frailty, an important and frequent condition in elderly patients, will assume central importance in patient selection for TAVR by virtue of the extensive comorbidities present in this population. To the extent that AS may contribute to the declining health state, AVR or TAVR may reverse frailty. In this case, frailty may be a marker for treatment benefit. Conversely, if the individual is frail from multiple other organ system declines, frailty may be a marker of treatment risk.

The initial hemodynamic performance of TAVR valves must be similar or superior to that ob-
tained with surgical AVR. This is crucial because high residual transprosthetic gradients result in less symptomatic improvement and poorer regression of left ventricular mass. Transprosthetic gradients are a function of prosthetic size as well as the specific type of prosthesis and can result in patient–prosthesis mismatch. There are only limited clinical data on the durability of TAVR valves – up to 2 years – in the PARTNER trial and up to 5 years in other registry experiences. The fundamental clinical need for durability may depend in part on the specific patient population. In the PARTNER trial, the mean age at implant was 83 years, and serious comorbidities were frequent. In this setting, the need for durability of 20 years is less important than if the patient selection criteria are broadened to include patients in their early to mid 60s who have isolated AS without comorbid conditions. In this latter group, the TAVR valve must have at least equivalent clinical durability to currently available surgically implanted valves.

Quality of life is a key patient-centered outcome especially in the old patient. Although death is the lowest possible functional status, for many, survival marked by reduced physical function in a background of previous disability may be worse than death. The PARTNER study highlights that all patients improved, with no significant differences in NYHA functional class improvement. Improvements following TAVR in vitality, physical functioning, and general and mental health scores have been identified with physical function demonstrating the greatest improvement. Patients who do not experience improvement are more likely to have comorbidities that contribute to continued symptoms and impair quality of life, such as COPD and reduced EF.

Medical therapy
There are no proven medical treatments to prevent or delay the disease process in the aortic valve leaflets. However, evaluation and modification of cardiac risk factors is important in patients with aortic valve disease to prevent concurrent coronary artery disease (CAD). The association of AS with risk factors similar to those associated with atherosclerosis had suggested that intervention may be possible to slow or prevent disease progression in the valve leaflet. Anyway the medical therapy is the real challenge of the AV stenosis and the aim of the future research especially in the elderly, often characterized by high surgical risk, where a medical therapy could avoid an intervention and improve prognosis.

Calcific aortic stenosis represents the most common heart valve disease in the elderly population. Recent evidence have demonstrated that active biological events lead to a progressive degeneration of aortic valve leaflets mainly regulated by lipids and inflammation. Clinical manifestation is frequently insidious at the onset and can be highly variable among patients with similar degrees of valve stenosis. The onset of symptoms represents an indication to surgical replacement. Echocardiography has become the key tool for the diagnosis and evaluation of aortic valve disease, and is the primary non-invasive imaging method for aortic valve stenosis assessment. Despite substantial contemporary experience with successful aortic valve replacement in elderly patients, multiple series have documented that 30% to 40% of patients with severe AS do not undergo surgery owing to advanced age. In summary, a substantial percentage of patients with AS are judged to be inoperable for surgery based primarily on the physician's or surgeon's determination of operative risk and survivability. Growing evidence indicate that in unoperable patients, transcatheter aortic valve implantation may represent a valid alternative to surgery with excellent results in terms of quality of life and survival.

Key words: Aortic stenosis, Lipids, Elderly, Prosthetic valve
References


Femminella GD, Rengo G, Pagano G, et al. β-adrenergic receptors and G protein-coupled receptor kinase-2 in...


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94 Percutaneous balloon aortic valvuloplasty. Acute and 30-day follow-up results in 674 patients from the NHLBI Balloon Valvuloplasty Registry. Circulation 1991;84:2383-97.


