Aortic Valve Sclerosis, Mitral Valve Sclerosis and Coronary Artery Disease: The hypothesis of a common pathogenesis

Francesco Massoni¹*, Lidia Ricci², Serafino Ricci³

¹, ², ³, Department of Anatomical Science, Histological, Legal Medicine and Locomotor, “University Sapienza” of Rome

ABSTRACT
The aortic valve sclerosis (AVS) is associated with cardiovascular event independently of the stenosis. In particular, the association with coronary artery disease (CAD) and mitral valve sclerosis (MVS) is frequent. The authors present a review of the literature on the possible pathogenetic mechanism that leads to an acute cardiovascular event in case of concomitant AVS, MVS and CAD. In particular, is discussed the mechanism of atherosclerosis that involves the three structures by the best scientific evidence found in the literature.

Keywords: Aortic Valve Sclerosis, Mitral Valve Sclerosis, Coronary Artery Disease

INTRODUCTION
The gradual increase in fibrosis and calcification of the aortic semilunar is defined as Aortic Valve Sclerosis (AVS) recognized as the initial stage of a process that will lead to stenosis, and thus to the compromise of outflow of blood from the left ventricle¹. The prevalence of AVS has been estimated from 25% to 30% in patients >65 years of age and up to 40% in those >75 years ². These patients are largely asymptomatic and is difficult to recognize also because of the qualitative and quantitative echocardiographic variability². The flow through a valve sclerotic is not normal with an aortic jet according to someone³ ≤2,5 m/s and according to other⁴ <2,0 m/s, and when detectable by echocardiography there is an increased risk of cardiovascular events. The AVS is associated with an increased risk of adverse clinical events independent of the development of aortic stenosis, which occurs in only 16% of patients⁵. In the literature are referred mainly Coronary Artery Disease (CAD)⁶, left ventricular hypertrophy⁷ and mitral valve lesions⁸. The authors present a review of the literature on the possible pathogenetic mechanism that leads to an acute cardiovascular event in case of concomitant AVS, Mitral Valve Sclerosis (MVS) and CAD. In particular, is discussed the mechanism of atherosclerosis that involves the three structures by the best scientific evidence found in the literature.

DISCUSSION
The histological modification in AVS consist of an inflammation of remodeling extracellular matrix with fibrosis, thickening of the valve, in addition to angiogenesis and calcification⁹.

*Corresponding Author
Dr. Francesco Massoni,
Viale Regina Elena, 336 – 00161 Roma
Email: francesco.massoni@uniroma1.it
associated with a reduced rate of AS progression: statins inhibit the rate-limiting step in cholesterol biosynthesis, with pleiotropic effects consisting in disruption of inflammatory pathways, down-regulated inflammatory cytokines, and inhibited secretion of matrix metalloprotease. In animal studies the statins reduced the protein expression of adhesion molecules, osteoblast and markers of proliferation, reduced accumulation of macrophages, and improved CRP concentrations in serum and decreased the incidence of calcification. However, they are retrospective studies with small samples, with short-term follow-up and no information on the effectiveness of the therapy in various degrees of severity of the disease. The only double-blind, randomized, controlled trial did not demonstrate a benefit of intensive lipid-lowering therapy on the progression of calcific AS. Just as trial showed no benefit. The anti-inflammatory effect of statins results in a reduction of macrophage infiltration in the treated valves with macrophages that delete lipids and other dangerous substances. The association of AVS with CAD is based on shared risk factors (age, male gender, smoking, hypertension and hyperlipidemia), over that common pathophysiological mechanisms (rupture of the basal membrane, lipid deposition and infiltration of inflammatory cells).

Figure 2: Coronary atheroma in the left anterior descending coronary

However, it is still strongly debated the vision of the AVS as a primary degenerative process compared to the indicator of an underlying atherosclerotic phenomenon that also affect the mitral valve.

Figure 3: Mitral Valve Sclerosis opening left atrium

The opinion that presents AVS or Mitral Valve Sclerosis as a marker of atherosclerotic disease was contested by some authors, because less than 50% of patients who need aortic valve replacement requires simultaneous coronary artery bypass surgery. However, atherosclerosis is not necessarily obliterans and atherosclerosis can not be excluded on the basis of a diagnostic test (coronary angiography) that often is not sensitive enough to identify small atherosclerotic plaques. A proposed solution is to identify subtypes with increased risk: the screening of all asymptomatic subjects with AVS by echocardiography is not cost effective and then Tolstrup et al. suggest to recognize the subtype "mixed nodular and diffuse AVS" that is highly associated with CAD (a 4-fold increased risk for CAD and surgical revascularization). In this case even minimal irregularities in coronary artery wall are probably associated with deterioration and may cause the Slow Coronary Flow (SCF), defined as late opacification in the epicardial coronary arteries without significant stenosis based on the coronary images. Although the pathophysiology of SCF is uncertain and there are many hypotheses, endothelial dysfunction and atherosclerosis are among these. Also the symptomatology is certainly a helpful tool for risk stratification. In a study of Conte et al. on 93 patients with chest pain undergoing to coronary angiography (the cardiac enzymes were all negative and no previous diagnosis of cardiac ischemic disease), obstructive CAD (obCAD) was present in 29 patients (31%). Patients with obCAD had a higher prevalence of AVS (38 vs 14%, P = .02). The odds ratio for obCAD in the presence of AVS was 3.7 (95% confidence interval 1.3-10.4, P = .01). In addition, MVS is a common finding with a prevalence of up to 35% in patients with coronary artery disease sharing traditional cardiovascular risk factors as well as a correlation with the severity of coronary artery disease. Also left ventricular concentric hypertrophy, which often is associated with AVS, could be not the result of a compensatory phenomenon of systolic overload, but the effect of endothelial dysfunction, which would act as a stimulus to growth in the thickness of the wall. This condition characterizing a state of chronic circulatory insufficiency even if slight, could be complicated by a functional overload with consequent hypertension and lethal acute pulmonary edema. The hypothesis of pathogenetic association of AVS, MVS and CAD in atherosclerotic disease is certainly underestimated, but equally interesting is to investigate the valuable of therapeutic applications that could result in the management of patients with multidrug therapy.

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