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## Editorial

# Pathological Biomineralization in the Calcific Aortic Valve

## Editorial

The prevalence of moderate to severe calcific aortic valve stenosis in patients ≥75 years old is 2.8% and only 40% of patients with surgical indication undergo aortic valve replacement because of high perioperative risk, older age, lack of symptoms, and patient/family refusal [1]. In the absence of hemodynamically significant left ventricular (LV) outflow obstruction, calcific aortic valve disease (CAVD) prevalence raises up to 25% in patients aged from 65 to 74 years old [2,3] and independently predicts cardiovascular (CV) event, overall and CV mortality. As the population ages and CAVD incidence and prevalence increase, it is crucial a deeper understanding of the patho-physiology of heart valve calcification that could provide novel insight into medical therapeutic approaches to delay or modify the disease course. In the human body, several physiological processes of calcification take places and mineralized deposits are present, as bones, enamel and dentin. More than that, pathological mineralization can lead to ectopic calcification and pathologies as urinary stones, vascular calcification and calcific heart valve stenosis. Macroscopically, in aortic valve sclerosis there is an initial thickening of the valve leaflets and formation of calcium nodules, usually corresponding to the nodules of Arantio near the aortic surface, in association to angiogenesis, while end-stage calcific aortic stenosis is characterized by large, heavily calcific, nodular masses within the aortic cusps that protrude into the sinuses of Valsalva, thus interfering with valve opening along the aortic surface. While in the past heart valve calcification was seen as a passive, degenerative course of aging, evidences have shown that is an active, cell-mediated process with similarities to bone development (osseus metaplasia) [4]. In fact all of the markers of bone differentiation including the non-collagenous bone matrix proteins osteopontin, osteocalcin, bone sialoprotein and the osteoblast transcription factor Cbfa1 were found increased in the calcific aortic valve that express an osteoblast phenotype [5]. Studies on the pathobiology of CAVD showed that the calcific process begins deep into the valve tissue, near the margins of attachment. As for vascular calcification, oxidized low-density lipoproteins (LDL) play an important role in the initiation [6], in association with angiotensin-converting enzyme (ACE) and its product, angiotensin II. ACE has been found colocalized with apolipoprotein B, the primary protein found on LDL, in aortic valve lesions and also associated with plasma LDL, which may deliver ACE to aortic valve lesions [7]. In addition, oxidative stress is increased in calcified aortic valves, due to reduction in expression and activity of antioxidant enzymes and perhaps to uncoupled nitric oxide synthases (NOS) activity [8]. The presence of reactive oxygen species associated to inflammatory cytokines, growth factors, altered shear stress and hypertension could be the triggers for valvular interstitial cells (VICs) pathological differentiation in myofibroblasts and osteoblasts. The so activated VICs produce matrix metalloproteinases, involved in extracellular matrix remodeling, and increase angiogenic activity, thus creating the perfect microenvironment to promote mineralization. In particular valve calcification is composed of calcium phosphate crystals that form biominerals, deposited on a bone-like matrix of collagen, osteopontin, and other minor bone matrix proteins. The spatial organization of fibrils can create the crystal-growing niche, where pathological biomineralization can take place because of the specific physical-chemical characteristics that lead to mineral precipitation so that crystal can grow with a regular shape [9]. Nowadays *bioapatite* is the term most used in different scientific fields to indicate the mineral component of normal mineralized tissues and pathological calcification. This term is considered as indicative of an impure carbonate-containing apatite but, at present, the International Mineralogical Association Commission on New Minerals, Nomenclature and Classification (IMA-CNMNC) has not fully accepted it. We used infrared and Raman spectroscopy to demonstrate the exact crystallographic structure of bioapatite. In fact, in the calcified deposits, after calcium [Ca] and phosphorus [P], the carbonate group [CO3] is the most important constituent. The percentage of [CO3] ranges from 5 to 10% in weight and its dominant location is in place of [PO4] [10]. The [CO3] substitution is linked to the major solubility and chemical reactivity of the inorganic phase both in vitro and in vivo. Moreover, nanometer scale investigations revealed that the pathological crystals are closely bound with the organic matrix and are characterized by variable size and shape, organized on different spatial scale. There is a high heterogeneity within calcific aortic valve nodules, where fully mineralized and partially mineralized areas are both present, representing two different stages of pathological mineralization [11]. Moreover, slightly but significant differences in terms of Ca and P amount exist between tricuspid and bicuspid CAVD. Even if macroscopically bicuspid valves show an accelerated and heavier calcification, chemically the concentration of Ca:P and their the mean weight % are significantly reduced compared to tricuspid aortic valve or calcific mitral valve (Figure 1).

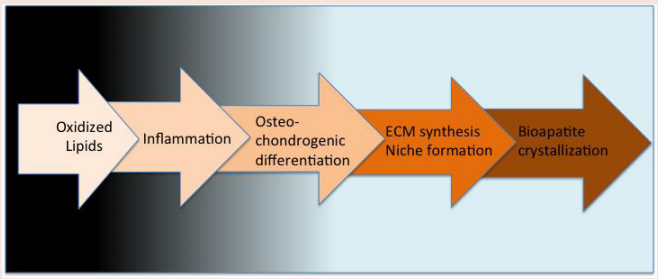


**Figure 1:** Schematic diagram of pathologic biomineralization in cardiac valve stenosis. Oxidatively modified lipids promote inflammation with release of inflammatory cytokines to stimulate osteo-condrogenic differentiation of valvular interstitial cells (VICs) and stiffening of their extracellular matrix (ECM) with synthesis of new and less compliant matrix proteins. The newer ECM spatial disposition supports the development of compartmental niches with specific physico-chemical condition. In the niche the accumulation of high concentrated extracellular fluids takes place, leading to the mineral precipitation and crystallization of bioapatite.

Our nanoscale observations indicate that the formation of pathological bioapatite nanocrystals within heart valves is related to the presence of a highly heterogeneous bioapatite. Growth processes may occur in different microenvironments (each one with its own physico-chemical characteristics) influencing the shape of the biomineralization.

The presence of compartmental niches within the extracellular matrix assumes a relevant role in the formation of ectopic biomineralization in human heart valves as well as the action of the organic substrate on the crystals features.

These innovative findings at nanometer scale unveil novel insight into pathological calcification and could open new perspective to promote further studies on a novel medical approach to treat aortic valve calcification.

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