Editorial

Pathological Biomineralization in the Calcific Aortic Valve

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 to develop new ideas for understanding of the pathobiology 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 place 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, accelerated and heavier calcification, chemically the concentration of calcium [Ca] and phosphorus [P], and their the mean weight % are significantly reduced compared to the collagenous bone matrix proteins osteopontin, osteocalcin, bone sialoprotein and the osteoblast transcription factor Cbfa1 were found increased in the calcific aortic valve that express osteocalcin, bone sialoprotein and the osteoblast transcription factor Cbfa1. [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 osteopontin, bone sialoprotein and the osteoblast transcription factor Cbfa1. Moreover, slightly but significantly differences in terms of Ca and P amount exist between tricuspid and bicuspid CAVD. Even if macroscopically bicuspid valves show an organized on different spatial scale. There is a high heterogeneity within the organic matrix and are characterized by variable size and shape, the major solubility and chemical reactivity of the inorganic phase location is in place of [PO4]3−. The [CO3] substitution is linked to the carbonate group [CO3] that 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]3− [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 the 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).
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.

References