

Received: 2012.06.21  
Accepted: 2012.10.22

## Calcific aortic valve damage as a risk factor for cardiovascular events

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### Summary

Aortic valve calcification (AVC) is a common disease of the elderly. It is a progressive disease ranging from mild valve thickening to severe calcification with aortic valve stenosis. Risk factors for AVC are similar to those for atherosclerosis: age, gender, hypercholesterolemia, diabetes, hypertension, smoking and renal failure. AVC shares many similarities to atherosclerosis, including inflammatory cells and calcium deposits, and correlates with coronary plaque burden. Presence of AVC is associated with increased risk of adverse cardiovascular events. The objective for this review is to discuss the clinical features, natural history and prognostic significance of aortic valve calcifications, including mechanical and hemodynamic factors of flow distribution.

**Key words:** aortic valve calcification • multi-slice computed tomography • coronary calcium score • atherosclerosis

**PDF file:** <http://www.polradiol.com/fulltxt.php?ICID=883626>

### Aortic Stenosis

Aortic stenosis (AS) is the most frequent valvular disease in adults [1,2]. After hypertension and coronary artery disease, it is the third most common cause of myocardial damage. Prevalence of clinically relevant aortic stenosis in people over 65 years old is about 2% and increases with age [3]. After the age of 75 years the proportion raises to 3% and to 4% after the age of 80 [4]. Since rheumatic fever is now sporadic, atherosclerosis is considered the most common cause of aortic valve sclerosis (AVS). Fortunately, AVS progression to hemodynamically relevant stenosis is rare [4–6]. A population study on 2 000 patients showed that only 16% of AVS cases progress to AS and severe stenosis develops in only 2.5% of patients [6]. Despite the seemingly small percentage of cases of severe AS development, considering the prevalence of AVS, particularly in the elderly, and increasing lifespan, we must expect the problem to grow. Currently, about 50 thousand aortic valve replacement surgeries take place in Europe and the United States and a large proportion of patients require simultaneous coronary artery bypass grafting [7]. Transcatheter Aortic Valve

Implantation (TAVI) is the alternative in people with high operative risk. Such patients often require prior revascularization through coronary intervention involving angioplasty and stent implantation.

### Risk Factors for Progression of Aortic Valve Sclerosis to Hemodynamically Relevant Stenosis

It is estimated that valve area decreases yearly by about 0.1 cm<sup>2</sup> in people with mild aortic stenosis progressing to AS [8,9]. Flow rate increases during that time by about 0.3 m/s, which corresponds to an increase in transvalvular gradient by about 3.4 mmHg up to 12 mmHg [8–11]. Eight years usually pass from the diagnosis of AVS to development of clinically significant stenosis. In many patients, despite features of aortic valve damage (AVS) the disease does not progress to hemodynamically relevant stenosis requiring cardiac surgery or TAVI.

Among the risk factors for AVS progression to hemodynamically relevant stenosis we include, among other things, high degree of valve calcification and presence of coronary

calcifications [10,12]. Peter et al. [13] showed that we might expect quick progress of mild or moderate stenosis when the defect is accompanied by coronary artery disease. The process of valvular and coronary calcification progresses simultaneously [14]. If the coronary artery calcification index in computed tomography (CCS) is  $>10$  Agatston units, the number of valvular calcifications increases by  $24.54 \pm 3.2\%$  per year [14]. Risk factors for atherosclerosis such as: advanced age, obesity, smoking, dyslipidemia, diabetes, renal failure, including raised serum creatinine, calcium and phosphate concentrations, as well as presence of mitral ring calcifications, predispose to an increase in transvalvular gradient and a decrease in valve area [6,15], although the data from various observations regarding various risk factors are not entirely consistent [12].

### Aortic Valve Sclerosis and Coronary Calcifications

Aortic valve sclerosis is more common in men than women. Leaflet thickening and risk of calcific AV damage doubles with every decade of life [4]. After the age of 65 years the percentage of people with AVS in general population reaches 29% and increases to 40% in people older than 75 years, only to reach 48% to 57% in a population above 80 years [4,12].

Calcific aortic sclerosis coexists with coronary artery disease in about 40% of patients. The risk of myocardial infarction is significantly larger in those patients than in case of coronary artery disease without coexisting AV damage [16]. In a population-based MESA (*Multi-Ethnic Study of Atherosclerosis*) study, which included people between 45 and 84 years old (mean 62 years), aortic valve calcifications (AVC) were found all together in 13% of subjects [17]. This percentage increased with the severity of coronary artery calcification. In CCS examination, for values ranging: 1–99 Agatston units, 100–399 Agatston units and 400 or more Agatston units the frequency of AVC was 14%, 25% and 38%, respectively [17]. It means, that the greater the degree of coronary artery calcification, the more likely it is to observe aortic valve calcification in computed tomography (Figure 1). In other words, identification of calcifications on the aortic valve predicts with large probability the presence of coronary lesions. Aortic valve calcification is rare in the absence of coronary artery calcifications (about 5%) and, in such cases, is a manifestation of pathologies other than atherosclerosis.

Many observations suggest that aortic valve calcification is not a passive phenomenon. Endothelial cells and myofibroblasts, among other things, actively participate in it and the process itself is very similar to atherosclerotic arterial disease [18], as evidenced by endothelial dysfunction accompanying AVS and histological picture of degenerated leaflets usually containing signs of chronic inflammation and extracellular matrix calcification [19,20].

As long as 150 years ago Virchow and Rokitansky noted that vascular calcifications exhibit many similarities to osseous tissue. Newest studies corroborate that multipotential cells, such as fibroblasts and smooth muscle cells, participate in formation of calcifications due to the ability to differentiate into osteoblasts, which are involved in extracellular matrix calcification. Osteoblastic transformation of



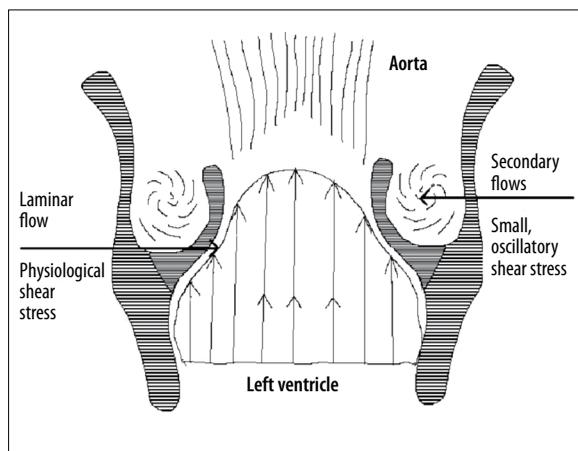
**Figure 1.** Calcification of aortic valve leaflets shown in multi-slice computed tomography imaging. A fragment of coronary stent is visible in the right coronary artery (segment 2). Minute calcifications are also visible in the left anterior descending and circumflex branch. Disseminated coronary artery atherosclerosis often accompanies AVS.

cells from the mesenchymal lineage is initiated by hemodynamic factors (oscillatory shear stress), leading to increased production of, i.a. BMP protein (*Bone Morphogenic Protein*), as well as by metabolic disorders accompanying renal failure and diabetes such as: hyperphosphatemia, hypercalcemia and oxidative stress [21].

An indirect argument for common pathomechanism of AVS and atherosclerosis is such that sclerosis and subsequent calcification of aortic valve leaflets is promoted by the same classical risk factors that cause endothelial dysfunction, as well as hemodynamic factors involving formation of secondary flows, where the vessel wall is exposed to low/oscillatory shear stress [22,23]. Influence of flow-related (hemodynamic) factors on development of calcifications is evidenced by the fact, that they are formed on the aortic side of leaflets, which is exposed to turbulent flows and oscillatory shear stress, while the ventricular surface, subjected to laminar flow and physiological shear stress, is protected from atherosclerotic damage (Figures 2, 3) [24].

Another example indicating the influence of hemodynamic factors on valvular damage and calcification is bicuspid valve, which is characterized by disrupted flow [25,26]. With time, almost all patients with this congenital anomaly develop more or less severe AS. However, valvular damage occurs two decades earlier in comparison to a normal, tricuspid valve. Altered flow hemodynamics contributes to aortic dilatation, which often accompanies bicuspid aortic valve.

Endothelium exhibits several mechanisms of counteracting the adverse effects of flow (low/oscillatory shear stress). However, these mechanisms become impaired in the presence of numerous risk factors that lead to endothelial dysfunction. In such case, vascular wall becomes susceptible to damage caused by disrupted flow.



**Figure 2.** Distribution of shear stress on aortic valve leaflets. Laminar flow and physiological shear stress on the ventricular surface of AV leaflets constitute a hemodynamic factor facilitating endothelial integrity and promoting production of anti-inflammatory agents. On the other hand, turbulent flow and resulting low, oscillatory shear stress on the aortic surface of AV leaflets and in the coronary sinus area lead to increased endothelial permeability and pro-atherogenic phenotypic transformation, including augmented matrix calcification.

Calcific aortic valve damage is an important predictor of coronary artery disease. Cumulative amount of aortic valve and mitral ring calcifications demonstrated in computed tomography or ultrasound examination correlates with CCS [27]. Pressman et al. [27] express the view that presence of AVS in echocardiography suggests high likelihood of advanced atherosclerotic lesions in epicardial arteries and should be an indication for coronary artery disease evaluation. Messika-Zeiotum et al. [12] demonstrated that the extent of coronary artery calcifications in EBCT is more pronounced in people with AVC regardless of sex and age. Respective CCS values in patients with AVC amounted to:  $441 \pm 802$  compared with  $256 \pm 566$  in people without AVC. Moreover, in the discussed study, coronary artery calcifications were more frequent in the presence of AVC.

### Dyslipidemias and Aortic Valve Sclerosis

Identical risk factors facilitate calcific aortic valve damage and coronary artery disease. The reasons for both leaflet degeneration and atherosclerosis are multifactorial and not entirely known. In population studies AVS is more

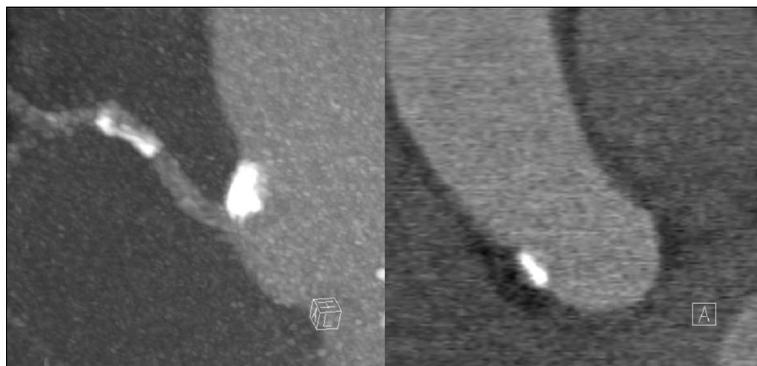
often accompanied by hypertension and diabetes [4,12]. Interestingly, predictive strength of particular risk factors for aortic valve damage is similar to that for coronary artery disease [28].

Several studies demonstrated a relationship between dyslipidemia, including increased concentration of serum total cholesterol and LDL fraction, reduced HDL level, and AVS [4,29,30]. However, not all studies corroborate these results. For example, the *Helsinki Ageing Study* [31] did not confirm dyslipidemia as a risk factor for the occurrence of aortic valve calcifications. Moderate significance of dyslipidemia for progression of aortic valve damage is evidenced by the randomized clinical studies [32,33], as well as a metaanalysis conducted on nearly 4 000 patients [34]. Studies failed to demonstrate that lipid-lowering therapy could slow down the progression of stenosis, although its use seems justified by an increased risk of acute coronary syndromes [35]. It is believed that lipid dyslipidemia may be of significance at early stages of aortic leaflet damage through deterioration of endothelial function. In case of changed transvalvular flow conditions, involving augmentation of atherogenic secondary flows, high level of cholesterol no longer play an important role and disease progression is determined by abnormal hemodynamics. Mechanical damage is an important element of disease progression, analogously to atherosclerotic plaque formation. This phenomenon involves „reading” of atherogenic shear stress by the endothelium located on the aortic surfaces of valve leaflets and transforming it into biological signals (increased production of adhesion, pro-inflammatory and pro-calcification factors) [36].

### Aortic Valve Sclerosis as a Prognostic Factor for Cardiovascular Events

Aortic valve sclerosis is associated with increased morbidity and mortality from cardiovascular causes. In a prospective observational study *Cardiovascular Heart Study*, which included 1 610 people over 65 years old, AVS was associated with a 40% increase in the risk of myocardial infarction and 50% increase in the risk of cardiovascular death [37]. Similarly to another prospective cohort study, which included 2 000 patients with AVS, the risk of cardiovascular events was almost twice as high [38]. Other studies also confirm that AVS constitutes an independent predictive factor for myocardial infarction and stroke [39].

The reason for AVS increasing the risk of cardiovascular events is not precisely known. One of the explanations may



**Figure 3.** Multi-slice computed tomography imaging. Atherosclerotic aortic wall calcification (right coronary sinus near the site of origin of right coronary artery). Partially calcified atherosclerotic plaque in the proximal right coronary artery.

be provided by observations documenting common coexistence of AVC and coronary artery disease. Additionally, the severity of atherosclerosis is greater than when the valve remains undamaged [12,27,39,40]. Patients with AVS more frequently present with multivessel disease and high plaque burden [41]. Also, as demonstrated by Wong et al. [42], mixed plaques, more susceptible to breaking, constitute a great proportion of lesions present in AVS patients.

## Conclusions

Aortic valve calcifications are often seen in CCS examinations or coronary artery angiography performed using multi-slice computed tomography. Risk factors and causes of development of AVC and coronary calcifications are similar. Presence of classical risk factors common for atherosclerosis and AVS points to the influence of endothelial dysfunction manifesting as, i.a. decreased production of anti-atherosclerotic factors (e.g. nitric oxide). Flow conditions, including formation of secondary flows in the area where endothelium is most susceptible to disturbed flows and

pro-atherogenic, low and oscillatory shear stress is another mechanism common for both disorders. Hemodynamic hemodynamic milieu, with concomitant endothelium susceptibility on "injury" caused by flow in response to an "injury" caused by flow (low and oscillatory shear stress) explains the not at random localization of lesions in the coronary arteries as well as why calcification involves aortal surfaces of AV leaflets and aortic wall calcifications occur most often in the area of coronary sinuses. Presence of AVC is an unfavorable prognostic factor for the occurrence of cardiovascular events, which should be attributed to the accompanying advanced coronary atherosclerosis, including presence of unstable plaque.

## Abbreviations

**AS** – Aortal Stenosis; **AV** – Aortic Valve; **AVC** – Aortic Valve Calcification; **AVS** – Aortic Valve Sclerosis; **CCS** – Coronary Calcium Score; **EBCT** – Electron Beam Computed Tomography; **SPECT** – Single Photon Emission Computer Tomography; **TAVI** – Transcatheter Aortic-Valve Implantation.

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