Aortic valve calcification in 499 consecutive patients referred for computed tomography

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Abstract

Introduction: Aortic valve calcification (AVC) is the most common cause of aortic stenosis. The aim of the study was to assess the prevalence of aortic valve, coronary artery and aortic calcifications and to evaluate the correlation between calcification of the aortic valve, coronary arteries and aorta.

Material and methods: The study included 499 patients aged 60 years and over who underwent coronary computed tomography because of chest pain. Beside coronary artery calcium score (CAC), we evaluated AVC and ascending aorta calcifications (AAC).

Results: Aortic valve calcification was found in 144 subjects (28.9% of the whole study population). Prevalence of CAC and AAC was higher than AVC and amounted to 73.8% and 54.0%. Prevalence of AVC, CAC and AAC was significantly lower in the group of patients ≤ 70 years than in the group of patients > 70 years of age (p = 0.0002, p < 0.0001, p < 0.0001). Aortic valve calcification was more often observed in men than women (34.7% vs. 25.4%, p = 0.02). Degree of aortic valve calcification was also significantly higher among men than women (median score 4 vs. 0, p = 0.01). Similar observations were true for CAC and AAC, where both prevalence and degree of calcification was higher among men than women. In the whole study population no correlation was noted between AVC and CAC or AAC (p = 0.34, p = 0.85). There was a significant correlation between AAC and CAC (p < 0.0001).

Conclusions: Despite some similarities in pathological mechanism and risk factors, a degenerative defect of the aortic valve could be independent of atheromatous lesions in the coronary arteries and aorta.

Key words: aortic valve, calcification, computed tomography.

Introduction

Aortic valve stenosis is the most common valvular disease. Most frequently the defect is of degenerative etiology (82%), involving gradual fibrotic thickening of the valve, followed by calcification that resembles osteogenesis [1, 2]. It was believed that calcification of the aortic valve is a passive process occurring as a natural result of ageing. However, results of more recent studies demonstrated that it is a complex mechanism, involving deposition of lipoproteins, chronic inflammation and the calcification cascade [3].
Some researchers claim that development of valve calcification resembles the atherosclerotic process [4, 5]. In their opinion, it is started by epithelial injury. Accumulation of inflammatory cells – macrophages and T cells – is observed in both processes. Valve cells differentiate into osteoblasts under the influence of various factors such as inter leukin 1 (IL-1), transforming growth factor β (TGF-β), and tumor necrosis factor α (TNF-α) [6–8]. Development of aortic valve calcification involves multiple signaling pathways, e.g. extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein (MAP) kinase, nuclear factor-κB (NF-kB), or the receptor activator of NF-κB (RANK) and its ligand RANKL [9].

Some studies have demonstrated that factors leading to calcification of the aortic valve are similar to the risk factors for coronary artery disease (CAD) and atherosclerosis, including age, male gender, body weight, nicotine addiction, arterial hypertension, diabetes and dyslipidemias [10–12]. Genetic factors seem equally important in the development of changes leading to the degenerative form of aortic stenosis. The most common of them include presence of the 4 apoE allele, mutation of the NOTCH1 gene and vitamin D receptor polymorphism, and genetic variation in the apolipoprotein(a) gene (LPA) locus [13–15]. The pathological mechanism of degenerative aortic sclerosis and precise association with the atheromatous process as well as a complete list of causative factors have not been clearly determined yet. The level of calcification of vessels and aortic valve can be determined using computed tomography (CT). The examination also allows the lumen and wall of a vessel to be evaluated, and provides information regarding the morphology of the aortic valve – the number of cusps, presence of raphe and area of the valve [16–21].

The purpose of the study was to assess: (1) prevalence of calcifications of the aortic valve, coronary arteries and aorta in consecutive patients referred for diagnostic evaluation of coronary atherosclerosis using CT; (2) correlation between calcifications involving the aortic valve, coronary arteries and aorta.

Material and methods

Between September 2011 and December 2012, consecutive patients aged 60 and over referred for CT diagnostic assessment of coronary atherosclerosis in order to exclude CAD were included in the study. These referrals were prompted by chest pain symptoms. A total of 499 patients were included: 315 females (63.1%) and 184 males (36.9%). Mean age was 69.5 ± 6.5 years (70.1 ± 6.6 years for females and 68.5 ± 6.3 years for males). Patients were divided into two groups based on the mean age. The first group consisted of patients aged less than 70 years of age (276 individuals), and the second group included patients over 70 years of age (223 individuals).

Blood creatinine level and estimated glomerular filtration rate (eGFR) were determined for each patient before CT examination. Creatinine clearance was calculated according to the Cockcroft-Gault formula. A detailed history taken from all patients included comorbidities, allergies and any previous procedures on coronary vessels or cardiac valves. Coronary CT angiography was performed using a dual-source Somatom Definition scanner (Siemens, Forchheim, Germany). Each study began with determining the coronary artery calcium score (CAC). Calcifications were defined as areas with a density of > 130 Hounsfield units and volume of at least 1 mm³. Calcifications were evaluated using the Agatston score. Coronary CT angiography was not performed if CAC was > 1000. The contrast volume ranging from 60 ml to 120 ml was injected at a rate of 5–6 ml/s. To induce maximal coronary vasodilatation, patients were given 0.8 mg of nitroglycerin, except for patients with severe aortic stenosis, in whom the dose was reduced to 0.4 mg or not administered at all. If the resting heart rate was above 65 bpm or extrasystoles were present, metoprolol was administered intravenously in sequential doses of 2.5 mg (up to 15 mg). Verapamil was given in patients with contraindications to β-blockers (e.g. severe asthma). Conventional invasive coronary angiography was subsequently performed in patients with at least one > 50% stenosis, artifacts due to calcifications, or motion artifacts. The acquisition protocol was retrospectively gated with an electrocardiogram. The CT tube voltage was 100 kV in patients with a body mass of < 80 kg and 120 kV in the remaining patients. Tube current ranged from 370 mAs to 450 mAs and was set automatically according to a protocol to reduce radiation dose (Care4Dose, Siemens). Pitch ranged from 0.2 to 0.5 depending on the heart rate during acquisition. Radiation dose was 4.6 mSv to 16.2 mSv, depending on the acquisition parameters and the scanning range. Besides coronary vessels, the CT examination also involved the aortic valve and a visible part of the ascending aorta. The aorta was evaluated to the tracheal bifurcation level. The evaluation also involved assessment of aortic valve calcification (AVC) and ascending aorta calcification (AAC). Scans were evaluated by radiologists and cardiologists experienced in both invasive and non-invasive coronary vessel diagnostics.

Exclusion criteria were the following: diagnosed aortic valve disease, regardless of its severity, CAC ≥ 1000 Agatston units (AU), history of
coronary angioplasty, history of coronary artery bypass grafting (CABG), condition after cardiac surgical therapy of the aortic and mitral valves, arrhythmia (atrial fibrillation, frequent ventricular and supraventricular premature beats), eGFR < 60 ml/min/1.73 m², allergy to iodine contrast agents, and lack of patient’s consent. The study was approved by the local Bioethics Committee.

Statistical analysis

The data are presented as medians (if values were non-parametric) or percentages. A χ² test and a Wilcoxon rank sum test were used for comparisons between groups for non-normally distributed variables as appropriate. Correlations between AVC, CAC and AAC scores were calculated using Pearson’s correlation. All analyses were performed using SAS statistical software. Value of p < 0.05 (two-sided) was considered as statistically significant.

Results

Aortic valve calcification was demonstrated in 144 subjects (29% of the whole study population). The baseline characteristics of the study subjects are summarized in Table I. Prevalence of calcification of the aortic valve, coronary arteries and aorta was significantly lower in the group of patients ≤ 70 years of age than in the group of patients > 70 years of age (Table II). Also the degree of calcification (measured with cardiac calcium scoring) of the aortic valve, coronary arteries and the aorta increased with age (Table III). In the whole study population, the prevalence and degree of AVC, CAC and AAC were significantly higher in males than in females (Tables II, III). Significant changes in coronary vessels (> 50% stenosis) were diagnosed in 148 patients (58 females and 90 males). Coronary artery stenosis was more common in subjects with AVC (p < 0.0001).

No correlation was noted between AVC and CAC or AAC in the whole study population (p = 0.34, p = 0.85). After patients were divided into two age groups, a significant correlation between AVC and CAC was noted only in subjects > 70 years of age (p = 0.0009). In the total population and in both age groups (≤ 70 and > 70 years), there was a significant correlation between AAC and CAC (p < 0.0001, p = 0.0014, p = 0.0002, respectively). Bicuspid aortic valve was noted in 4 individuals (0.8%).

Discussion

Considering the fact that aortic stenosis has become the most common cardiac defect in adults, an increased interest is observed in various methods of aortic valve imaging. These methods are aimed at detecting not only the presence of aor-
tic stenosis but also the processes that may lead to development of the defect, e.g. calcification of the valve. Computed tomography (performed also for non-cardiological reasons) has become a tool commonly used for evaluating the degree of calcification of the valve or vessels. Numerous studies on the prevalence of AVC have been performed using this method [22, 23].

Raju et al. evaluated incidence of AVC in 416 consecutive patients examined with CT; AVC was identified in 22.8% of the examined population [24]. In the study by Messika-Zeitoun et al. on 262 patients aged 60 and older, AVC rate evaluated with CT was 27% [25]. In the Multi-Ethnic Study of Atherosclerosis (MESA) study that included 6809 individuals aged 45–84 years, AVC was found in 13% of the study population [26]. Therefore it seems that prevalence of AVC is not precisely determined and depends on the number and/or characteristics of the study group. The majority of studies have demonstrated that prevalence of AVC and the degree of valve calcification depend on age [27, 28]. In the study by Walsh, incidence of AVC was 3% for subjects < 50 years of age, 6% for subjects 50–59 years of age, 17% for subjects 60–69 years of age, and 34% for subjects ≥ 70 years of age (p < 0.0001) [29]. Also, in the present study, prevalence and degree of AVC were higher in the older age group.

A correlation between gender and AVC is a different matter. Some studies indicate that more advanced AVC is observed in males than in females [30, 31]. Aggarwal et al. demonstrated that among patients diagnosed with aortic stenosis of similar severity, AVC is lower in females than in males (1703 ±1321 AU vs. 2694 ±1628 AU; p < 0.0001) [32]. On the other hand, Koos et al., analyzing AVC in 402 individuals aged 32–91 years undergoing chest CT, found no correlation between gender and AVC [33].

Our study revealed a significant correlation between gender and the prevalence and degree of AVC in the whole study population.

Some authors claim that the valve calcification process may be an equivalent of the atheromatous process. Others, however, stress some important differences between these two processes. First, the basic role in valve calcification is played by fibroblasts [34]. In the case of vessels, there are smooth muscle cells that, under the influence of certain factors (e.g. IL-1, TGF-β, TNF-α), differentiate into osteoblasts [35, 36]. The manifestation of the disease is another dissimilarity. In CAD the atheromatous plaque may crack or become eroded, leading in consequence to an acute coronary syndrome. That is not observed in aortic stenosis.

Considering a possible link between AVC and atherosclerosis, some studies were carried out involving evaluation of AVC and CAC using CT examination. Blaha et al. used CT to assess the degree of calcification of the aortic valve and coronary vessels in 8401 subjects without a diagnosed ischemic heart disease [37]. Patients with AVC had greater mean CAC (421 ±748 AU vs. 121 ±344 AU, p < 0.0001). A significant correlation between CAC and AVC (p < 0.0001) was observed. Koos et al. evaluated calcifications of the aortic valve and coronary vessels in patients with aortic stenosis [38]. No correlation between the AVC and the total coronary calcium scores was observed. In the present study there was no correlation between AVC and CAC in the whole population. Figure 1 shows an example of heavy calcification of the aortic valve without coronary artery calcification. Figure 2 shows the opposite situation. After dividing the patients into two age groups, a correlation between AVC and CAC was noted in patients > 70 years old. Perhaps the pathological mechanism...
of atherosclerosis among subjects aged 70 years old or younger. Besides evaluating AVC and CAC, CT was also used for analyzing calcifications within the descending aorta and the whole thoracic aorta. In the MESA study, Takasu et al. found a strong association between descending thoracic aortic calcification and CAC [39]. Wong et al. evaluated calcification of the aortic valve, coronary vessels and the thoracic aorta in 1754 males and 986 females aged 20–79 years, without a diagnosed CAD [40]. A significant correlation was found between calcification of the aortic valve, coronary vessels and thoracic aorta. Our study also demonstrated a correlation between AAC and CAC.

Some researchers underline the fact that the same risk factors are responsible for AVC and atherosclerosis [41–43]. There have been a number of retrospective evaluations of statins in aortic stenosis, suggesting an average 50% reduction in the rate of progression of aortic stenosis with statin use [44].

However, large prospective studies completed at a later time did not confirm that hypothesis [45–47]. The SALTIRE (Scottish Aortic Stenosis and Lipid Lowering Therapy), SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) and ASTRONOMER (Aortic Stenosis Progression Observation: Measuring the Effects of Rosuvastatin) trials indicate that lipid-lowering treatment, being so favorable, at a later time did not confirm that hypothesis [45–47].

The data collection was confined to one center. We studied exclusively patients referred for coronary artery diagnostics because of chest pain. We excluded young patients (below 60 years of age), with kidney failure or with previously diagnosed aortic valve disease. Results in this group could be different. Coronary CT angiography was not performed if CAC was > 1000 AU. Persons with hypertension, diabetes or hypercholesterolemia were diagnosed and treated adequately before inclusion in our study.

In conclusion, calcification of the aortic valve, coronary arteries and aorta was frequent in our patients (occurring respectively in one third, three quarters and half of the study population). Furthermore, their prevalence and degree increased with age. In the whole study population there was no significant correlation between the prevalence and degree of calcification of the aortic valve and coronary vessels. A significant correlation was noted only in subjects over 70 years old. A significant correlation exists between calcification of the ascending aorta and coronary arteries. Despite some similarities in pathological mechanism and risk factors, a degenerative defect of the aortic valve could be independent of atheromatous lesions in the coronary arteries and aorta.

**Conflict of interest**

The authors declare no conflict of interest.

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