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Aortic root, not valve, calcification correlates with coronary artery calcification in patients with severe aortic stenosis: A two-center study

Michael Henein [a,*], Peter Hällgren [a], Anders Holmgren [a], Karen Sörensen [b], Pranvera Ibrahimi [a], Klaus Fuglsang Kofoed [c], Linnea Hornbech Larsen [c], Christian Hassager [c]

[a] Department of Public Health and Clinical Medicine, Umeå University and Heart Centre, Sweden
[b] Department of Diagnostic Radiology, Umeå University Hospital, Sweden
[c] Department of Cardiology and Radiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

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A B S T R A C T

Background: The underlying pathology in aortic stenosis (AS) and coronary artery stenosis (CAS) is similar including atherosclerosis and calcification. We hypothesize that coronary artery calcification (CAC) is likely to correlate with aortic root calcification (ARC) rather than with aortic valve calcification (AVC), due to tissue similarity between the two types of vessel rather than with the valve leaflet tissue.
Material and methods: We studied 212 consecutive patients (age 72.5 ± 7.9 years, 91 females) with AS requiring aortic valve replacement (AVR) in two Heart Centers, who underwent multidetector cardiac CT preoperatively. CAC, AVC and ARC were quantified using Agatston scoring. Correlations were tested by Spearman's test and Mann–Whitney *U*-test was used for comparing different subgroups; bicuspid (BAV) *vs* tricuspid (TAV) aortic valve.
Results: CAC was present in 92%, AVC in 100% and ARC in 82% of patients. CAC correlated with ARC (rho = 0.51, $p < 0.001$) but not with AVC. The number of calcified coronary arteries correlated with ARC (rho = 0.45, $p < 0.001$) but not with AVC. 29/152 patients had echocardiographic evidence of BAV and 123 TAV, who were older ($p < 0.001$) but CAC was associated with TAV even after adjusting for age ($p = 0.01$). AVC score was associated with BAV after adjusting for age ($p = 0.03$) but ARC was not. Of the total cohort, 82 patients (39%) had significant coronary stenosis (>50%), but these were not different in the pattern of calcification from those without CAS. CAC was consistently higher in patients with risk factors for atherosclerosis compared to those without.
Conclusion: The observed relationship between coronary and aortic root calcification suggests a diffuse arterial disease. The lack of relationship between coronary and aortic valve calcification suggests a different pathology.

1. Introduction

Aortic stenosis (AS) is the most common valve disease in the West with a prevalence of 2% in adults ≥65 years, and is most often of a non-rheumatic aetiology [1,2]. AS was previously thought to result from disturbed mechanical forces applied on the valve leaflets, but recent evidence suggests an active cellular process with histological features and risk factors similar to those of atherosclerosis [3]. Yet, <50% of AS patients requiring aortic valve replacement (AVR) have significant obstructive coronary artery disease [4].

Aortic valve calcification (AVC) is a characteristic feature of AS[5]. Its presence increases the risk of developing stenosis [6] and its extent correlates with stenosis severity [7–9] and predicts related mortality [10], even in those with subclinical valve pathology [11]. Calcification may also affect the coronary arteries (CAC) and is strongly related to atherosclerosis, but although prevalent in obstructive coronary artery disease (CAD), such relationship is not

* Corresponding author.
E-mail address: Michael.henein@umu.se (M. Henein).

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Abbreviations

ARC	aortic root calcification
AS	aortic stenosis
AV	aortic valve
AVA	aortic valve area
AVC	aortic valve calcification
AVR	aortic valve replacement
BAV	bicuspid aortic valve
CABG	coronary artery by-pass grafting
CAC	coronary artery calcification
CAD	coronary artery disease
CAS	coronary artery stenosis
CAVD	calcific aortic valve disease
CCAs	calcified coronary arteries
CCTA	coronary computed tomography angiography
CV	cardiovascular
ECG	electrocardiography
HU	Hounsfield units
ICA	invasive coronary angiography
IQR	interquartile range
LAD	left anterior descending artery
LCx	left circumflex artery
LMA	left main artery
MDCT	multidetector computed tomography
RCA	right coronary artery
SD	standard deviation
STJ	sinotubular junction
TAV	tricuspid aortic valve
TAVI	transcatheter aortic valve implantation
TTE	transthoracic echocardiography

mutually exclusive [12]. Indeed, high CAC score has been shown to be associated with increased risk of cardiovascular (CV) events, even after adjusting for risk factors [13–16].

AVC and CAC can accurately be quantified using cardiac CT scanning and the Agatston method [17]. While CAC measurements are recommended for better risk stratification of patients at intermediate risk for CAD [18], AVC does not play a routine clinical role. AVC score has been shown to correlate with CAC score in insignificant aortic valve pathology [6,19–21], but the relationship between the two in patients with significant AS is far less studied, despite its impact for the transcatheter aortic valve implantation (TAVI) procedure [22]. Of mention, aortic root calcification (ARC) in AS patients, although frequently seen on echocardiography, has never been formally quantified in the context of calcified cardiac structures [4,23]. We hypothesize that in patients with AS, CAC correlates much stronger with ARC, on the basis of shared arterial tissue, rather than with leaflet calcification.

2. Material and methods

2.1. Study population

Patients with AS referred for AVR at two Heart Centers, Umeå University Hospital, Sweden and Copenhagen University Hospital, Denmark were included and none of them was less than 50 years of age.

2.1.1. Umeå cohort

This consisted of patients with severe symptomatic AS who underwent AVR at Umeå University Hospital between November 2010 and September 2014. They are all part of an ongoing study 'Calcific Aortic Valve Disease-CAVD'. Patients with rheumatic pathology, kidney failure (creatinine >120 μmol/L), parathyroid disease, significant coronary artery stenosis (CAS) (>50%), redo aortic valve (AV) surgery, concomitant major mitral or aortic surgery, steroid medication, calcium supplement and cholecalciferol medication or coronary stenting were excluded. All patients received cardiac multidetector CT (MDCT) before surgery in addition to the standard pre-operative evaluation by transthoracic echocardiography (TTE) and invasive coronary angiography (ICA). The study was approved by the Regional ethics committee of Umeå (Dnr: 08-118M) and the local committee on radiation protection. Written informed consent was obtained from all patients. Of the 46 patients considered for inclusion 6 were excluded due to motion artefacts compromising the accuracy of CT calcification measurements (n = 2), PCI stents (n = 1), steroid treatment (n = 3), parathyroid disease (n = 1), significant CAS (n = 1) and combined calcium and cholecalciferol treatment (n = 2).

2.1.2. Copenhagen cohort

This consisted of patients who participated in a previous study on CAD in AS [24]. The cohort of the previous study consisted of patients referred to Copenhagen University Hospital between March 2008 and March 2010 for elective AVR with or without concomitant coronary artery by-pass grafting (CABG). Exclusion criteria were: known allergy to iodine contrast media, impaired renal function (creatinine >130 μmol/L), and age less than 40 years. Patients included in the study underwent ECG-gated cardiac MDCT including coronary computed tomography angiography (CCTA) in addition to the routine pre-operative evaluation by TTE, ICA and aortic arch MDCT. The study was approved by the local Research and Ethics Committee (J. nr. H-B-2009-027). Of 179 patients from the previous study, 7 were excluded due to; age less than 50 years (n = 3), AVC and ARC not quantified (n = 1), coronary stents (n = 1) and dialysis (n = 2).

Conventional risk factors for CAD and atherosclerosis were also evaluated in the two cohorts. Diabetes was defined as fasting plasma glucose ≥7.0 mmol/L on at least two different occasions or the use of insulin or oral hypoglycemic medications. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, on repeated measurements or the use of hypotensive medications. Hypercholesterolemia was defined as untreated total serum cholesterol ≥5.0 mmol/L or the use of cholesterol-lowering agents. Smoking was taken as regular smoking over the past 6 months and ex-smoking as regular cigarette smoking for more than 6 months before surgery. Body mass index (BMI) was calculated using the formula: weight/height^2 (kg/m^2).

2.2. CT scanning protocol and image analysis

For the Umeå cohort, image acquisition was performed using a 64-MDCT (LightSpeed VCT, GE Healthcare, Milwaukee, WI, USA). Tube voltage was 120 kV, tube current was 190 or 240 mA depending on BMI and gantry rotation time was 350 ms. The CT scan was prospectively ECG gated at 65% of the R–R interval. No medication was administered before the scan. The images were analyzed on a workstation (Advantage 4.4, GE Medical systems, Milwaukee, WI, USA). Calcium scores were obtained using