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Intima-media thickness of the descending aorta in patients with bicuspid aortic valve

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ABSTRACT

Objective: A bicuspid aortic valve (BAV) is associated with accelerated aortic valve disease (AVD) and abnormalities in aortic elasticity. We investigated the intima-media thickness of the descending aorta (AoIMT) in patients with AVD with or without an ascending aortic aneurysm (AscAA), in relation to BAV versus tricuspid aortic valve (TAV) phenotype, type of valve disease, cardiovascular risk factors, and single-nucleotide polymorphisms (SNPs) with a known association with carotid IMT.

Methods and results: 368 patients (210 with BAV, 158 with TAV,); mean age 64 ± 13 years) were examined using transesophageal echocardiography (TEE) before valvular and/or aortic surgery. No patient had a coronary disease (CAD). The AoIMT was measured on short-axis TEE images of the descending aorta using a semi-automated edge-detection technique. AoIMT was univariately ($P < 0.05$) related to age, blood pressure, smoking, creatinine, highly sensitive C-reactive protein, HDL, valve hemodynamics and BAV. In the TAV subgroup it was also associated with the rs200991 SNP. Using multivariate regression analysis, age was the main determinant for AoIMT ($P < 0.001$), followed by male gender ($P = 0.02$), BAV was no longer a significant predictor of AoIMT. AoIMT was still related to the rs200991 SNP in TAV ($P = 0.034$), and to creatinine in BAV ($P = 0.019$), when other variables were accounted for.

Conclusions: Intima-media thickness of the descending aorta is not affected by aortic valve morphology (BAV/TAV); age is the main determinant of AoIMT. Genetic markers (SNPs) known to influence IMT in the carotid artery seem to correlate to IMT in the descending aorta only in patients with TAV.

1. Introduction

A bicuspid aortic valve (BAV) is prone to accelerated valve calcification leading to premature aortic valve disease (AoVD) and is associated with altered elastic properties [1–3], aneurysms (AscAA) [4,5], and dissection of the ascending aorta [6]. Wall changes in the ascending aorta correlating to the flow jet pattern in BAV patients with AoVD have been described [7]. Although the disturbances in flow in BAV have been demonstrated in the entire aorta, including the descending aorta [8], there are only a scarce number of studies on descending aortic function and morphology [9–11].

Intima-media thickness (IMT) in the descending aorta (AoIMT) has been studied in relation to coronary artery disease (CAD) and stroke [12]. Non-laminar flow has been shown to affect the IMT, triggering migration of smooth muscle cells and monocytes as well as causing intimal hyperplasia [13,14]. To our knowledge, there are no reports examining the AoIMT in patients with a BAV versus those with a tricuspid aortic valve (TAV), or its relation to different hemodynamic environments due to different aortic valve and aortic pathologies. Therefore, we examined the relationship between AoIMT and aortic valve phenotype (BAV/TAV) and type of AoVD. We also tested its possible relation to some single-nucleotide polymorphisms (SNPs) recently reported to influence carotid intima-media thickness (CIMT) [15].

2. Methods

2.1. Study population

The initial population comprised 400 patients included in the Advanced Study of Aortic Pathology (ASAP), which is a prospective

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single-center study performed at the Karolinska University Hospital, Stockholm, Sweden. Consecutive patients aged 18 years or over with AoVD and/or an AscAA that required elective surgery were recruited, provided they were willing to participate and free of CAD according to coronary angiography. Prior to surgery, transesophageal echocardiography (TEE) was performed on 386 patients under general anesthesia. Segments with aortic plaque were excluded, why 8 patients could not be analyzed. Further, 9 patients were excluded due to suboptimal image quality while the AoIMT could be measured in 369 patients, constituting 96% of the TEE sample. Characteristics of different subgroups of patients included in this study were described previously [11]. On inclusion, patients answered a questionnaire to assess cardiovascular risk factors. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured, and blood samples were taken for biochemical analyses. The mean blood pressure (MBP) was calculated as MBP = DBP + 1/3 (SBP–DBP). Classification of the valve phenotype was made by visual inspection of the valve intraoperatively by the surgeon. Three cusps and three commissures signified a TAV; two cusps and two commissures -with or without a raphe - signified a BAV. This information was missing in one case, so 368 patients were included in the final subgroup analysis. Each subject gave written consent for participation in the study, which was approved by the Regional Ethics Review Board, Stockholm, Sweden.

2.2. Transthoracic echocardiography (TTE)

All but three patients underwent TTE before surgery, using a Philips iE33 ultrasound scanner (Philips Medical Systems, Bothell, WA, USA). Doppler and two-dimensional echocardiography measurements were performed according to the current standards (ASE 2005, 2009) [16,17]. Aortic regurgitation (AR) was graded as 0–3 (0, none; 1, mild; 2, moderate; 3, severe) according to the 2003 ASE guidelines [18], the PISA method was not used for classification. The patients were classified according to findings on TTE into four groups: aortic stenosis (AS), AR, AscAA, or with combined disease (MIX). Three patients could not perform TTE and therefore could not be classified preoperatively by this study protocol due to logistics. The lesion was defined as AS when the peak gradient (P_{max}) > 50 mm Hg and mean gradient (P_{mean}) > 40 mm Hg, and/or aortic valve area < 1 cm^2. AR was defined as an AR grade = 3 not fulfilling the AS criteria. AscAA was defined as an ascending aortic diameter of 45 or 50 mm (BAV or TAV groups, respectively) and not fulfilling the criteria for AS or AR. The MIX group consisted of patients with disease, which did not fulfill the criteria for AS, AR, or AscAA above, based on the results of TTE performed within the study protocol [19]. In patients being allocated to the MIX group TTE results differed from the primary evaluation mostly due to the fact that additional diagnostic modalities have been incorporated or different examination conditions influenced the results at the time of clinical decision making regarding cardiac surgery.

2.3. Transesophageal echocardiography

TEE was performed in the operating room with the patient under general anesthesia before surgery using a Sequoia c512 ultrasound scanner (Siemens Medical Systems, Mountain View, CA, USA) with transducer frequency of 6 or 7 MHz, mean frame rate 70 Hz. The ECG was recorded on the ultrasound images. Scanning of the descending aorta was performed in short-axis view at three predefined distances from the teeth (30, 35, 40 cm), with the 35 cm level approximately representing the level of the left atrium in the majority of patients as described previously [11]. The gain settings were adjusted to obtain an optimal quality of the image. From the three levels, we selected the level (preferably 35 cm) with the best-defined intima-media interface for measurement. Aortic valve morphology (BAV/TAV) using TEE images was determined according to the classification of Sievers and Schmidtke [20].

All the TTE and TEE examinations were read by highly experienced physicians working at the echo lab. For the TTE, all exams were divided among a group of 4 physicians. The TEE images were interpreted and IMT measurements were performed by one single reader.

2.4. Intima-media thickness of descending aorta

Measurements of AoIMT were performed off-line using a Syngo Arterial Health Package semi-automated edge-detection program (version 3.5; Siemens Medical Systems), allowing detection of the echogenic lines of the intima-media complex in a 10-mm-wide segment that could be adjusted to the curvature of the vessel in short axis (Fig. 1).

The best-quality end-diastolic image with good perpendicular alignment was selected and a region of interest (ROI) was placed manually over the far wall of the descending aorta in short-axis view. The ROI length was set shorter than 10 mm in a small number of patients because of suboptimal image quality. Tracings of the intima-blood and media-adventitia borders were adjusted manually when needed. The mean AoIMT was measured from two consecutive heart beats.

2.5. Reproducibility

The intra- and interobserver variabilities of measurements were determined for AoIMT variables in 27 patients. For intraobserver variability, the same observer repeated the measurements after 1 week, whereas interobserver variability was assessed from measurements performed by two experienced independent observers. The intra- and interobserver variabilities for AoIMT expressed as a coefficient of variation (CV%) in this study were 11% and 10%, respectively.

2.6. Blood analyses

The plasma concentrations of creatinine, highly sensitive C-reactive protein (hs-CRP), HDL, LDL and serum concentrations of cholesterol and triglycerides were estimated by the Karolinska University laboratory using standard methods (Unicel DXC 800 Synchron; Beckman Coulter, Brea, CA, USA).

2.7. Single nucleotide polymorphism analysis

Genotypes were extracted from previously described genotyping using the Illumina Human 610W-Quad BeadArrays (Illumina Inc., San Diego, CA, USA) at the SNP technology platform at Uppsala University [21]. In 338 patients, we studied the rs200991 SNP in the HIST1H2BN locus and the rs4888378 SNP in the BCAR1-CFDP1-TMEM170A locus, identified previously as determinants of carotid IMT [15]. The patients in whom SNP analysis were performed were evenly spread throughout the study. In some cases the analysis was not possible due to logistical reasons. The Genome Studio software from Illumina was used for genotype calling and quality control.

2.8. Statistical analyses

Analyses were performed using commercially available SPSS software (version 22; IBM Corp., Armonk, NY, USA). Data are presented as mean ± SD or medians and (25–75th percentiles). For comparisons between groups, Student's *t* test and analysis of variance (ANOVA) were used. Skewed variables were log transformed before analyses. Tukey's test for *post hoc* analysis was performed in conjunction with ANOVA. The Chi-squared test was used to analyze nominal or categorical variables. Correlations between the variables were estimated using Pearson's product–moment correlation coefficient (r). Univariate and stepwise forward multivariate regression analyses were used to evaluate the predictors of AoIMT. Colinearity was analyzed to assess the relationships between the variables included in the models. $P < 0.05$ was considered significant. In multivariate analysis, determinants of AoIMT with a classification cutoff of $P < 0.10$ were presented in the model.