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Original article

Association between pentraxin 3 levels and aortic valve calcification

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ABSTRACT

Objective: Aortic valve calcification (AVC) reflects the state of aortic valve sclerosis (AVS), which is a precursor to aortic valve stenosis (AS). Therefore, we investigated the presence of AVC in patients who underwent coronary computed tomography angiography (CTA), which is an effective tool for evaluating early-stage AVC, and examined the association between plasma levels of pentraxin 3 (PTX3) and AVC.
Methods and results: The subjects consisted of 162 consecutive patients who underwent CTA and in whom we could measure plasma levels of PTX3. We divided the patients into an AVC group ($n = 42$) and a non-AVC group ($n = 120$), as assessed by CT. Furthermore, we divided the patients without AS, assessed by echocardiography, into non-AS AVC ($n = 23$) and non-AS non-AVC groups ($n = 60$). We analyzed the predictors of the presence of AVC in all patients by a logistic regression analysis. AVC was independently associated with PTX3, in addition to age, chronic kidney disease, and coronary artery calcification. We also examined the predictors of the presence of AVC in patients without AS. PTX3, in addition to age, was an independent predictor of the presence of AVC in patients without AS. Finally, we found that adding PTX3 to the model containing age improves the specificity and, therefore, positive predictive value for AVC.
Conclusions: PTX3, in addition to age, was shown to be an independent predictor of AVC in patients without AS. The combination of age and PTX3 may be a better approach to the evaluation of AVC than either of these alone.

Introduction

Aortic valve stenosis (AS) is predominantly a disease of the elderly [1,2]. It is difficult to diagnose aortic valve sclerosis (AVS), which is a precursor of AS, non-invasively. However, aortic valve calcification (AVC) is a useful index for evaluating the severity of AVS. Although echocardiography can be used to judge the presence of AVC, it is not objective. On the other hand, computed tomography (CT) can evaluate the presence of AVC objectively and easily, and can be used to diagnose the phase of AVS.

Several large population-based studies previously presented clinical risk factors for calcific aortic valve disease [3,4]. These risk factors closely resemble those for atherosclerotic cardiovascular disease: age, gender (male), hypertension (HTN), dyslipidemia (DL), smoking, diabetes mellitus (DM), and metabolic syndrome. These factors cause AVS with minute calcifications, and such calcification increases due to compounding factors, including oxidative stress, and can lead to AS, which, in turn, can influence hemodynamics [5]. On the other hand, it is difficult to diagnose AVS, which has not yet reached AS by noninvasive methods.

Although CT can be used to objectively and easily evaluate the presence of AVC, and is a useful tool for evaluating the phase of AVS, exposure to radiation is a major problem, and thus it may not be appropriate for screening of AVC. As an alternative to CT, many reports have described associations between cardiovascular disease or atherosclerosis and levels of pentraxin 3 (PTX3) [6,7], although PTX3 may be essentially atheroprotective [8]. In addition, in 2010, Naito et al. reported that PTX3 may be a biomarker of AS [9]. Otto et al. reported that early lesions in degenerative AS are the

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result of an active inflammatory process with some similarities (lipid deposition, macrophage and T-cell infiltration, and basement membrane disruption) to atherosclerosis, and inflammatory cytokines released by infiltrated macrophages in the aortic valve lead to adverse pathophysiological changes [10]. PTX3 is expressed in several cell types including human atheroma-associated macrophages, fibroblasts, vascular smooth muscle cells, and endothelial cells [11]. Therefore, we hypothesized that PTX3 may be a useful predictive biomarker in the presence of AVC. We evaluated patients with or without AVC who underwent coronary CT angiography (CTA) and examined the association between AVC and PTX3.

Methods

Study subjects

We enrolled 162 consecutive subjects who had undergone CTA due to clinically suspected coronary artery disease (CAD) and in whom plasma PTX3 levels were measured. Patients in whom we could not precisely evaluate coronary stenosis due to severe calcification or AVC due to previous aortic valve replacement, or who had acute coronary syndrome, Kawasaki disease, Marfan syndrome, or a bicuspid aortic valve, were excluded. We divided the patients into an AVC group ($n = 42$) and a non-AVC group ($n = 120$), as assessed by CT. Furthermore, 88 subjects in whom we could evaluate the presence of AS by echocardiography were divided into AS ($n = 5$) and non-AS groups ($n = 83$). Next, we divided the patients in the non-AS group into non-AS AVC ($n = 23$) and non-AS non-AVC groups ($n = 60$).

The protocol in this study was approved by the ethics committee of Fukuoka University Hospital [IRB #11-06(09-089)], and all subjects gave their written informed consent to participate.

Evaluation of aortic valve calcification, coronary artery calcification, and coronary artery stenosis using CT

All patients were scanned by a 64-multi-detector row CT on an Aquilion 64 (TOSHIBA, Tokyo, Japan). The use of beta-blocker and nitroglycerin before scanning was left to the physician's discretion. We used plain CT to evaluate coronary artery calcification (CAC) and AVC before contrast CT. Calcification was quantified on a workstation (ZIOSTATION, ZIO SOFT, Qi Imaging, Redwood City, CA, USA) with scoring software. CAC and AVC were defined on CT images as the presence of more than 2 contiguous pixels with greater than 130 Hounsfield Units. The regions of interest in the coronary artery and aortic valve were marked at the workstation by an experienced cardiologist. A 70-ml bolus of contrast medium (Omnipaque, 350 mg iodine/ml, Daiichi Sankyo Co., Ltd., Tokyo, Japan) was injected at a flow rate of 3.6 ml/s, and followed by 35 ml of contrast agent and 30 ml of saline solution, each at a flow rate of 1.8 ml/s, with a dual injector. The region of interest was placed within the ascending aorta, and the scan was started when the CT density reached 100 Hounsfield Units higher than the baseline CT density. The scan was performed between the tracheal bifurcation and the diaphragm with the following parameters: collimation width 0.5 mm, rotation speed 0.4 s/rotation, tube voltage 135 kV, and effective tube current 360 mA.

All segments were assessed according to the 15-segment American Heart Association coronary artery model [12]. Overall, 15 coronary artery segments were assessed in all patients. Narrowing of the normal contrast-enhanced lumen to $\geq$50% that could be identified in multiplanar reconstructions or cross-sectional images was defined as significant stenosis in CAD.

Echocardiography

Patients were examined by echocardiography (Vivid 6, GE Healthcare, Little Chalfont, UK). Of the 162 patients, 118 underwent a comprehensive examination including 2D, pulsed-wave Doppler, continuous-wave Doppler, and color Doppler echocardiography, and the aortic valve area and/or velocity could be measured in 88 patients. We identified patients with AS in whom the aortic valve area was less than 1.5 cm^2 or the aortic valve maximum velocity was more than 2 m/s.

Evaluation of atherosclerotic risk factors and biochemical markers

Age, gender, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (the difference between the SBP and DBP readings), serum levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), uric acid (UA), hemoglobin A1c (HbA1c) and random blood glucose (BG), estimated glomerular filtration rate (eGFR), high-sensitivity C-reactive protein (hsCRP), PTX3, smoking status (current vs. nonsmoker), and medication use were collected and measured in all patients. In all subjects, we also measured the visceral fat area (VFA), subcutaneous fat area (SFA), and waist circumference. BP was determined as the mean of two measurements obtained in an office setting by the conventional cuff method using a mercury sphygmomanometer after at least 5 min of rest. The characteristics of the patients with regard to history of HTN, DL, DM, and history of smoking were obtained from medical records. Patients who had a current SBP $\geq$140 mmHg, and/or DBP $\geq$90 mmHg, or who were receiving antihypertensive therapy were considered to have HTN. Patients with LDL-C $\geq$140 mg/dl, TG $\geq$150 mg/dl, and/or HDL-C $<$40 mg/dl, or who were receiving lipid-lowering therapy were considered to have DL [13]. Patients with random BG $\geq$200 mg, fasting BG $\geq$126 mg, HbA1c $\geq$6.5%, or who were taking a glucose-lowering drug were considered to have DM. Hyperuricemia (HU) was defined as a serum UA level of $\geq$7.0 mg/dl or the administration of uric acid-lowering drugs. Chronic kidney disease (CKD) was defined as an eGFR level of $<$60 ml/min/1.73 m^2.

Statistical analysis

Statistical data analyses were performed using the SAS (Statistical Analysis System) Software Package (Ver. 9.4, SAS Institute Inc., Cary, NC, USA) at Fukuoka University (Fukuoka, Japan). Continuous variables are shown as the mean $\pm$ standard deviation. Categorical and continuous variables were compared between the groups by a chi-square analysis and unpaired *t*-test, respectively. When continuous variables did not show a normal distribution expressed as a median value and interquartile range, we performed a Wilcoxon rank-sum test. The Spearman rank correlation coefficient was used to evaluate associations between the groups. We used a multiple logistic regression analysis to evaluate independent predictors of AVC and selected age, gender, BMI, smoking, HTN, DL, DM, and CKD in addition to CAC as independent variables. The association of age and PTX-3 with AVC in patients without AS was examined by logistic regression analysis. The discriminative abilities of age and PTX-3 were assessed by a receiver-operating characteristic (ROC) curve analysis. Area under the ROC curve (AUC) was estimated using the concordance (or c) statistics [14–17]. Youden index was used as a criterion to determine the optimum threshold (cut-off point) for age or PTX3 to discriminate AVC [18]. Youden index was calculated as maximum (sensitivity + specificity − 1) [19]. Areas under two ROC curves were compared using logistic regression analysis [17]. Net reclassification improvement (NRI) [14,15,20] was