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Original Article

Predictive Value of Aortic Valve Calcification for Periprocedural Myocardial Injury in Patients Undergoing Percutaneous Coronary Intervention

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***Aims*: Previous studies have shown that aortic valve calcification (AVC) was associated with cardiovascular events and mortality. On the other hand, periprocedural myocardial injury (PMI) in percutaneous coronary intervention (PCI) is a well-known predictor of subsequent mortality and poor clinical outcomes. The purpose of the study was to assess the hypothesis that the presence of AVC could predict PMI in PCI.**

***Methods*: This study included 370 patients treated with PCI for stable angina pectoris. AVC was defined as bright echoes >1 mm on one or more cusps of the aortic valve on ultrasound cardiography (UCG). PMI was defined as an increase in high-sensitivity troponin T level of >5 times the upper normal limit (>0.070 ng/ml) at 24 hours after PCI.**

***Results*: AVC was detected in 45.9% of the patients (n=170). The incidence of PMI was significantly higher in the patients with AVC than in those without AVC (43.5% vs 21.0%, p<0.001). The presence of AVC independently predicted PMI after adjusting for other significant variables (odds ratio 2.26, 95% confidence interval 1.37−3.74, p=0.002). Other predictors were male sex, age, estimated glomerular filtration rate, and total stent length. Furthermore to predict PMI, adding AVC to the established risk factors significantly improved the area under the receiver operating characteristic curves, from 0.68 to 0.72, of the PMI prediction model (p=0.025).**

***Conclusion*: The presence of AVC detected in UCG could predict the incidence of PMI.**

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Key words: Percutaneous coronary intervention, Periprocedural myocardial injury, Aortic valve calcification

Introduction

Aortic valve calcification (AVC) has been regarded as a marker of systemic atherosclerosis[1-5]. Its existence can predict future cardiovascular disease (CVD)[6-8]. In the clinical settings, AVC can be easily detected by using ultrasonic echocardiography (UCG).

On the other hand, periprocedural myocardial injury (PMI) is the most common complication of percutaneous coronary intervention (PCI)[9-11]. PMI is known to be associated with subsequent mortality and other poor clinical outcomes after PCI[12, 13]. Therefore, a simple method to predict the incidence of PMI in PCI procedure is needed. Until recently, only few data are available for assessing the relationship between the presence of AVC and PMI in PCI procedures.

Aim

The aim of this study was to evaluate the predictive value of AVC for the incidence of PMI in patients who had undergone elective PCI.

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Methods

Study Population

This observational study included 370 consecutive patients undergoing successful PCI for stable angina pectoris at Nagoya University Hospital between September 2010 and December 2014. In advance, UCG was performed for all enrolled patients. Exclusion criteria included patients with congestive heart failure, who were undergoing hemodialysis (HD) treatment, with elevated preprocedural cardiac biomarkers before PCI, and/or with lesions that required rotational atherectomy. Written informed consent was obtained from all patients before their procedures, and the study protocols were approved by the institutional ethics committee.

Coronary stenotic lesions were treated with the standard PCI techniques. All of the patients received dual antiplatelet therapy with aspirin (100 mg/day) and thienopyridine derivatives before PCI and received 70 U/kg of unfractionated heparin immediately before the procedure. An additional bolus of 1000 to 2000 U was given every hour if the procedure lasted for >1 hour. Because glycoprotein IIb/IIIa inhibitors have not been approved in Japan yet, no patient was treated with them. The vascular access and type of procedure (angioplasty only, angioplasty and stenting, or primary stenting; total balloon inflation time; and inflation pressure) were determined by the interventional cardiologist according to the patients' characteristics.

Coronary angiograms were reviewed by two experienced observers blinded to the clinical information. Quantitative coronary analysis (QCA) was performed by using the cardiovascular measurement system. Contrast-filled guiding catheters were used for magnification calibration. Each angiographic sequence was preceded by an intracoronary injection of nitroglycerin. QCA was used to measure the minimal lumen diameter, reference vessel diameter, and percent diameter stenosis.

We performed UCG according to the recommendations of the American Society of Echocardiography. In this study, AVC was defined as bright echoes >1 mm on one or more cusps of the aortic valve as previously reported[14]. Mitral annulus calcification (MAC) was also evaluated. Two physicians blinded to other clinical information evaluated the UCG recording. If the physicians disagreed regarding the presence of AVC or MAC (12 cases in the present study), a final decision was made by consensus. We defined Aortic valve stenosis (AS) as an increased anterograde velocity over 2.6 m/s by continuous wave Doppler ultrasound) across the valve.

After an overnight fast of 12 hours, blood samples were obtained from all of the patients. Cardiac enzyme concentrations were measured just before and 24 hours after the procedure. An electrochemiluminescence immunoassay (Roche Diagnostics, Tokyo, Japan) was used to measure high-sensitivity troponin T level. In this method, the upper normal limit of the reference range was defined as 0.014 ng/ml for high-sensitivity troponin T. PMI was defined as an increase in high-sensitivity troponin T level of >5 times (>0.070 ng/ml) the upper normal limit at 24 hours after PCI[15].

Hypertension was defined as a systolic pressure ≥140 mm Hg or a diastolic pressure ≥90 mm Hg, or current antihypertensive medication use. Diabetes mellitus was defined as a current diagnosis of diabetes, having a fasting plasma glucose concentration ≥126 mg/dl or glycosylated hemoglobin concentration ≥6.5% (National Glycohemoglobin Standardization Program), or the use of any antihyperglycemic medication. The estimated glomerular filtration rate (eGFR) was calculated according to the new Japanese equation as follows: eGFR (ml/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 (in women)[16].

Statistical Analysis

Continuous variables were generally presented as mean ± standard deviation (SD) or median (interquartile range) if they were non-normally distributed. Categorical variables were presented as a percentage. Comparisons were made by using the Student's *t*-test for normally distributed variables and the Kolmogorov-Smirnov test for non-normally distributed variables. Categorical data were assessed by using the Fisher exact probability test. To identify independent predictors of PMI, multivariate logistic regression analysis was performed for each parameter used as the dependent variable. To assess whether the accuracy of predicting PMI would improve after adding AVC, estimates were calculated by using the area under the receiver operating characteristic (ROC) curves for PMI, in a baseline model with established risk factors those are identified without catheter examination, including sex, age, hypertension, diabetes, smoking, and eGFR, and in an enriched model containing the established risk factors plus AVC. A probability of less than 5% was considered to represent a statistically significant difference. Analysis was performed by using SPSS version 11.0 (SPSS Inc., Chicago, Illinois, USA) and R version 3.2.2 computer software (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Table 1. Patients' characteristics

Variable	Periprocedural Myocardial Injury		*p* Value
	No (*n*=254)	Yes (*n*=116)	
Men	209 (82.3)	83 (71.6)	0.01
Age (year)	68.7±9.4	72.5±8.7	<0.001
BMI (kg/m^2)	23.8±3.4	23.8±4.2	0.92
Hypertension	190 (74.8)	92 (79.3)	0.35
Diabetes mellitus	111 (43.7)	44 (37.9)	0.30
Hyperlipidemia	204 (80.3)	87 (75.0)	0.25
Current smoker	57 (22.4)	22 (19.0)	0.51
Previous MI	47 (18.5)	22 (19.0)	0.51
Previous PCI	99 (39.0)	48 (41.4)	0.66
Previous CABG	18 (7.1)	10 (8.6)	0.61
Previous ASO	14 (5.5)	6 (5.2)	0.93
Aortic jet velocity (m/s)	1.22±0.44	1.34±0.44	0.01
AS	3 (1.2)	1 (0.9)	0.79
eGFR (ml/min/1.73 m^2)	70.2±18.7	59.7±21.7	<0.001
Fasting glucose (mg/dl)	114.9±33.6	112.0±35.8	0.48
Hemoglobin A1c (%)	6.41±1.09	6.35±1.00	0.66
Brain natriuretic peptide (pg/dl)	48.5 (15.0-85.1)	100 (48.3-441.4)	0.37
Ca (mg/dl)	9.01±0.48	9.00±0.49	0.68
P (mg/dl)	3.30±0.48	3.30±0.53	0.97
Medications			
ACE-I and/or ARB	144 (56.7)	67 (57.8)	0.85
Ca-channel blocker	109 (42.9)	44 (37.9)	0.37
β blocker	89 (35.0)	43 (37.1)	0.71
Diuretics	42 (16.5)	26 (22.4)	0.18
Statin	211 (83.1)	98 (84.5)	0.73
Vasodilator	109 (42.9)	50 (43.1)	0.97

Values are mean±SD, median (interquartile ranges) or number (%)
BMI=Body mass index, MI=Myocardial infarction, PCI=Percutaneous coronary intervention, CABG=coronary artery bypass graft, ASO=Arteriosclerosis obliterans, AS=Aortic valve stenosis, eGFR=estimated glomerular filtration rate, ACE-I=Angiotensin-converting-enzyme inhibitor, ARB=Angiotensin-receptor blocker.

Results

Among the 370 patients, 116 (31.4%) had PMI. Clinical characteristics of the patients with and without PMI are shown in **Table 1**. Patients with PMI were more likely to be female, be older, and have lower eGFR. Aortic valve flow velocity was higher in PMI group than no PMI group. However, AS was not associated with occurrence of PMI. **Table 2** shows the lesion and procedural characteristics in this study. No significant difference was found in lesion complexity according to American Heart Association (AHA) classification and the presence of true bifurcation lesions and chronic total occlusion. In addition, no significant differences in maximum inflation pressure, total inflation times, use of distal protection device, and the occurrence of side branch occlusion or distal embolism were found between patients with and without PMI. By contrast, more stents were implanted, and the total length of implanted stents was longer in patients with PMI compared to those without PMI. In addition, the occurrence of slow slow/no flow was higher in patients with PMI. There was no coronary dissection with flow limitation.

AVC was detected in 170 patients (45.9%). The incidence of PMI was significantly higher in patients with AVC compared to those without AVC (43.5% vs 21.0%, $p<0.001$; **Fig. 1**). The presence of MAC was not associated with incidence of PMI (36.6% in patients with MAC and 30.1% in those without MAC, $p=0.32$).

Table 3 shows the results of the multiple logistic regression analysis of the risk factors for PMI. The presence of AVC was an independent predictor of PMI after adjusting for all other significant variables ($p=0.002$), as were male sex, age, eGFR, and total

Table 2. Lesion characteristics and procedure

Variable	Periprocedural Myocardial Injury		*p* Value
	No (*n* = 254)	Yes (*n* = 116)	
Coronary lesion location			0.11
Left main trunk	6 (2.4)	3 (2.6)	
Left anterior descending	119 (46.9)	39 (33.6)	
Left circumflex	58 (22.8)	34 (29.3)	
Right coronary	78 (30.7)	43 (37.1)	
Bypass graft	2 (0.8)	0 (0.0)	
AHA/ACC type B2 or C	139 (54.7)	70 (60.3)	0.31
True bifurcation lesion	27 (10.6)	11 (9.5)	0.85
Chronic total occlusion	16 (6.3)	3 (2.6)	0.20
QCA			
Minimum lumen diameter (mm)	0.81 (0.58-10.90)	0.51 (0.38-0.77)	0.21
Reference diameter (mm)	2.57 ± 0.62	2.53 ± 0.56	0.64
% stenosis (%)	71.7 ± 14.0	73.6 ± 13.5	0.29
Lesion length (mm)	10.8 (9.1-16.2)	14.2 (10.7-20.5)	0.01
Procedure			
POBA only	21 (8.3)	8 (6.9)	0.65
Number of stents	1.03 ± 0.46	1.15 ± 0.55	0.04
Total stent length (mm)	16.0 (12.0-24.0)	18.0 (12.8-27.5)	0.05
Drug-eluting stent use	107 (42.1)	54 (46.6)	0.43
Direct stenting	90 (35.4)	37 (31.9)	0.51
Maximum pressure inflation (atm)	16.9 ± 4.3	17.4 ± 4.1	0.30
Total inflation time (seconds)	100 (70-160)	83 (45-218)	0.14
Distal protection	4 (1.6)	2 (1.7)	0.61
Side branch occlusion	1 (0.4)	2 (1.7)	0.233
Slow flow / No flow	2 (0.8)	7 (6.0)	0.005
Distal embolism	1 (0.4)	1 (0.9)	0.57

Values are mean ± SD, median (interquartile ranges) or number (%)
QCA = Quantitative coronary angiography, POBA = Percutaneous old balloon angioplasty

stent length.

We analyzed the accuracy of predicting PMI by adding AVC to the established risk factors that were identified without catheter examination. The established factors included sex, age, hypertension, diabetes, smoking, and eGFR. Adding the presence of AVC to the established risk factors improved the prediction of PMI, as shown by the increase in the area under the ROC curve (**Table 4**).

Discussion

The presence of AVC is well known to be associated with cardiovascular risk factors, including age, sex, hypertension, dyslipidemia, diabetes, and smoking[1-4]. Moreover, recent studies have revealed a significant association between the presence of AVC and coronary artery disease (CAD), and that patients with AVC are at high risk of death from cardiovascular causes and myocardial infarction[2, 4, 5]. In addition, AVC provides predictive information for restenosis after PCI with a drug-eluting stent in patients undergoing maintenance HD[17]. Thus, AVC may be considered as a manifestation of atherosclerosis.

The prevalence of valve calcification has been reported to be 8%−12% in patients without chronic kidney disease (CKD) and 20%−31% in non-dialysis-dependent patients with CKD[18, 19]. In patients undergoing long-term HD therapy, valve calcification is more common, with a reported prevalence of 50%−77%[18, 20]. In the present study, the prevalence of AVC was slightly high (45.9%). Patients with CAD had many cardiovascular risks associated with AVC. In the study, many of the patients had decreased eGFR. Such characteristics might influence high rate of prevalence of AVC in the study. A previous study has shown that the severity of vascular calcification is associated not only with calcium, phosphorus, and parathyroid hor-

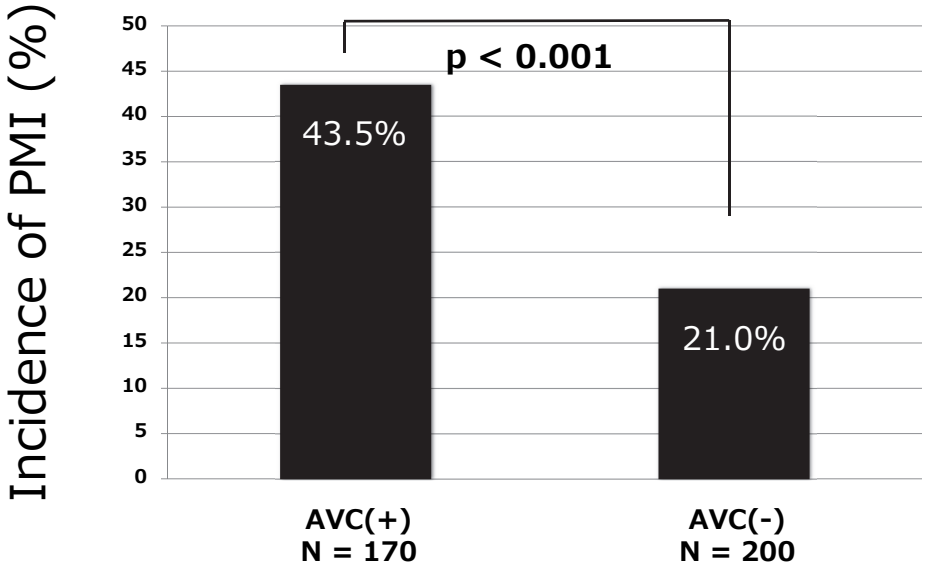

Fig. 1. Relationship between AVC and the occurrence of PMI
PMI = Periprocedural myocardial injury, AVC = Aortic valve calcification

mone imbalance but also with abnormalities of various calcium-regulatory factors such as fibroblast growth factor 23 (FGF23) and serum Klotho expression in pre-dialysis CKD patients[21, 22]. Unfortunately, we could not measure PHT level in all of the patients and did not have the opportunity to measure FGF23 and Klotho expression levels. Thus, the association between the presence of AVC and these biomarkers could not be determined in the present study.

Prior studies have evaluated imaging modalities such as computed tomography (CT) and intravascular ultrasound (IVUS) and optical coherence tomography (OCT), and they have found quantifiable predictors of PMI such as remodeling index, calcification, fibrous cap thickness, lipid core and plaque burden[23-25]. In this study, we use integrated backscatter-IVUS, patients with AVC had more calcified component in their plaque of culprit lesions than those without AVC (data not shown). Although there were no differences in lipid component in this study, previous study shows valve calcification is a maker of the vulnerable characteristics of coronary artery plaque[26]. In addition, progression of coronary calcification is seen in the outer rim of the necrotic core (NC)[27]. Fractured calcification might become either mechanical stress on NC or nodule followed by thrombosis during balloon angioplasty and stent implantation. Although the findings of CT, IVUS, and OCT are precise and promising, such modalities are more expensive and more invasive than UCG alone. Because UCG is a cheap and less labor intensive option, we believe that our findings are very important.

Table 3. Multivariate logistic regression analysis to identify predictors of periprocedural myocardial injury

	Odds Ratio	95% CI	*p* value
Male	0.55	0.31−0.99	0.048
Age (years)	1.02	0.99−1.05	0.22
eGFR (ml/min/1.73 m^2)	0.98	0.96−0.99	<0.001
Total stent length (mm)	1.02	1.00−1.04	0.048
AVC	2.26	1.37−3.74	0.002

CI = Confidence interval, eGFR = estimated glomerular filtration rate, AVC = Aortic valve calcification

Previous study shows that a patient SYNTAX score of > or =17 predicted PMI[28]. In this study, there were more patients with intermediate to high SYNTAX score in the patients with AVC than those without only in de novo lesions (data were not shown). Complexity might influence the occurrence of PMI.

Whether PMI or the underlying predisposing causative factors of PMI directly increases mortality is controversial[29, 30]. Cutlip *et al*. reported that CK-MB elevation may simply be an indicator, albeit imperfectly, of a group of patients who are at high baseline risk, such as those with severe underlying atherosclerotic disease, rather than a cause of or surrogate for increased mortality[30]. They concluded that low-to-moderate level CK-MB elevation did not predict outcomes. However, even a small area of microvascular obstruction or necrosis caused by peripheral embolization may become a future cause of arrhythmogenesis

Table 4. Discriminatory ability of two risk prediction models for periprocedural myocardial injury

Models	Area under ROC curve	95% CI	p for difference
Established risk factors	0.68	0.62−0.74	Reference
+AVC	0.72	0.67−0.78	0.02

Established risk factors included sex, age, hypertension, diabetes, smoking and estimated glomerular filtration rate
ROC curve=Receiver operatorating characteristics curve, CI=Confidence interval, AVC=Aortic valve calcification

or low arrhythmic threshold[31]. In addition, microembolization may also diminish ischemic tolerance and hence increase subsequent infarction size[32]. Patients undergoing PCI within a degenerate saphenous vein graft and patients with significantly depressed baseline left ventricular systolic function are at high risk of PMI with worse prognosis[33, 34]. Therefore, strategies to protect from PMI should be considered, including the use of distal protection devices, some drugs such as nicorandil, ischemic or remote ischemic preconditioning, and new drugs or technique, when treating patients with high risk of PMI.

Conclusion

In conclusion, presence of AVC independently predicted PMI in patients undergoing PCI. Because AVC is detected easily by using UCG, it may be useful for risk stratifications in elective PCI.

Disclosures

H.I. received lecture fees from Astellas Pharma Inc., Astrazeneca Inc., Daiichi-Sankyo Pharma Inc. and MSD K.K. T. M. received lecture fees from Bayel Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Kowa Co., Ltd., MSD K.K., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K.K., Pfizer Japan Inc., Sanofi-aventis K.K., and Takeda Pharmaceutical Co., Ltd. T.M.received unrestricted research grant for Department of Cardiology, Nagoya University Graduate School of Medicine from Astellas Pharma Inc, Daiichi Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Kowa Co., Ltd., MSD K.K., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K.K., Otsuka Pharma Ltd., Pfizer Japan Inc., Sanofi-aventis K.K., Takeda Pharmaceutical Co., Ltd., Teijin Pharma Ltd.

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