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Original article

The combined assessment of flow-mediated dilation of the brachial artery and brachial-ankle pulse wave velocity improves the prediction of future coronary events in patients with chronic coronary artery disease

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ABSTRACT

Background and purpose: Measurement of either flow-mediated endothelium-dependent dilatation (FMD) of the brachial artery, brachial-ankle pulse wave velocity (baPWV), or intima-media thickness (IMT) of the carotid artery is useful for risk assessment of future cardiovascular events. This study examined whether combination of these vascular parameters may have an additive effect on the ability of traditional risk factors to predict coronary events in patients with chronic coronary artery disease (CAD).
Methods: Patients (n = 923) with stable CAD had measurements of FMD, baPWV, and maximum IMT (maxIMT), and were prospectively followed up for <8.5 years or until a coronary event – cardiac death, non-fatal myocardial infarction (MI) or unstable angina pectoris (uAP) requiring unplanned coronary revascularization.
Results: During the follow-up period, 116 events occurred (29 cardiac deaths, 46 non-fatal MIs and 41 cases of uAP). A multivariate Cox proportional hazards analysis showed that FMD (HR 0.50, 95% CI 0.38–0.66) and baPWV (HR 1.52, 95% CI 1.27–1.82) but not maxIMT were significant predictors of coronary events. Based on the concordance statistics, the predictive value of traditional risk factors [area under the receiver operating characteristic curve (AUC), 0.67] was increased more by the addition of FMD and baPWV combined (AUC, 0.75) compared with the addition of either maxIMT, FMD, or baPWV alone, or the combination of maxIMT and FMD or maxIMT and baPWV (AUC, 0.67, 0.71, 0.71, 0.71 and 0.71, respectively).
Conclusions: The combined addition of FMD and baPWV to the risk assessment algorithms may be useful for risk stratification of chronic CAD patients.

Introduction

Non-invasive vascular function tests are widely used and have been shown to be useful to assess the risk of future cardiovascular (CV) events [1–14]. The relevant vascular tests include flow-mediated dilation (FMD) of the brachial artery to assess endothelial function, pulse wave velocity (PWV) to assess arterial stiffness, and intima-media thickness (IMT) of the carotid artery to assess atherosclerotic plaque burden and/or medial hypertrophy [1–14]. These vascular parameters predicted CV events [1,4–14], and the addition of each of these vascular parameters had a significant incremental effect on the ability of traditional risk factors to predict future CV events [9,10,12–14]. In general, the clustering of traditional risk factors increases the likelihood of future CV events [15,16]. However, it remains unknown whether the combination of these vascular parameters may also have additive effects on the ability of traditional risk factors to predict future CV events. Moreover, it remains unknown which combination among PWV, FMD, and IMT has the greatest predictive value for CV events.

These vascular parameters are not necessarily correlated with each other [17–20], and their correlation depends on the types of patients that are evaluated [17–20]. When these vascular parameters have no correlation, they may reflect different aspects of arterial structural or functional impairment in the study patients.

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In this case, the combination of these vascular tests could have additive value for risk assessment. However, it remains unclear whether these vascular parameters are correlated with each other in patients with coronary artery disease (CAD) and high CV risk. Thus, we assessed FMD of the brachial artery, brachial-ankle PWV (baPWV), and IMT of the carotid artery in patients with chronic CAD, and tested the hypothesis that combined assessment of these vascular parameters may have an additive effect on the ability of traditional risk factors to predict future coronary events in patients with chronic CAD.

Methods

Study patients

This study screened 1553 consecutively enrolled patients with stable CAD at the cardiology section of Yamanashi University Hospital from January 1, 2002 to March 31, 2010. All the patients had routine non-invasive vascular measurements including FMD of the brachial artery, baPWV, and IMT of the carotid artery. The inclusion criteria were: (1) stable CAD with an organic stenosis of >70% of at least one major coronary artery or previous coronary revascularization; (2) no episode of angina at rest and no changes in the frequency of angina in response to sublingual nitroglycerin in the previous 3 months. Exclusion criteria were: (1) acute coronary syndrome, stroke, cardiogenic shock, pulmonary edema, major surgery, trauma or serious infectious disease within 4 weeks prior to enrollment; (2) neoplasm, significant hepatic or inflammatory disease; (3) chronic renal failure or serum creatinine >2.5 mg/dL, congestive heart failure, or left main coronary trunk disease; or (4) other serious diseases. This study finally enrolled 940 patients who met all of the inclusion and exclusion criteria. The baseline characteristics of the patients are summarized in Table 1. All the patients gave written, informed consent for the study at enrollment. The study was conducted in agreement with guidelines approved by the ethics committee of Yamanashi University Hospital.

Follow-up study

After the baseline data including the vascular parameters had been obtained at our hospital, the 940 patients were followed-up prospectively every 2 months at a hospital by the patients' primary physicians for a period of <102 months, or until the occurrence of a coronary event that included cardiac death, non-fatal myocardial infarction (MI), or refractory unstable angina pectoris (uAP) requiring unplanned coronary revascularization. The time to the first event was evaluated prospectively. Cardiac deaths were defined as sudden cardiac death or pump failure death. Acute MI and uAP were diagnosed by the presence of acute ischemic symptoms lasting ≥20 min within 48 h before admission to the hospital, and electrocardiographic changes. Acute MI was diagnosed when creatine kinase-MB levels increased by at least 2 times the upper limit of normal or when troponin T levels were >0.1 ng/mL. The diagnosis of MI and uAP was confirmed by coronary angiography. Medical therapies for the enrolled study patients are outlined in Table 1.

The follow-up data were obtained every three months from the patients' primary physicians and then collated by the investigators (K.K., Y.K.), who were blinded to the patient characteristics at enrollment. All endpoint data were checked strictly for accuracy, consistency, and completeness of follow-up by the other investigators (D.F., Y.S.), who also had no knowledge of the baseline characteristics. Additional information was obtained from the physicians as required. Two of the investigators (W.S., T.N.) were responsible for checking all the data, carrying out the analyses, and maintaining security of the data files.

Measurement of flow-mediated dilation in the brachial artery

Vasodilator responses in the brachial arteries were measured using B-mode ultrasound images with a 7.5-MHz linear array transducer (HP-5500, Phillips Corp., Tokyo, Japan) according to our previously validated method [8,9]. The brachial artery was scanned in the antecubital fossa in a longitudinal fashion. After

Table 1
Baseline characteristics of the patients.

	Total patients (n = 923)	Patients with events (n = 116)	Patients without events (n = 807)
Age (years)	65 ± 12	67 ± 11	65 ± 12*
Male gender, n (%)	660 (72)	86 (74)	574 (71)
Hypertension, n (%)	551 (60)	87 (75)	464 (57)
Current smoking, n (%)	513 (56)	65 (56)	448 (55)
Diabetes mellitus, n (%)	311 (34)	59 (51)	252 (31)*
History of ACS, n (%)	304 (33)	45 (39)	259 (32)
LDL-C (mg/dL)	118 (95, 140)	122 (98, 145)	110 (90, 130)*
HDL-C (mg/dL)	46 (38, 56)	43 (37, 54)	47 (38, 57)
Triglyceride (mg/dL)	124 (92, 171)	132 (96, 168)	123 (92, 172)
Multivessel CAD, n (%)	379 (41)	78 (58)	301 (38)*
Systolic BP (mmHg)	139 ± 27	138 ± 27	136 ± 28
LVEF (%)	60.6 ± 13.3	59.9 ± 13.9	60.7 ± 13.3
CRP (mg/dL)	0.23 (0.06, 0.32)	0.24 (0.06, 0.33)	0.20 (0.05, 0.30)
BMI (kg/m^2)	23.7 ± 3.3	23.6 ± 3.4	23.7 ± 3.3
maxIMT (mm)	0.9 (1.4, 2.2)	0.95 (1.5, 2.6)	0.9 (1.4, 2.1)*
baPWV (cm/s)	1651 ± 381	1833 ± 378	1625 ± 375*
FMD (%)	6.1 ± 3.1	4.2 ± 3.4	6.3 ± 3.6*
Medication, n (%)			
Aspirin	728 (79)	118 (88)	610 (77)
Statin	303 (32)	38 (29)	265 (33)
ACEI/ARB	471 (51)	76 (56)	395 (50)
Beta blocker	151 (16)	27 (20)	124 (15)

Data are expressed either as the mean value ± SD, median and range (25 and 75th percentile), or as number (%) of patients. ACS, acute coronary syndrome; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CAD, coronary artery disease; BP, blood pressure; LVEF, left ventricular ejection fraction; CRP, C-reactive peptide; BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; maxIMT, maximum intima-media thickness; baPWV, brachial-ankle pulse wave velocity; FMD, flow-mediated vasodilatation of the brachial artery.

* $p < 0.05$ vs. patients with events.