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Original Article

Assessment of arterial stiffness in patients with familial hypercholesterolemia

Hayato Tada, MD*, Masa-aki Kawashiri, MD, Atsushi Nohara, MD, Akihiro Inazu, MD, Hiroshi Mabuchi, MD, Masakazu Yamagishi, MD

Department of Cardiovascular and Internal Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Japan (Drs Tada, Kawashiri, Nohara, Inazu, Mabuchi and Yamagishi)

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BACKGROUND: Recently, the concept of severe familial hypercholesterolemia (FH) has been proposed to identify individuals at an extremely high risk of developing coronary artery disease (CAD) among patients with FH. Although the adverse effects of arterial stiffness have been proven in the general population, insufficient data exist regarding its clinical impact in patients with FH.

OBJECTIVES: This study aimed to assess the association between arterial stiffness and CAD in patients with FH.

METHODS: We examined 245 patients with FH (162 males; mean age, 46 ± 17 years) and brachial-ankle pulse wave velocity (baPWV) measurements. We assessed baseline characteristics including lipid profiles, other traditional risk factors, the presence of CAD, and the baPWV.

RESULTS: Multivariable logistic analysis adjusted for age, sex, hypertension, diabetes, smoking, and low-density lipoprotein cholesterol revealed that the baPWV was independently associated with CAD (odds ratio [OR]: 1.25, 95% confidence interval: 1.10–1.41; $P = .000372$; per 100 cm/s). Moreover, considering the baPWV with other traditional risk factors improved the risk discrimination of CAD (C-statistics 0.736 vs 0.799; $P = .006067$). Compared with the reference group without hypertension and low baPWV, patients with hypertension and high baPWV had a significantly higher OR for CAD (OR: 18.68, 95% confidence interval: 6.62–60.62; $P = 1.7 \times 10^{-7}$).

CONCLUSIONS: Arterial stiffness assessed by the baPWV was significantly associated with the presence of CAD in patients with FH. Such assessments are useful in the risk stratification of CAD and are independent of hypertension in patients with FH.

Introduction

Familial hypercholesterolemia (FH; OMIM #143890) is characterized by the clinical triad of primary hyper-low-density lipoprotein (LDL)-cholesterolemia, tendon xanthomas, and premature coronary artery disease (CAD).[1,2]

Although all individuals with FH are at an elevated risk of developing CAD based on their lifelong burden of LDL cholesterol accumulation, the degree of disease severity remains diverse.[3,4] Identifying individuals at a higher risk of developing cardiovascular events and aggressively addressing modifiable risk factors in this population may be beneficial with respect to patients' health outcomes and treatment cost. In this regard, we have demonstrated that traditional risk factors, such as hypertension and the presence of an FH mutation, are associated with an increased risk of CAD in patients with FH.[5]

* Corresponding author. Department of Cardiovascular and Internal Medicine, Kanazawa University Graduate School of Medicine, 13-1 Takara-machi, Kanazawa, 920-8640, Japan.
E-mail address: ht240z@sa3.so-net.ne.jp
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Hypertension is one of the major causal risk factors for CAD.[6] Arterial stiffness assessed by pulse wave velocity (PWV), which is strongly associated with hypertension, is associated with the risk of developing major cardiovascular events, including cardiovascular death, myocardial infarction, and stroke, independent of hypertension, in the general population.[7–9] However, insufficient data exist regarding the clinical impact of this simple and noninvasive measurement of the prevalence of CAD in patients with FH. Therefore, in this study, we aimed to assess the association between arterial stiffness and CAD in patients with FH.

Methods

Patient population

Totally, 245 consecutive patients fulfilling the clinical criteria of FH determined by the Japan Atherosclerosis Society (fulfilling 2 out of 3 clinical criteria: (1) LDL cholesterol ≥ 180 mg/dL (2) tendon xanthoma [tendon xanthoma on the backs of the hands, elbows, knees, and so forth or Achilles tendon hypertrophy; X-ray for the assessments of Achilles tendon thickness ≥ 9 mm] or xanthoma tuberosum; (3) a family history of FH or premature CAD within the patient's second-degree relatives)[10] and with the assessments of the presence of CAD as well as the brachial-ankle PWV (baPWV) measurements between January 2006 and December 2015 were retrospectively analyzed.

Biochemical analysis

Blood samples were collected for performing assays after overnight fasting before either lipid-lowering treatment or after medication discontinuation for at least 4 weeks. Serum levels of total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol were enzymatically determined (Qualigent, Sekisui Medical, Tokyo, Japan) using an automated instrumentation based on previously described assays.[11] Genomic DNA was isolated from peripheral blood white blood cells according to standard procedures and was used for polymerase chain reaction. The coding regions of FH-associated genes are LDL receptor and proprotein convertase subtilisin/kexin type 9 [*PCSK9*]. The genotypes of all patients in the present study were determined as previously described.[12]

Clinical assessments

Hypertension was defined as a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg or receiving treatment with antihypertensive medications. The presence of diabetes was defined as previously described by the Japan Diabetes Society.[13] The essential point is the confirmation of chronic hyperglycemia, assessed by either (1) fasting plasma glucose level of 126 mg/dL (7.0 mmol/L); (2) 2-hour value of 200 mg/dL (11.1 mmol/L) in 75 g oral glucose tolerance test (OGTT); (3) casual plasma glucose level of 200 mg/dL (11.1 mmol/L); or (4) HbA1c 6.5%. Smoking status was defined according to current smoking habits. The presence of CAD was defined as lumen diameter stenosis of >50% in a major coronary artery, either by coronary computed tomography angiogram and/or coronary angiogram.[14] The indications of our coronary angiogram, including computed tomography are either of (1) any types of chest discomfort, (2) changes in electrocardiogram, or (3) patients' request. Each patient was classified according to the number of diseased vessels as having 1-, 2-, or 3-vessel disease (patients with disease in 3 vessels or left main trunk disease).

Arterial stiffness as represented by PWV

baPWV measurements were taken using an automated apparatus (Colin VP-1000, Omron, Kyoto, Japan).[15] All technicians from our single center were similarly trained and accredited. A standardized temperature was maintained in the examination room. Right and left baPWVs were automatically calculated as the length/transit time between the right arm and both ankles, and the mean of the right and left PWVs was calculated.

Ethical considerations

The present study was approved by the Ethics Committee of Kanazawa University. All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Written informed consent to participate in the present study was obtained from all patients.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation and categorical variables as counts and percentages. For values without normal distribution, the median and interquartile range were reported. Mean values of continuous variables were compared using Student's *t*-test for independent data, and median values were compared with the nonparametric Wilcoxon Mann-Whitney rank-sum test. Categorical variables were compared using the chi-square test. Multivariable analysis of independent predictors of adverse outcome was performed using the logistic regression model. The patients were divided into 4 groups according to their hypertensive status and presence of high arterial stiffness (baPWV at or over the age- and sex-specific median). The age- and sex-specific median values were described previously.[16] Odds ratios (ORs) for CAD were calculated using logistic regression with adjustment for age, sex, diabetes, smoking, and LDL cholesterol, with the nonhypertensive and lower baPWV group serving as the reference. The Cochran-Armitage trend test was used