Pulse Wave Velocity in Familial Combined Hyperlipidemia

Ewoud ter Avest, Suzanne Holewijn, Sebastian J. H. Bredie, Lambertus J. H. van Tits, Anton F. H. Stalenhoef, and Jacqueline de Graaf

Background: In the present cross-sectional study we investigated whether familial combined hyperlipidemia (FCH) is associated with an increased arterial wall stiffness, and whether measures of arterial wall stiffness in FCH family members could contribute to cardiovascular risk stratification.

Methods: Ninety-eight subjects with FCH and 230 unaffected relatives filled out a questionnaire about their smoking habits, medical history, and medication use. Fasting venous blood was drawn after discontinuation of any lipid-lowering medication. Pulse wave velocity (PWV) and augmentation index (AIx) were determined by applanation tonometry as surrogate markers of arterial stiffness.

Results: Patients with FCH had a significantly increased PWV compared to their unaffected relatives (9.07 ± 2.75 *v* 8.28 ± 2.62 m/sec, $P = .005$), whereas AIx was not increased (21.6 ± 12.7 *v* 15.6 ± 14.1, $P = .96$). Age- and gender-adjusted PWV was an equally good predictor of the presence of cardiovascular disease (CVD) in FCH family members as the most predictive combination of age- and gender-adjusted clinical and biochemical risk factors, including total cholesterol, HDL-cholesterol, and systolic blood pressure (area under the receiver operating curve (ROC) [AUC] 0.83 [0.76–0.90] *v* AUC 0.84 [0.78–0.91], $P = .83$). Addition of PWV to the multivariable prognostic model, including these age- and gender-adjusted traditional risk factors, did not increase the predictive ability for CVD (AUC 0.84 [0.79–0.89]).

Conclusions: Patients with FCH are characterized by an increased arterial stiffness. The PWV predicts the presence of CVD equally well as any combination of clinical and traditional biochemical risk factors, but PWV has no additional value in addition to traditional risk factor screening in FCH families. Am J Hypertens 2007;20: 263–269 © 2007 American Journal of Hypertension, Ltd.

Key Words: Familial combined hyperlipidemia, pulse wave velocity, augmentation index, cardiovascular risk stratification, arterial stiffness, pulse wave analysis.

Familial combined hyperlipidemia (FCH) is the most common form of heritable lipid disorder, with a prevalence of up to 5% in the general population, and 10% to 20% in survivors of myocardial infarction.[1,2] It is characterized by several phenotypes, including elevated plasma levels of total cholesterol (TC), triglycerides (TG), or apolipoprotein B (ApoB). Other characteristics of FCH are decreased plasma levels of HDL-cholesterol, the presence of small dense LDL particles, a decreased insulin sensitivity, and the presence of visceral obesity.[3–5] All of these clinical and biochemical characteristics may contribute to the observed increased risk of cardiovascular disease (CVD) in subjects with FCH.[6]

However, FCH is a heterogeneous disorder with a highly variable phenotypic expression between subjects. Phenotypic expression varies even within subjects over time.[7] Because of the variability in expression, quantification of a subset of cardiovascular risk factors (as usually happens in clinical practice) might result in suboptimal prediction of CVD risk in an individual. Another major problem in clinical medicine is that at every level of traditional risk factor exposure, there is a large interindividual variation in the amount of atherosclerosis and the development of CVD. Therefore, an indicator that directly reflects the presence of atherosclerosis in the vessel wall (and thereby the overall effect of all potential risk factors)

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From the Department of Medicine, Division of General Internal Medicine (EA, SJHB, LJHT, AFHS, JG) and Vascular laboratory, Division of Surgery (SH), Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.

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Address correspondence and reprint requests to Dr. Ewoud ter Avest, 463 Division of General Internal Medicine, Radboud University Medical Centre Nijmegen, PO Box 9101, 6500 HB Nijmegen, the Netherlands; e-mail: e.teravest@aig.umcn.nl

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is expected to yield a better risk prediction. Pulse wave velocity (PWV) and augmentation index (AIx) are attractive candidate representatives of such an overall effect. The AIx is a marker of pressure wave reflection, whereas PWV is a surrogate measure of arterial wall stiffness. An increased arterial wall stiffness has been associated with both the severity of coronary artery disease[8] and carotid artery disease.[9] Furthermore, increased arterial wall stiffness has been associated with coronary risk scores in healthy subjects[10] and, more important, it has been shown to predict future morbidity and mortality in hypertensive and diabetic populations.[11,12] Very recently, it was shown that PWV is an independent predictor of coronary heart disease and stroke in apparently healthy subjects.[13,14]

In the present cross-sectional study we investigated whether PWV and AIx, as determined with applanation tonometry, are disturbed in patients with FCH compared to their normolipidemic relatives. Furthermore, we investigated whether PWV and AIx can be used to stratify CVD risk in FCH family members with additional power beyond traditional risk factor screening.

Methods

Study Population

The study population consisted of 32 families, comprising 343 subjects. These families were ascertained through probands exhibiting a combined hyperlipidemia, as described previously.[7,15,16] The FCH diagnosis was based on absolute apoB levels in combination with plasma TG and TC levels, adjusted for age and gender, using our recently published nomogram.[16] In total 98 subjects were diagnosed as FCH and 230 as unaffected relatives. Cardiovascular disease was defined by stroke, myocardial infarction (MI), angina pectoris (AP), peripheral vascular disease, or revascularization procedure. When the presence of CVD was suspected by the clinical investigator, further details were sought from the patients' general practitioner or from any relevant hospital records. In total, 43 subjects were diagnosed with CVD, including 4 subjects with stroke, 12 subjects with previous MI, 14 subjects with AP, 6 subjects with peripheral vascular disease, and 12 subjects with a revascularization procedure. Twenty-six percent ($n = 11$) of these subjects were diagnosed with CVD based on the presence of two or more manifestations of CVD. All individuals with secondary causes of hyperlipidemia (diabetes, renal or hepatic insufficiency, hypothyroidism, or medication), with the apo E2/E2 genotype, or tendon xanthomas were excluded. The Medical Ethics Committee of the Radboud UMC approved the study protocol, and all participants provided written informed consent.

Clinical Measurements

All subjects filled out a lifestyle questionnaire about their previous medical history, and their medication use, with special attention to the use of vasoactive medication, defined as the use of one or more of the following drug classes on a regular, daily basis: angiotensin-converting enzyme (ACE) inhibitors, angiotensin II inhibitors, nitrates, calcium-channel blockers, diuretics, or β-blockers.

Waist circumference was measured at the level of the umbilicus. Systolic and diastolic blood pressures (BP) were measured at the brachial artery using an oscillometric sphygmomanometer (Critikon model no.1846; Critikon Inc., Tampa, FL), and mean arterial pressure (MAP) was calculated as: Diastolic BP + 0.33 (Systolic BP − Diastolic BP).

Biochemical Analyses

Venous blood was drawn after an overnight fast, and plasma TC and TG concentrations were determined using commercially available enzymatic reagents (Hitachi 747; Roche, Almere, The Netherlands). Very low density lipoprotein (VLDL)-cholesterol was isolated from whole plasma by ultracentrifugation at density (d) = 1.006 g/mL for 16 h at 36,000 rpm in a fixed angle rotor. The HDL-cholesterol was determined by the polyethylene glycol 6000 method.[17] The LDL-cholesterol was calculated by subtraction of VLDL-cholesterol and HDL-cholesterol from plasma TC. Total plasma apoB concentration was determined by immunonephelometry.[18] Both high-sensitive C-reactive protein (hsCRP) (Dako, Glastrup, Denmark) and plasma oxidized LDL (oxLDL) (Mercodia, Uppsala, Sweden) were determined by ELISA. Plasma glucose was determined by a commercially available glucose oxidation method (GOD-PAP, Hitachi 747; Roche Molecular Biochemicals, Indianapolis, IN). Serum insulin concentration was assessed by means of an in-house radioimmunoassay (interassay coefficient of variation: 10.3%).[19] Insulin resistance was assessed by the Homeostasis model assessment (HOMA).[20]

Augmentation Index and Pulse Wave Velocity Measurements

All measurements were taken in the supine position in a temperature-controlled room (22°C) after a brief period (at least 5 min) of rest.[21] Peripheral arterial pressure waveforms were recorded by applanation tonometry at the radial artery, using the commercially available Sphygmocor system version 7.1 (Atcor Medical, Sydney, Australia). The corresponding central waveform was then derived by applying a validated integral transfer function on the average peripheral waveform,[22,23] and subjected to further analysis to determine AIx, defined as the difference between the first and second peak of the central arterial waveform, expressed as a percentage of the pulse pressure. Because AIx is influenced by heart rate,[24] an index normalized for heart rate of 75 beats per minute (AIx@75) was used. To determine PWV, pulse waveforms were recorded at two sites sequentially (right carotid artery and left femoral artery), and wave transit time was calculated using the