DIABETES, LIPIDS AND METABOLISM

Impaired endothelium-dependent vascular reactivity in patients with familial combined hyperlipidaemia

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Background: Familial combined hyperlipidaemia (FCHL) is associated with a markedly increased risk of premature coronary artery disease. This study was designed to evaluate whether preclinical atherosclerotic functional abnormalities are detectable in the arteries of patients with FCHL.

Methods: 60 subjects were recruited for the study: 30 probands of families with FCHL (mean (standard deviation (SD)) age 48 (10) years, 77% men), defined by fasting total plasma cholesterol or triglyceride concentration >250 mg/dl (>6.5 mmol/l cholesterol, >2.8 mmol/l triglyceride) and by the occurrence of multiple lipoprotein phenotypes within a family, and 30 age-matched and sex-matched healthy controls. All subjects underwent high-resolution B-mode ultrasound examination and the brachial arterial reactivity, a marker of endothelial function, was measured by a semiautomated computerised program. Lipid profile, resting blood pressure, body mass index (BMI), smoking status, insulin and homocysteine levels were also determined.

Results: Compared with controls, patients with FCHL had significantly higher BMI, diastolic blood pressure and insulin levels. No difference was observed in baseline brachial diameter between the two groups (mean (SD) 3.45 (0.51) mm for FCHL v 3.60 (0.63) mm for controls; $p=0.17$). In response to flow increase, the arteries of the controls dilated (mean (SD) 8.9% (4.9%), range 2.3–20.8%), whereas in the patients with FCHL, brachial arterial reactivity was significantly impaired (5.5% (2.5%), range 0–10.1%; $p=0.002$). In multivariate linear regression analysis, apolipoprotein B and BMI were independent determinants of brachial artery response to reactive hyperaemia.

Conclusions: The findings of our study suggest that vascular reactivity is impaired in the arteries of patients with FCHL.

Familial combined hyperlipidaemia (FCHL) is a genetically complex lipid disorder, first recognised in 1973 by Goldstein *et al.*¹ characterised by increased levels of plasma cholesterol or triglycerides in relatives of the same family. The intrafamilial variability of the lipid phenotype probably results from the interaction of multiple genes, some of which have been identified, and environmental factors.^{2–6} Several metabolic abnormalities have been described in patients with FCHL, including very low density lipoprotein and apolipoprotein (apo) B overproduction, presence of small, dense low-density lipoprotein (LDL) particles, increased production of apolipoprotein C III and insulin resistance, that may contribute to the increased atherosclerotic risk associated with such a condition.^{7–12}

Endothelial function plays an important part in cardiovascular homeostasis, promoting vasodilatation and inhibiting platelet aggregation, monocyte adhesion and smooth-muscle proliferation.¹³

Over the past decade, high-resolution ultrasonography has been used to evaluate endothelial function non-invasively by measuring changes in brachial artery diameter owing to increased blood flow induced by pressure cuff inflation/deflation.¹⁴ Flow-mediated brachial arterial reactivity is impaired in people with overt atherosclerosis and in asymptomatic subjects with coronary risk factors.^{15–17}

This study was designed to evaluate whether endothelial dysfunction is present in the systemic arteries of asymptomatic adults with FCHL.

METHODS

Thirty middle-age probands of 30 families with FCHL regularly attending a lipid clinic were included in the study. FCHL was diagnosed according to the following criteria: (1) fasting total

plasma cholesterol or triglyceride concentration >250 mg/dl (>6.5 mmol/l cholesterol, >2.8 mmol/l triglyceride), confirmed by a repeated measurement and (2) multiple lipoprotein phenotypes (Fredrickson's classification IIa, IIb or IV) within a family. At the time of investigation, patients had not taken lipid-lowering drugs for at least 3 weeks. Secondary causes of hyperlipidaemia (eg, diabetes mellitus, hypothyroidism, liver and kidney disease and alcohol misuse) were excluded in all cases by biochemical testing of blood glucose, thyroid-stimulating hormone, serum creatinine, transaminases and γ -glutamyl transpeptidase. Subjects taking drugs influencing lipid metabolism and with other forms of genetic hyperlipidaemia were also excluded. Thirty normolipidaemic people matched for sex and age, participating in a community-based screening of cardiovascular risk factors, were also studied.

All subjects gave written informed consent to the study.

Clinical and biochemical assessment

Measurements were made in hospital outpatient facilities according to standardised protocols. Body mass index (BMI), used as a measure of general obesity, was calculated as weight (in kg) divided by height (in m²).

Sitting brachial blood pressure was measured twice, with the patient seated, after a resting period of 10 min, by using a random zero sphygmomanometer. A standard questionnaire was used to collect information about smoking habits and familial history of cardiovascular disease. Premature cardiovascular disease was defined as the clinical evidence of a

Abbreviations: apo, apolipoprotein; BMI, body mass index; FCHL, familial combined hyperlipidaemia; LDL, low-density lipoprotein

myocardial infarct or cerebrovascular incident before the age of 60 years.

After an overnight fast, blood samples were obtained by venepuncture from all subjects. Serum total cholesterol and triglyceride levels were determined using standard enzymatic methods. High-density lipoprotein cholesterol was determined after precipitation by sodium fosfotungstate. LDL cholesterol was calculated by Friedewald's formula. Serum apo B measurements were obtained using commercially available immunonephelometric methods. Fasting glucose levels were enzymatically determined by the hexokinase method. Fasting insulin levels were determined by enzyme immunoassay (Boehringer Mannheim Immunodiagnosics on ES 300 instrument, Mannheim, Germany). Homocysteine was measured by high-performance liquid chromatography.

Brachial arterial reactivity evaluation

Ultrasound studies were carried out with an ESAOTE AU4 equipped with a broad-band (multiple frequency 10–13 MHz) linear array transducer. Scans were recorded on super VHS videotape for offline analyses. One expert reader who was blinded to subjects' clinical condition made brachial arterial reactivity measurements.

Subjects were asked to be fasting and refrain from smoking and physical activity for 2 h before the examination. In all studies, the brachial artery was scanned longitudinally, optimising gain settings to provide the clearest interfaces between the lumen and vessel wall, and magnifying images with the resolution box function.

The ultrasonographic protocol included initial recording of brachial artery diameter and Doppler blood flow velocity, after which a blood pressure cuff was placed around the left forearm and inflated to a pressure of 300 mm Hg for 4.5 min, followed by sudden deflation. The consequent increase in blood flow (reactive hyperaemia) is a powerful stimulus for endothelial nitric oxide release and resulting brachial artery vasodilatation. Brachial blood flow velocity was continuously recorded for 15 s after deflation and brachial artery diameter was measured at 45–60 s. Diameter measurements were made using a computerised analysing system based on automated detection of the echo structures, with the option of making manual corrections by the operator.¹⁸ Flow-mediated brachial arterial reactivity was expressed as the percentage change in arterial diameter taken 45–60 s after cuff release relative to the baseline diameter. Brachial blood flow was determined as the product of mean velocity, estimated by means of pulsed Doppler at a <60° angle, and arterial cross-sectional area. Hyperaemic flow was calculated as the maximum flow within the first 15 s after cuff deflation divided by the flow during the baseline scan.

For assessment of the reproducibility, 15 scans were selected randomly for repeated measurements, 30 days apart. The mean intraobserver variability for measurement of flow-mediated vasodilatation was 1.5% (standard deviation (SD) 0.9%).

In a group of 14 cases and controls, the intima-media thickness of the common carotid artery and carotid bifurcation was also assessed.

Statistical analysis

Statistical analyses were carried out using SPSS V. 11.0. Results are reported as mean (SD) unless otherwise indicated. Comparisons between cases and controls were made using paired Student's *t* test and χ^2 analysis for continuous and categorical variables, respectively. Pearson's correlation coefficients were calculated to assess the univariate association between brachial arterial reactivity and cardiovascular risk factors. As previous studies have shown, the percentage brachial artery diameter change to reactive hyperaemia is

inversely correlated with the baseline diameter; the correlation between these two variables was evaluated. Multivariate linear regression analysis was carried out to find independent determinants of flow-mediated vasodilatation. Significance was inferred at $p < 0.05$.

RESULTS

Table 1 presents the characteristics of the two study groups. Compared with controls, patients with FCHL had significantly higher BMI, diastolic blood pressure and insulin levels. Of the patients with FCHL, 9 (30%) reported a familial history of premature cardiovascular disease.

Table 2 shows the results of brachial arterial ultrasonographic evaluation. Baseline brachial diameter, blood flow volume and percentage increase in blood flow during reactive hyperaemia did not differ between the two groups. In response to flow increase, the arteries of the controls dilated (mean (SD) 8.9% (4.9%), range 2.3–20.8%), whereas in the patients with FCHL, brachial arterial reactivity was significantly impaired (5.5% (2.5%), range 0–10.1%; $p = 0.002$).

An increased intima-media thickness (mean (SD)) of both common carotid artery and carotid bifurcation was found in patients with FCHL (0.76 (0.10) v 0.68 (0.09); $p < 0.05$, and 1.05 (0.16) v 0.92 (0.13); $p < 0.05$, respectively).

On univariate analysis, brachial arterial reactivity was inversely correlated with BMI ($r = -0.42$), systolic blood pressure ($r = -0.38$), LDL cholesterol ($r = -0.44$) and apo B ($r = -0.53$), but not with vessel size. In a multivariable linear regression analysis, apo B and BMI were independent determinants of brachial artery response to reactive hyperaemia (multiple r value 0.85, adjusted $r^2 = 0.67$, F value 15.5; table 3).

The variables included in the model were those that were significantly related to brachial arterial reactivity in the univariate analysis (BMI, systolic blood pressure, LDL cholesterol and apo B). Apo B, rather than LDL cholesterol, was chosen as a variable in the model because of the lower p value.

Table 1 Clinical and biochemical characteristics of patients with familial combined hyperlipidaemia and controls

	FCHL (n = 30)	Controls (n = 30)	p Value
Age (years)	48 (10)	48 (10)	—
Men (%)	77	77	—
Familial history of premature CVD (%)	30	7	0.001
BMI (kg/m ²)	27.9 (3.0)	24.9 (1.8)	0.001
Systolic blood pressure (mm Hg)	128 (16)	126 (10)	0.51
Diastolic blood pressure (mm Hg)	82 (9)	67 (7)	0.001
Smokers (%)	27	21	0.77
Total cholesterol (mmol/l)	7.14 (1.42)	4.27 (0.72)	0.001
Triglycerides (mmol/l)	3.66 (1.63)	1.05 (0.64)	0.001
HDL cholesterol (mmol/l)	1.16 (0.34)	1.21 (0.31)	0.61
LDL cholesterol (mmol/l)	4.31 (1.63)	2.56 (0.78)	0.001
Apo B (g/l)	1.32 (0.27)	0.89 (0.21)	0.001
Glucose (mmol/l)	5.22 (0.78)	4.99 (0.72)	0.27
Insulin (pmol/l)	77.8 (43.7)	50.0 (18.1)	0.001
Homocysteine (μmol/l)	10 (3)	9 (3)	0.42

BMI, body mass index; CVD, cardiovascular disease; FCHL, familial combined hyperlipidaemia; HDL, high-density lipoprotein; LDL, low-density lipoprotein; —, matched by design.

Values are mean (SD).

For triglycerides, insulin and homocysteine the p values refer to the testing of log transformed variables.

Table 2 Brachial arterial evaluation in patients with familial combined hyperlipidaemia and controls

Brachial artery functional variables	FCHL (n=30)	Controls (n=30)	p Value
Basal diameter (mm)	3.45 (0.51)	3.60 (0.63)	0.17
Basal flow velocity (cm/s)	20 (9)	21 (9)	0.89
Basal flow volume (ml/min)	92 (60)	85 (56)	0.72
Brachial arterial reactivity (%)	5.5 (2.5)	8.9 (4.9)	0.002
Hyperaemic flow velocity (cm/s)	98 (22)	105 (24)	0.65
Hyperaemic wall shear rate (s ⁻¹)	277 (58)	296 (66)	0.59
Hyperaemic flow volume (%)	290 (140)	320 (150)	0.55

FCHL, familial combined hyperlipidaemia.
Values are mean (SD).

DISCUSSION

Autopsy evidence that atherosclerosis begins years before the development of clinical sequelae and progresses silently¹⁹ has led to an extensive and ongoing search for measurable indices of atherosclerotic disease. The use of simple, valid ultrasound-based methods allowed preclinical structural and functional abnormalities to be detected non-invasively in a large number of people with traditional and non-traditional cardiovascular risk factors.²⁰

In this study, using high-resolution B-mode ultrasound, we showed that brachial arterial reactivity, a marker of endothelial function, was impaired in middle-aged asymptomatic patients with FCHL. Evidence suggests that the impairment of brachial vasodilator function parallels progressive coronary endothelial dysfunction,²¹ and may help to identify subjects at higher risk of developing clinical symptoms. Furthermore, we found an increased carotid intima-media thickness, a preclinical indicator of atherosclerotic burden of the arterial wall, in patients with FCHL.

Few previous studies carried out on patients with FCHL focused on the carotid intima-media thickness, providing conflicting results. Keulen *et al*²² found an increase of about 0.6 mm in common carotid intima-media thickness in middle-aged patients with FCHL, without previous cardiovascular disease when compared with age-matched and sex-matched controls. In 39 Finnish families with FCHL, the average carotid intima-media thickness of the patients with verified coronary heart disease was not considerably different from that of their unaffected relatives.²³ The use of different criteria to establish the diagnosis of FCHL may help to explain the different results. In the family members with FCHL in our study, the impaired endothelial function was related to apo B levels. Increased apo B levels have been found in patients with FCHL independent of the lipid phenotype expression, and have been reported to be as effective as lipid levels in classifying patients at increased cardiovascular risk. Owing to the low variability over time, increased apo B levels have been proposed as one of the main criteria for the diagnosis of such a condition.^{24–26} The lipoproteins in which apo B is transported may promote endothelial damage principally via oxidative mechanisms, increasing leucocyte production of reactive oxygen species, which, in conjunction with high intimal levels of LDLs, generate oxidised LDLs able to reduce the synthesis and release of endothelial nitric oxide.²⁷

In patients with FCHL, an increased BMI was another independent determinant of impaired brachial arterial reactivity. Neurohormonal factors, including insulin resistance, have been reported to cause preclinical arterial functional changes in subjects with excess of body mass.^{28–29} However, in this study, fasting insulin level, an indirect measure of insulin resistance, was not related to brachial arterial reactivity. The independent association of BMI with impaired vascular reactivity might be

Table 3 Multivariate regression analysis for determinants of brachial arterial reactivity in patients with familial combined hyperlipidaemia

	B	Standard error	p Value
Apo B	−15.02	3.04	0.001
BMI	−1.26	0.30	0.001

Apo, apolipoprotein; B, B slope of the regression line; BMI, body mass index.

mediated by inflammatory mechanisms, in view of evidence showing increased levels of C reactive protein and several cytokines in overweight people.^{30–31}

A limitation of this study should be taken into account: concerns about the willingness of controls to undergo the procedure led us not to give a standard antianginal dose of glyceryl trinitrate to assess endothelium-independent vasodilation. However, several previous studies have shown a preserved vasodilator response to glyceryl trinitrate in the brachial artery of asymptomatic patients with risk factors for coronary artery disease.

In conclusion, our findings suggest that endothelial dysfunction occurs in the systemic arteries of asymptomatic patients with FCHL. In such a population, the examination of arterial wall function using a non-invasive ultrasonographic method may provide important information on early changes in the course of developing atherosclerosis.

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Competing interests: None declared.

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IMAGES IN CARDIOLOGY

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Right ventricular pacing-induced hypotension

A cardiologist was consulted to evaluate a patient with intermittent hypotension. A 71-year-old woman with a history of coronary artery disease and coronary bypass surgery, type 2 diabetes and sick sinus syndrome s/p dual-chamber pacemaker implantation had been admitted to the intensive care unit with pulmonary oedema.

The problem was a ventricular pacing-related decrease in systolic blood pressure from 110 to 70 mm Hg. Even few ventricle-paced beats led to a significant decrease in systolic blood pressure that corrected after the return of native conduction. Programmed atrioventricular interval was short and thus led to intermittent atrial synchronous ventricular pacing. As the atrioventricular synchrony was preserved, the decrease in cardiac output was not due to the classic pacemaker syndrome. The decrease in cardiac output was most likely secondary to right

ventricular apical pacing that results in an asynchronous ventricular contraction. To avoid unnecessary right ventricular pacing, a longer atrioventricular interval was programmed and hypotensive episodes resolved (panels A and B).

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