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The prevalence of peripheral vascular disease in familial hypercholesterolaemia

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Objectives. In patients with familial hypercholesterolaemia (FH), the prevalence of haemodynamically significant peripheral vascular disease (PVD) was measured in relation to lipoproteins, general risk factors and the presence of coronary artery disease (CAD).

Design. A case control study.

Setting. The outpatient lipid clinic of a university hospital (tertiary referral centre).

Subjects. Patients with heterozygous FH [n = 68; age 45.8 ± 11.6 years; untreated LDL-cholesterol 9.2 ± 2.0 mmol L⁻¹] were compared with control subjects matched for gender, age, weight, smoking and presence of hypertension [n = 27; age 44.0 years; LDL-cholesterol 3.8 ± 1.3 mmol L⁻¹].

Main outcome measures. PVD was assessed during cholesterol-lowering treatment using ankle/arm blood pressure ratios and analyses of Doppler-derived blood flow velocities in the femoral artery at rest and during reactive hyperaemia. The diagnosis of CAD was assessed clinically.

Results. Haemodynamically significant PVD was found in 21 (31%) FH patients and in one (3.7%) control subject, predominantly localized in the femoro-popliteal vessels. CAD was present in 30 (44.1%) FH patients and in one (3.7%) control subject. PVD could be demonstrated in 50% of FH patients with CAD [relative risk 3.2 (95% CI 1.4–7.2)] and in 19% as the first manifestation of vascular disease. Males and females were equally affected. Mean arterial blood pressure of FH patients with PVD was higher compared to FH patients without PVD.

Conclusions. Haemodynamically significant PVD appears to be more prevalent in FH patients than is generally assumed, especially in those with CAD. A relation with lipoprotein levels could not be demonstrated.

Keywords: atherosclerosis, coronary heart disease, Doppler spectrum analysis, familial hypercholesterolaemia, peripheral vascular disease.

Introduction

Familial hypercholesterolaemia (FH) is an autosomal dominant disorder caused by one of several mutations in the gene on chromosome 19 coding for the low-density lipoprotein (LDL) receptor [1, 2]. The disorder is characterized by elevated levels of LDL cholesterol, tendocutaneous xanthomata and premature coronary artery disease (CAD) [1]. Individuals homozygous for the genetic defect have extremely high serum cholesterol levels and they mostly develop CAD and peripheral vascular disease (PVD) in the first or second decade of life [1, 3]. Clinical manifestations of CAD in heterozygous subjects appear in over 50% prior to their fifties; men develop CAD in their third to fifth decade and women about 10 years later [4, 5]. In contrast, PVD seems to occur only at a slightly increased frequency and is considerably less prevalent than premature CAD [4, 6]. The prevalence of intermittent claudication in heterozygous FH has been reported as between 8 and 16% [7–10]. Nevertheless, the occurrence of bruits
The ankle/arm systolic pressure ratio has been found in 62–65% of asymptomatic heterozygous FH patients [10, 11]. Apparently, PVD in heterozygous FH is much more prevalent subclinically, only causing symptomatology in advanced cases [12, 13]. Sophisticated non-invasive ultrasonic Doppler techniques are now available to facilitate the diagnosis of PVD. The ankle/arm systolic pressure ratio at rest and during hyperaemia is a reproducible method to determine the presence of arterial insufficiency in the lower limbs [14]. To differentiate between haemodynamically significant stenotic segments located in the aorto-iliac or the femoro-tibial tract, measurement of ankle/arm systolic pressure ratio should be combined with the assessment of the haemodynamic status of the aorto-iliac tract. Usually, invasive intra-arterial pressure measurement in the common femoral artery in rest and during reactive hyperaemia are used to assess the functional status of the aorto-iliac tract (the "golden standard"). Several studies have shown that these invasive pressure measurements can be replaced by analysis of the blood flow velocities in the common femoral artery obtained non-invasively by Doppler spectrum measurements [12, 15]. This method has proven to be an accurate, non-invasive and easy-to-perform screening-test to assess functionally and haemodynamically significant stenosis in the aorto-iliac tract. Moreover, the performance of Doppler spectrum analyses during reactive hyperaemia has been shown to enhance the sensitivity to detect haemodynamically significant aorto-iliac pathology [16].

The present study was undertaken to determine the prevalence of PVD by non-invasive measurements of the ankle/arm systolic pressure ratio and a Doppler spectrum analysis of blood flow velocities in the common femoral artery, both at rest and during reactive hyperaemia, in heterozygous FH patients and matched normocholesterolemic control subjects. The presence of PVD will be related to lipids and lipoproteins, general risk factors, and the presence of CAD.

Materials and methods

Subjects

A consecutive series of 72 unrelated patients known to have definite heterozygous FH were recruited from the outpatient lipid clinic of the St Radboud University Hospital of Nijmegen, Nijmegen, The Netherlands, to which they had been referred by either general practitioners or hospital specialists. Four patients refused to take part in the study, one because of poor general health. The diagnosis of familial hypercholesterolaemia was based on the following criteria: LDL cholesterol above the ninety-fifth percentile for sex and age (in general > 8.0 mmol L⁻¹); the absence of a secondary hyperlipoproteinaemia; the presence of tendon xanthomata; signs or symptoms of CAD before the age of 55 in males or the age of 60 in females; and/or a first-degree family member with hypercholesterolaemia or tendon xanthomata or CAD before the age of 55 and 60 in males and females, respectively. The criteria for CAD were the presence of angina (history of exercise-associated chest pain), myocardial infarction (proven by electrocardiogram and/or serum enzyme changes), angiographically proven disease or a history of coronary artery bypass surgery. Hypertension was defined as systolic blood pressure > 160 mmHg and diastolic blood pressure > 90 mmHg in a supine position at rest. Patients with diabetes mellitus were excluded (fasting glucose > 6.0 mmol L⁻¹ and haemoglobin A₁C > 6.4%). The control subjects consisted of 27 volunteers from the same hospital, matched for gender, age, weight, presence of hypertension and smoking habits. They were selected on the basis of their serum total cholesterol levels (below 6.5 mmol L⁻¹), and the absence of systemic or metabolic diseases.

Information was recorded from 68 FH patients and 27 control subjects, including the presence of angina and intermittent claudication, details of past medical history, family history, smoking status, alcohol consumption, previous treatment for hyperlipoproteinaemia, and present use of drugs. Medical records of the FH patients were used for verification of this information, including previous lipid and lipoprotein levels. Vital signs were measured, the body mass index was calculated, and the presence of tendon xanthomata, xanthelasmas, arcus cornealis and peripheral pulsus were noted.

Lipid and lipoprotein measurements

Fasting concentrations of total cholesterol, serum triglycerides, high-density lipoprotein (HDL) cholesterol and LDL cholesterol were measured in both groups. For the FH group, mean levels of at least two measurements without lipid lowering treatment and four measurements during treatment, with intervals of 2–3 months, were recorded before the vascular measurements were taken. Lipoprotein(a) \([Lp(a)]\) levels were only measured during hypolipidemic drug treatment in the FH group. Serum total cholesterol and triglycerides were determined by enzymatic methods (CHOD-PAP, no. 237574, Boehringer Mannheim GmbH, Mannheim, FRG and Sera-PAK, no. 6639, Miles, Milan, Italy, respectively). HDL-C was determined using the polyethylene glycol 6000 precipitation method [17]. LDL-C was calculated by subtraction. \(Lp(a)\) was measured by a specific radio-immunoassay [apolipoprotein(a) RIA 100, Pharmacia Diagnostics AB, Uppsala, Sweden].

Doppler spectrum analysis and ankle/arm systolic pressure ratio measurement

In one session, blood flow velocities in the common femoral arteries and ankle/arm systolic pressure ratios of both limbs were recorded, both at rest and during reactive hyperaemia, as described earlier [16]. In short, Doppler signals were obtained from the common femoral artery with an 8 MHz bidirectional continuous-wave Doppler apparatus (Medasonics Inc., Mountain View, CA, USA). The probe was placed just below the inguinal ligament. Reactive hyperaemia was induced by thigh cuff compression for 5 min at a pressure of at least 50 mmHg above the systolic arterial thigh pressure. Doppler spectra during reactive hyperaemia were obtained approximately 15 s after relief of the thigh compression. Doppler signals were processed by a real-time spectrum analyser (Radionics SA8000; Scarborough, Ontario, Canada), and subsequently, digitally stored on a computer for off-line analysis. Maximum-frequency waveforms were calculated from the spectra and several parameters were calculated that describe the shape of the waveforms [18]. Based on a combination of six of these Doppler parameters [duration of the acceleration phase \((T_{max})\), slope of the deceleration phase \((S_{down})\), maximum frequency of receding curve \((F_{rec})\), and pulsatility index \((PI = F_{max} - F_{min}/F_{mean})\) of the at-rest spectra and duration of the acceleration phase \((T_{max})\) and resistance index \((RI = F_{max} - F_{diag}/F_{max})\) of the spectra during reactive hyperaemia], the presence of haemodynamic significant aorto-iliac pathology can be assessed accurately [16]. The same Doppler probe was used to determine the ankle/arm pressure index, using the systolic radial artery pressure and the highest pressure in either the dorsalis pedis or posterior tibial artery; the side with the highest radial artery systolic blood pressure at rest was used as the reference side for pressures during reactive hyperaemia. Haemodynamic significant vascular disease was defined as a ankle/arm pressure index at rest < 0.90 and/or a decrease of the pressure index during reactive hyperaemia ≥ 0.20.

Statistical analysis

Statistical analyses were performed with procedures available in the statistical package for social sciences (SPSS Inc., Chicago, IL, USA), using Student’s \(t\)-test or the Mann–Whitney U-test for differences in means, and the Yates’ corrected chi-squared test for differences in proportions. A \(P\)-value of less than 0.05 was considered to be significant. All results are expressed as mean ± SD, unless indicated otherwise.

Results

Subjects

A total of 68 patients (29 males and 39 females) with heterozygous FH and 27 control subjects (13 males and 14 females) were examined. The age distribution of the FH population was comparable to the control subjects (Fig. 1). The mean ages were 45.8 ± 11.6 years (range 22–68 years) for the FH patients and 44.0 ± 10.9 years (range 24–64 years) for the control group. The main cardiovascular risk factors are summarized in Table 1. No significant differences were found between the FH patients and the control subjects for the body mass index, smoking habits, alcohol consumption and hypertension. The presence of CAD in the FH population was significantly higher than in the control group, 44.1 versus 3.7%, respectively \((P < 0.001)\) (Table 1). Twelve FH patients had a myocardial infarction in the past and
Fig. 1 Age distribution in different cohorts (years) of patients with familial hypercholesterolaemia, with \((\text{FH}_{\text{pVn}+})\) ■, and without \((\text{FH}_{\text{pVn}-})\) □, peripheral vascular disease, and control subjects □.

Table 1 Characteristics of all patients with familial hypercholesterolaemia \((\text{FH}_{\text{TOTAL}})\), with \((\text{FH}_{\text{pVn}+})\) and without \((\text{FH}_{\text{pVn}-})\) peripheral vascular disease, and of control subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex (M/F)</th>
<th>Age (years)</th>
<th>BMI (kg m(^{-2}))</th>
<th>Smoking [n (%)]</th>
<th>Hypertension [n (%)]</th>
<th>MAP (mmHg)</th>
<th>Angina [n (%)]</th>
<th>ECG-changes [n (%)]</th>
<th>Claudication [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{FH}_{\text{TOTAL}})</td>
<td>29/39</td>
<td>45.8±11.6</td>
<td>24.7±3.1</td>
<td>25 (36.7)</td>
<td>7 (10.3)</td>
<td>96±11</td>
<td>24 (35.3)**</td>
<td>30 (44.1)**</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>(\text{FH}_{\text{pVn}+})</td>
<td>8/13</td>
<td>47.6±11.0</td>
<td>25.4±3.1</td>
<td>9 (42.8)</td>
<td>4 (19.0)</td>
<td>104±9***</td>
<td>11 (52.4)**</td>
<td>15 (71.4)***</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>(\text{FH}_{\text{pVn}-})</td>
<td>21/26</td>
<td>45.8±10.8</td>
<td>24.3±3.0</td>
<td>16 (64.0)</td>
<td>3 (6.4)</td>
<td>93±11</td>
<td>13 (55.9)</td>
<td>15 (31.9)</td>
<td>0</td>
</tr>
<tr>
<td>Controls</td>
<td>13/14</td>
<td>44.0±10.9</td>
<td>23.7±2.4</td>
<td>12 (44.4)</td>
<td>2 (7.4)</td>
<td>97±9</td>
<td>0</td>
<td>1 (3.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Values are means±SD or numbers (percentages); M/F, male/female; BMI, body mass index; MAP, mean arterial pressure (normal range 80–100 mmHg); differences versus control subjects: *0.001 ≤ P < 0.001; ** P < 0.001; differences versus \(\text{FH}_{\text{pVn}+}\): ***0.001 ≤ P < 0.001; **** P < 0.001.

10 had undergone coronary artery bypass surgery. One subject in the control group had a myocardial infarction in the past and was free from angina pectoris. The cumulative frequency of CAD in FH patients as a function of age of onset is shown in Fig. 2(a). The mean age of onset of CAD in the total FH group was 46.3±11.1 years (range 25–65 years, median 45 years), being 41.8±10.0 years and 53.2±9.1 years for men and women, respectively.

**Lipids and lipoproteins**

Without lipid lowering treatment, mean basal serum total cholesterol and LDL cholesterol levels in the FH group were strongly elevated (Table 2). HDL cholesterol concentrations were significantly lower and serum triglycerides did not differ in comparison to the control subjects. In the FH group, the mean Lp(a) level of 54.8±62.1 mg dL\(^{-1}\) (range
Table 2 Basal and treatment levels of lipids and lipoproteins, type and duration of lipid lowering treatment of all patients with familial hypercholesterolaemia (PH TOTAL, n = 68), with (PH PVD+, n = 21) and without (PH PVD-, n = 47) peripheral vascular disease, and of normocholesterolemic control subjects (n = 27).

<table>
<thead>
<tr>
<th>Group</th>
<th>Total cholesterol (mmol L⁻¹)</th>
<th>HDL-cholesterol (mmol L⁻¹)</th>
<th>LDL-cholesterol (mmol L⁻¹)</th>
<th>Triglycerides (mmol L⁻¹)</th>
<th>Lp(a) (mg dL⁻¹)</th>
<th>Medication (inhibitor/resin)</th>
<th>Treatment (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH TOTAL:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>basal</td>
<td>11.11 ± 1.84*</td>
<td>1.09 ± 0.32</td>
<td>9.19 ± 2.03</td>
<td>1.77 ± 0.73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment</td>
<td>7.35 ± 1.30*</td>
<td>1.17 ± 0.27</td>
<td>8.73 ± 2.08</td>
<td>1.84 ± 0.42</td>
<td></td>
<td></td>
<td>5.5 ± 3.7</td>
</tr>
<tr>
<td>PH PVD+:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>basal</td>
<td>11.37 ± 1.79</td>
<td>1.18 ± 0.33</td>
<td>8.73 ± 2.08</td>
<td>1.63 ± 0.67</td>
<td>50.3 ± 49.0</td>
<td></td>
<td>21/5</td>
</tr>
<tr>
<td>treatment</td>
<td>7.51 ± 1.32</td>
<td>1.26 ± 0.34</td>
<td>9.19 ± 2.09</td>
<td>1.75 ± 0.82</td>
<td></td>
<td></td>
<td>5.2 ± 3.2</td>
</tr>
<tr>
<td>PH PVD-:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>basal</td>
<td>10.93 ± 1.85</td>
<td>1.06 ± 0.33</td>
<td>9.19 ± 2.09</td>
<td>1.45 ± 0.61</td>
<td>57.0 ± 68.1</td>
<td></td>
<td>40/23</td>
</tr>
<tr>
<td>treatment</td>
<td>7.28 ± 1.28</td>
<td>1.15 ± 0.32</td>
<td>3.75 ± 1.30</td>
<td>1.61 ± 1.25</td>
<td></td>
<td></td>
<td>5.6 ± 3.9</td>
</tr>
<tr>
<td>Controls</td>
<td>5.79 ± 1.47</td>
<td>1.41 ± 0.40</td>
<td>3.75 ± 1.30</td>
<td>1.61 ± 1.25</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aValues are means ± SD; HDL-cholesterol, high-density lipoprotein cholesterol; Lp(a), Lipoprotein(a); inhibitor/resin, number of patients on HMG-CoA reductase inhibitors and/or resins, respectively; differences versus control subjects: *P < 0.001; no significant differences were found between PH PVD+ and PH PVD-.

Table 3 Prevalence of haemodynamically significant peripheral vascular disease (PVD) and Doppler spectrum waveform characteristics at rest and after reactive hyperaemia in patients with familial hypercholesterolaemia in comparison to normocholesterolaemic control subjects.

<table>
<thead>
<tr>
<th>Familial hypercholesterolaemia</th>
<th>PVD_{AI}</th>
<th>PVD_{FT}</th>
<th>PVD-</th>
<th>Controls†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>5 (7.4)</td>
<td>16 (23.5)</td>
<td>47 (69.1)</td>
<td>26 (96.3)</td>
</tr>
<tr>
<td>At rest</td>
<td>AAI</td>
<td>F_{max}</td>
<td>F_{min}</td>
<td>SI_{mean}</td>
</tr>
<tr>
<td></td>
<td>0.92±0.15*</td>
<td>4087±934*</td>
<td>-1314±991</td>
<td>-21±7*</td>
</tr>
<tr>
<td></td>
<td>0.93±0.12</td>
<td>7177±2645</td>
<td>-1622±405</td>
<td>-36±8</td>
</tr>
<tr>
<td></td>
<td>1.05±0.10</td>
<td>6909±2077</td>
<td>-1857±626</td>
<td>-33±13</td>
</tr>
<tr>
<td></td>
<td>1.09±0.12</td>
<td>6924±2496</td>
<td>-1827±630</td>
<td>-35±14</td>
</tr>
</tbody>
</table>

*Values are means±SD or numbers (percentages); PVD_{AI-}, aorto-iliac pathology; PVD_{FT-}, femoro-tibial pathology; PVD-, no peripheral vascular disease; AAI, ankle-arm pressure ratio; for explanation of Doppler parameters see 'Materials and methods' section.

†One patient with PVD is excluded. Differences versus FH_{FT-} and control subjects: *P < 0.01; **P < 0.001.

3.4–336.0 mg dL^{-1}, median 25.4 mg dL^{-1}) was higher than expected in normolipidaemic volunteers [19]. All FH patients were treated with lipid lowering drugs for a mean period of 5.5±3.7 years (range 0.6–15 years, median 4.7 years); 61 out of 68 (89.7%) patients were treated with a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (simvastatin or pravastatin), 28 out of 68 (41.2%) used a resin (cholestyramine or colestipol), and 21 out of 68 (30.9%) a combination of both groups of drugs (Table 2). During lipid-lowering treatment, the levels of total cholesterol, LDL cholesterol and HDL cholesterol in the FH group were still significantly different in comparison with the control subjects (Table 2).

Peripheral vascular disease

Vascular measurements were performed during lipid-lowering treatment. The ankle/arm pressure ratios at rest were 1.03±0.12 and 1.08±0.11 (P = 0.05), and 0.89±0.13 and 0.95±0.09 (P = 0.03) after reactive hyperaemia for all the FH patients and control subjects, respectively. One FH patient was known to suffer from intermittent claudication (a female; first symptoms at 38 years of age). Twenty-one out of 68 (30.9%, eight males and 13 females) FH patients had a pathological low ankle/arm systolic blood pressure ratio bilaterally or unilaterally (Table 3). In 39 out of 136 (28.6%) limbs, the pressure index was abnormal, so three patients exhibited a low ratio in only one leg. The patients with PVD were distributed equally within the different age groups (Fig. 1). The youngest patients with haemodynamically significant PVD were 31 years old (n = 3) and most patients were found in the 40–49-year-old age cohort. The mean age at which PVD was found for the total group, namely 47.2±11.0 years (range 31–64 years, median 47 years), was not different for men and women (47.8±12.4 and 46.8±10.6 years, respectively). The cumulative frequency of PVD as a function of the age of detection is shown in Fig. 2(b). The total frequency in the male population of 27.6% (8/29) was not significantly different when compared with 33.3% (13/39) in females.

Peripheral vascular disease was predominantly found in the femoro-tibial region in 16 out of 21 (76.2%) patients (Table 3). Eight of these 16 patients with a decreased ankle/arm index of < 0.90 and a normal Doppler spectrum were detected by measurements at rest, and the remaining eight patients had a decrease in the pressure index of ≥ 0.20 during reactive hyperaemia. Peripheral vascular disease in the aorto-iliac vessels, showing an abnormal Doppler spectrum of the femoral artery, was found in five out of 21 (23.8%) FH patients with a decreased ankle/arm index. Some parameters of the Doppler spectrum waveforms are shown in Table 3. Post-stenotic waveforms in patients with aorto-iliac pathology are
characterized by a decreased maximum frequency shift ($F_{max}$) and resistance index (RI), and an increase in the duration of the acceleration phase ($T_{max}$) [16, 20]. Only one out of 27 (3.7%, a female) control subjects had significant changes in the femoro-tibial tract, showing bilaterally pathological pressure indexes at rest and normal Doppler spectra. Comparison of the prevalence figures of PVD in the FH group and the control subjects showed significant differences, either expressed per patient ($P = 0.01$) or per limb ($P < 0.001$).

Characteristics of the FH patients with and without PVD are shown in Tables 1 and 2. No differences were found with regard to gender, age, body mass index, smoking habits, alcohol consumption, lipids levels (basal or during lipid lowering treatment), Lp(a) concentrations, and the duration and the type of administered lipid lowering drugs. Hypertension in the medical history of the FH patients with PVD was found more often. Only the mean arterial blood pressure before the vascular measurements was significantly higher in comparison with the patients without PVD: $104 \pm 9$ mmHg versus $93 \pm 11$ mmHg ($P < 0.001$), respectively. A tendency was observed in the FH patients with PVD to have more clinical symptoms of CAD (angina pectoris) than in those without PVD. Only ECG-changes at rest or during exercise tests had a significantly greater presence in the group with PVD: 71.4% versus 31.9% ($P = 0.006$), respectively. Thirty out of 68 (44.1%) of the total group of FH patients had CAD, 15 (50%) of whom had abnormal pressure indexes, whereas only six out of 38 (19%) patients without CAD had PVD. Therefore, the relative risk of finding haemodynamically significant PVD of the lower extremities in FH patients with signs or symptoms of CAD compared with FH patients without CAD is 3.17 (95%, confidence limits 1.40–7.17).

Discussion

Peripheral vascular disease in population studies is unequivocally associated with dyslipoproteinaemia [21, 22]. Our study addressed the question of the prevalence of PVD given the presence of well-defined FH. In FH populations, PVD has been reported in only 1.5% of cases as the first manifestation of vascular disease, whereas symptoms of CAD are the first feature in 94% [7]. In a prospective cohort study in subjects with heterozygous FH in England and Wales, a prevalence of intermittent claudication in the 40–59-year-old age group has been found in 8.8 and 9.7% of men and women, respectively [23]. In the present study, using non-Invasive measurements, haemodynamically significant lesions were present in approximately one out of three asymptomatic FH patients, and PVD was the first atherosclerotic manifestation in 19%. Of course, studies based on the detection of symptoms yield lower prevalence figures than those using non-invasive measurements, whereas the latter show intermediate figures when compared to studies using invasive angiographic methods [22, 24, 25].

The haemodynamically significant PVD prevalence figure of 31% seems lower than has been shown by others using pressure ratio index measurements [10, 11]. However, a higher cut-off point for a pathological ankle/arm pressure ratio index of < 0.97 has been used in these studies, and this may have overestimated the presence of PVD, since the use of a cut-off point of < 0.90 appears to be more predictive for significant obstruction [26].

In the past few years, there has been an increasing use of B-mode ultrasound in the assessment of atherosclerotic changes by measuring the intima-media thickness in the carotid and remoral artery [27, 28]. This method may show early atherosclerotic manifestations of the intima-media complex which will not interfere with flow in contrast with Doppler spectrum analysis. However, haemodynamically significant changes in blood flow are comparable for both methods: in a recent study using B-mode ultrasound assessment in patients with heterozygous FH, plaques causing haemodynamically significant changes in blood flow in the femoral artery were found in 14 out of 36 (39%) patients, a figure that is comparable to that found in the FH population of our study [28].

There is considerable variability in the clinical manifestation of patients with heterozygous FH [1]. The phenotypic expression may be influenced not only by differences in the underlying mutation, the apolipoprotein E phenotype, lipid and lipoprotein levels, and susceptibility to oxidative modification of LDL, but also by general risk factors such as gender, obesity, hypertension and smoking [5, 6, 29–32]. In our study, no significant differences between the FH patients with and without PVD were found with regard to lipid and lipoprotein levels and general risk factors, with the exception of a higher blood pressure...
before the vascular measurements. Therefore, moderate hypertension may have increased the risk of development of PVD in the group of FH patients we studied.

The present study also showed that PVD was mainly found in the femoro-tibial segments and less predominant affection of the proximal lower limb arteries in FH [10]. However, Rubba et al. have shown predominantly aorto-iliac pathology in FH using Doppler spectrum analysis of the common femoral artery at rest [33]. Using ultrasound methods as described in our study, only haemodynamically significant lesions (stenosis ≥ 50%) causing a decrease in arterial pressure or flow are documented, and addition of analyses during hyperaemia invariably increases the sensitivity of this method [16]. Therefore, the ultrasound measurements at rest of previous studies may have underestimated the presence of PVD. Since Doppler spectrum analysis at rest and during reactive hyperaemia accurately demonstrates the presence of aorto-iliac disease, even if atherosclerotic lesions of the femoral artery in multilevel occlusive disease exist, the presence of haemodynamically significant aorto-iliac pathology is probably not underestimated in our study [34]. Therefore, the primary predilection side of PVD in FH seems to be the proximal lower limb arteries or the femoral-popliteal segment. Generally, a comparison between the age of onset of symptoms of CAD and the age at which PVD was detected in this study is debatable. Still, CAD and PVD can be found only when haemodynamic significant atherosclerotic lesions are present. Indeed, manifestations of CAD can occur coexistent with PVD in FH patients [5, 11, 13, 25]. Our study showed that some patients develop CAD and PVD as early as the third decade of life, and that the mean age of onset of CAD was comparable to the mean age upon which PVD was detected (46 versus 47 years, respectively). Moreover, 50% of the patients with established CAD also exhibited PVD, whereas only 19% of the patients without CAD showed PVD. Therefore, these data show that there is a three-fold relative risk for (asymptomatic) PVD once a patient with heterozygous FH exhibits signs or symptoms of CAD.

In conclusion, haemodynamic significant PVD in patients with heterozygous FH is much more prevalent than is expected on clinical grounds, especially in those with CAD. Males and females are equally involved, and the preferential localization in the femoro-popliteal vessels was not related to the lipoprotein levels or general risk factors in this small group of patients, with the exception of hypertension.

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