Noninvasive Ultrasound Evaluation of Pressure Gradients in Aortic Root of Homozygotes for Familial Hypercholesterolemia

Fulvio Faccenda, Paolo Rubba, Agostino Gnasso, Paolo Pauciullo, Alfredo Postiglione, Claudio Cortese, and Mario Mancini

The aim of this study was to measure noninvasively by Doppler ultrasound the blood flow velocity at the level of the aortic root in patients with homozygous familial hypercholesterolemia (FH) to detect abnormal pressure gradients. Seven patients with homozygous FH and seven healthy controls matched for age and sex were included in the study. Continuous-wave Doppler (2 MHz) was used to measure the highest detectable velocity from the aortic root; the probe was positioned in the suprasternal notch. When an abnormal velocity was detected, the corresponding pressure drop was calculated from the formula: Delta P = 4Vmax^2. Each FH patient had an abnormal aortic velocity consistent with a pressure gradient across the valvular area. All the controls had normal aortic velocities (p < 0.01). The measurement of the pressure drop across the aortic valvular area in FH patients gives an estimate of the lesions produced by cholesterol deposition in a crucial area of the cardiovascular system near the origin of coronary arteries. The noninvasiveness of this method makes it an excellent method for obtaining parameters for follow-up and clinical trials. (Arteriosclerosis 10:710–713, September/October 1990)

Familial hypercholesterolemia (FH) is a metabolic disorder characterized by severe hypercholesterolemia and associated with premature and accelerated development of diffuse atherosclerosis. Coronary heart disease is the leading cause of death in patients with FH.1,2,3 Autopsies and angiographic and catheter studies4 have shown severe atherosclerotic lesions of the aorta and coronary arteries and a high prevalence of abnormal aortic pressure gradients in homozygous FH patients. Extracoronary lesions (in the carotids and lower limb arteries) are often detected in FH patients.5 While noninvasive methods have proved suitable and reliable in detecting and quantifying extracoronary arterial lesions and are sensitive enough to identify nonhemodynamically significant stenoses,5,6,7 no comparable methodology is available for coronary arteries.

FH patients show an accelerated cholesterol deposition at the origin of the aorta involving the aortic valve and the origin of coronary arteries.8 The degree of the resulting valvular stenosis might be used as an estimate of the aortic root involvement in a site that is near the origin of coronary arteries. Quantitative information concerning the severity of the lesions at this crucial anatomical site would be useful for better defining the cardiovascular prognosis and as an end point for follow-up studies evaluating cholesterol-lowering treatments.

Noninvasive Doppler ultrasound methods have been validated and are routinely utilized in the evaluation of patients with valvular heart disease.8,9,10 Stenoses cause an increase of blood flow velocity from which the pressure drop across the stenosis can be calculated.11 The aim of our study was to measure noninvasively by Doppler ultrasound the blood flow velocity across the aortic valvular area in homozygous FH patients so we could detect the prevalence and severity of abnormal pressure gradients.

Methods

Patients and Controls

Seven young patients (mean age 18 years, range 11 to 29 years) with homozygous FH and seven healthy controls matched for sex and age were included in the study. The diagnosis of homozygous FH was based upon the following criteria: 1) detection of plasma cholesterol above 600 mg/dl in a nonjaundiced child or young adult, 2) occurrence of tendon xanthomas before age 20, 3) evidence of vertical transmission of hypercholesterolemia. All the patients met these criteria. In three patients, the clinical and biochemical diagnosis was also supported by skin fibroblast cultures (one, receptor-negative; two, receptor-defective). Echo-Doppler examination of carotid arteries demonstrated carotid lesions in two of seven cases (in one patient the stenosis was >50%). Ankle pressure measurements with continuous-wave Doppler did not demonstrate abnormal values in any patient. No patient had Echo-Doppler abnormalities in the iliac arteries. Details of the diagnostic procedures used in the vascular examination have been reported.
Figure 1. Continuous-wave Doppler spectrum analysis of the aortic transvalvular flow obtained on a familial hypercholesterolemia patient. The increased $V_{\text{max}}$ (3.9 m/sec) is consistent with a pressure gradient of about 60 mm Hg between the left ventricle and the aorta.

All the patients had detectable systolic precordial murmurs. In patients O.M.G. and S.M.R., a catheter study performed about 1 year before the Doppler study had given the following values of aortic peak-to-peak pressure gradients: 41 mm Hg for O.M.G. and 96 mm Hg for S.M.R. The clinically healthy controls matched with the patients were children of administrative employees of the University of Naples. The patients and the controls gave their informed consent to the study.

Patient Lipid Therapy

All the patients had been on a fat-poor diet since the time of diagnosis. At the time of the aortic velocity measurement, six of seven patients had been without drug treatment for at least 1 month. One patient (R.G.) was taking Simvastatin. (Simvastatin is an inhibitor of hydroxy-methyl-glutary-CoA reductase produced by Merck Sharp and Dhome.)

Doppler Measurement of Aortic Flow Velocity

Continuous-wave Doppler with real-time spectrum analysis (Vingmed SD 100) was used to measure the maximum systolic flow velocity obtainable from the aortic valvular area and the ascending aorta. The probe (2 MHz) was placed on the suprasternal notch, directing the ultrasound beam towards the aortic valve: this “window” allows an approach almost parallel to the blood flow direction, which gives the maximum accuracy in velocity measurements. When the highest velocity was obtained, the real-time spectrum analysis was frozen on the oscillographic screen, and the maximum systolic velocity (m/sec) was automatically measured by a cursor. A permanent record was obtained from a printer (Mitsubishi Electric Europe GHBH, Ratingen, FRG, Figure 1). When velocity was abnormal according to standardized criteria, the corresponding pressure drop (maximal instantaneous difference) was calculated according to the following simplified formula derived from the Bernoulli principle:

$$\Delta P \text{ (mm Hg)} = 4 V_{\text{max}}^2 \text{ (m/sec)}$$

Other Methods

Blood samples were collected after a 12-hour fast. Serum cholesterol and triglyceride concentrations were measured enzymatically.

Height and weight were measured in patients and controls. Smoking habits and a history of angina, myocardial infarction, transient ischemic attacks, stroke, and intermittent claudication were investigated by questionnaires; two patients were found to have symptoms of angina pectoris. A rest electrocardiogram (ECG) was performed on patients and controls. Three patients had ECG evidence of left ventricular hypertrophy; in two of them, ST-T abnormalities were also present.

Statistical Analysis

The Wilcoxon rank sum test was used for comparing the FH patients and controls.

Results

Figure 2 summarizes the values of the maximum aortic velocity obtained in homozygous FH patients and in controls (calculated pressure gradients in mm Hg). *Normal upper limit.

Tables 2 and 3 show the main anthropometric, metabolic, and cardiovascular features of the patients.
Table 1. Cardiovascular Risk Factors, Anthropometric Data, and Aortic Blood Flow Velocities

<table>
<thead>
<tr>
<th></th>
<th>FH homozygotes</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>18±6</td>
<td>18±6</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>574±87a</td>
<td>178±28</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>88±34</td>
<td>62±12</td>
</tr>
<tr>
<td>Smokers (n)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>111±16</td>
<td>110±6</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>69±13</td>
<td>65±6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>152±14</td>
<td>151±13</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>43±13</td>
<td>51±21</td>
</tr>
<tr>
<td>Vmax (m/sec)</td>
<td>3.3±1.0a</td>
<td>1.2±0.2</td>
</tr>
</tbody>
</table>

Values are the means±SD.
*p<0.01 (2 a) for FH/controls.
TG=triglyceride, SBP=systolic blood pressure, DBP=diastolic blood pressure.

Among the four youngest patients (<18 years old), all were asymptomatic, with no Echo-Doppler evidence of iliac or carotid lesions and normal rest ECGs. Only one patient showed an aortic pressure gradient over 50 mm Hg. On the other hand, among the three patients older than 18 years, two had Echo-Doppler evidence of carotid artery lesions, all had ECG abnormalities (left ventricular hypertrophy and/or ST-T abnormalities), and two had aortic pressure gradients over 50 mm Hg. These were also the only two patients with a positive questionnaire for angina pectoris. O.M.G. and S.M.R. were both women of about the same age but with different receptor status (O.M.G. was receptor-negative, S.M.R. was receptor-deficient). The aortic pressure gradients were similar in these two patients, but carotid disease (bilateral) was detected only in the receptor-negative girl.

Discussion

The severity of the atherosclerotic involvement in the origin of the aorta was noninvasively evaluated in homozygous FH patients by continuous-wave Doppler ultrasound. The measurement of aortic transvalvular pressure gradient gives an estimate of the severity of the lesions in this area. In all seven homozygous FH patients, an abnormal pressure drop in the aortic root was demonstrated. This highly consistent finding confirms the concept of the hemodynamic relevance of cholesterol deposition in the area of the aortic root. The new finding is that a pressure gradient could be demonstrated in young patients without evidence of clinical disease. In this type of patient, an invasive catheter study is not thought to be indicated; therefore, the conditions of the aortic root are not known until clinical disease develops. The availability of a well-standardized and validated noninvasive method for pressure gradient determination offers the possibility of collecting information in asymptomatic patients. A thorough cardiovascular evaluation, including echocardiography and invasive procedures, may, of course, be indicated in an individual patient depending on the Doppler findings.

Clinical characterization before and during long-term follow-up should include the measurement of the aortic pressure drop to evaluate the prognostic value of this parameter.

The results of the present study were obtained by using a noninvasive Doppler method based on the Bernoulli principle: a stenotic lesion reduces the cross-sectional area of the arterial flow and causes an increased velocity. Because of the increase in kinetic energy associated with the acceleration of blood, there is a compensatory fall in potential energy or blood pressure. According to the Bernoulli principle and assuming that both the energy loss due to viscous effect and the velocity in the left ventricle are negligible, the following formula derives the pressure drop from the maximum systolic flow velocity:

$$\Delta P (\text{mm Hg}) = 4 \cdot \text{Vmax}^2 (\text{m/sec})$$

Continuous-wave Doppler with spectrum analysis allows accurate measurements of the maximum flow velocity. The parallel approach between the ultrasound beam and the flow direction obtained by investigating the aorta from the suprasternal notch minimizes the effects of the Doppler angle on velocity measurements. This single approach was chosen for the sake of better standardization and reproducibility in the view of serial examinations for follow-up studies. Validation studies have proved the reliability and accuracy of Doppler measurements of pressure drops versus catheter methods.

The present study applied this method for assessing patients with a disease in which the involvement of this crucial area of the cardiovascular system is peculiar. Although it is unlikely that these patients have overt valvular disease with heart failure, this method makes possible an evaluation of the severity of cholesterol deposition in the aortic root.

Table 2. Cardiovascular Risk Factors In Homozygous Familial Hypercholesterolemia Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Chol (mg/dl)</th>
<th>TG (mg/dl)</th>
<th>Receptor status</th>
<th>Smoking (cigs/day)</th>
<th>Wt (kg)</th>
<th>Ht (cm)</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RG</td>
<td>F</td>
<td>11</td>
<td>458</td>
<td>103</td>
<td>ND</td>
<td>0</td>
<td>25</td>
<td>133</td>
<td>90</td>
<td>60</td>
</tr>
<tr>
<td>MS</td>
<td>M</td>
<td>12</td>
<td>606</td>
<td>144</td>
<td>ND</td>
<td>0</td>
<td>32</td>
<td>137</td>
<td>106</td>
<td>64</td>
</tr>
<tr>
<td>AF</td>
<td>F</td>
<td>15</td>
<td>568</td>
<td>78</td>
<td>ND</td>
<td>0</td>
<td>35</td>
<td>140</td>
<td>114</td>
<td>60</td>
</tr>
<tr>
<td>MP</td>
<td>F</td>
<td>16</td>
<td>728</td>
<td>124</td>
<td>ND</td>
<td>0</td>
<td>52</td>
<td>168</td>
<td>96</td>
<td>68</td>
</tr>
<tr>
<td>OMG</td>
<td>F</td>
<td>19</td>
<td>553</td>
<td>48</td>
<td>Neg</td>
<td>0</td>
<td>50</td>
<td>160</td>
<td>126</td>
<td>60</td>
</tr>
<tr>
<td>SMR</td>
<td>F</td>
<td>22</td>
<td>637</td>
<td>45</td>
<td>Def</td>
<td>0</td>
<td>43</td>
<td>160</td>
<td>106</td>
<td>70</td>
</tr>
<tr>
<td>SL</td>
<td>M</td>
<td>29</td>
<td>469</td>
<td>76</td>
<td>Def</td>
<td>15</td>
<td>67</td>
<td>166</td>
<td>142</td>
<td>98</td>
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</tbody>
</table>

Chol=cholesterol, TG=triglyceride, Wt=weight, Ht=height, SBP=systolic blood pressure, DBP=diastolic blood pressure, Neg=negative, Def=defective, ND=not determined.
deposition near the origin of the coronaries. The noninvasivity of the method makes it an excellent way to arrive at parameters for follow-up and clinical trials that evaluate different lipid-lowering treatments.

The small number of patients in this study does not allow us to draw conclusions about the correlations between age and transaortic pressure gradient or between the severity of aortic involvement and other locations of cardiovascular lesions. However, the abnormal cardiovascular findings clustered in the three oldest patients, all of whom had ECG abnormalities; two had Echo-Doppler evidence of carotid lesions, and two had aortic pressure drops over 50 mm Hg. It is noteworthy that symptoms of angina were present in these two patients, suggesting that cholesterol deposition at the level of the aortic root may be related to the presence of ischemic symptoms in homozygous FH patients. Not surprisingly, the patients with the highest estimated intraventricular pressures were the same ones who had ECG evidence of left ventricular hypertrophy.

We now have this sensitive, noninvasive method and we know the high prevalence of abnormalities in persons who are homozygous for FH. Thus, studies on persons who are heterozygous for FH are now more than justified.

Acknowledgments

The authors are grateful to Merrill P. Spencer for introducing them to the fascinating area of cardiac Doppler ultrasound.

References


Table 3. Noninvasive Cardiovascular Findings in Homozygous Familial Hypercholesterolemia Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Aortic root* (mm Hg)</th>
<th>Intrav syst pressure† (mm Hg)</th>
<th>ECG</th>
<th>Int Car A stenosis</th>
<th>Vascular history</th>
</tr>
</thead>
<tbody>
<tr>
<td>RG</td>
<td>61</td>
<td>151</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MS</td>
<td>22</td>
<td>128</td>
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<td>AF</td>
<td>15</td>
<td>129</td>
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<td>MP</td>
<td>30</td>
<td>126</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMG</td>
<td>78</td>
<td>204</td>
<td>LVH; ST-T</td>
<td>16%-50%</td>
<td>Ang</td>
</tr>
<tr>
<td>SMR</td>
<td>86</td>
<td>192</td>
<td>LVH; ST-T</td>
<td>50%-80%</td>
<td></td>
</tr>
<tr>
<td>SL</td>
<td>35</td>
<td>201</td>
<td>LVH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Pressure drop.
†Estimated intraventricular systolic pressure (sum of systolic blood pressure+aortic pressure drop).
ECG=electrocardiogram, Int Car A=internal carotid artery, LVH=left ventricular hypertrophy, ST-T=abnormalities, Ang=angina.
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