Arterial Mechanical Changes in Children With Familial Hypercholesterolemia

Yacine Aggoun, Damien Bonnet, Daniel Sidi, Jean Philippe Girardet, Eric Brucker, Michel Polak, Michel E. Safar, Bernard I. Levy

Abstract—Atherosclerosis is preceded by a phase of changes in the arterial wall that could have functional consequences even before the appearance of atheromatous changes. We hypothesized that early alterations of the mechanical properties of the arterial wall could precede clinical and echographic modifications. We used an automatic, computerized, ultrasonic procedure to evaluate geometric and mechanical characteristics of the common carotid artery (CCA) in normotensive children with primary familial class IIA hypercholesterolemia (FH; n=30; mean±SD age, 11±2 years old; mean±SD systolic/diastolic blood pressure, 109±55/7 mm Hg). These subjects were compared with age-matched, nonobese control subjects (n=27; 11±3 years old; 112±10/55±7 mm Hg). Noninvasive ultrasonic measurements were performed by the same investigator to measure the CCA luminal systolic and diastolic diameters and intima-media thickness (IMT). The cross-sectional compliance, cross-sectional distensibility, and the incremental elastic modulus of the CCA wall were then calculated. Finally, we assessed the degree of reactive hyperemia in the brachial artery produced after distal cuff occlusion and release. The changes in brachial arterial diameter in response to reactive hyperemia (endothelium-dependent dilation) and to glyceryltriminitrate (endothelium-independent dilation) were then measured. In patients with FH, we observed a significant reduction of systodiastolic variations in diameter (by 20%, P<0.001) without a significant difference in IMT. Cross-sectional compliance and cross-sectional distensibility were significantly reduced in FH subjects (by 15%, P<0.05 and 19%, P<0.01, respectively). In parallel, the incremental elastic modulus was significantly increased (by 27%, P<0.01) in children with FH. No correlation was evident between the carotid incremental modulus and either IMT or plasma low density lipoprotein cholesterol level. There was no difference in diameter of the brachial artery at rest in control and FH subjects (3.0±0.5 versus 3.0±0.4 mm). The reactive hyperemia and glyceryltriminitrate dilation were also similar in the 2 groups. However, the flow-mediated dilation of the brachial artery was smaller in the FH subjects (4.2±2.9%) than in controls (9.0±3.1%, P<0.001). In FH, endothelium-dependent dilation was negatively correlated with the plasma low density lipoprotein cholesterol level (P<0.04). These results indicate that increased stiffness of the CCA wall in children with FH is independent of blood pressure and could be related to endothelial dysfunction. Thus, alterations in CCA wall mechanics could be early and easily measurable markers of atheromatous changes in the arterial wall. (Arterioscler Thromb Vasc Biol. 2000;20:2070-2075.)

Key Words: endothelium ■ flow-dependent dilation ■ arterial compliance

Hypercholesterolemia is a major risk factor for atherosclerosis. Overt atheroma, however, is preceded by a long “silent” phase of changes in the arterial wall. These preclinical alterations, including intima-media thickening (IMT), increased collagen fibrosis, and foam cell infiltration, are generally present at several sites in the arterial tree and seem indicative of overall (including coronary) atherosclerosis.1

In the early stage of hypercholesterolemia, endothelium function is modified and represents an early event in the natural history of vascular disease, in particular with impairment in endothelium-dependent relaxation, which has been recognized as an early abnormality.2–4 Indeed, nitric oxide (NO) is released by an increase in shear stress on the endothelial cell luminal surface as flow rises. Abnormalities in the reactivity of arteries, consisting of potential constriction and impaired relaxation, have been reported with hypercholesterolemia even in the absence of visible atherosclerotic lesions.5–7 In young patients (10 to 19 years old) with familial hypercholesterolemia (FH), the classic lipid and hemostatic risk factors as well as plasma total homocysteine are associated with echographic markers of early carotid atherosclerosis.8 We hypothesized that stiffening of large arteries could be an early marker of atherosclerosis, preceding IMT and the appearance of echographic plaques.
Therefore, the aim of the present study was to evaluate, by using an automatic, computerized, ultrasonic procedure, the geometric and mechanical properties of large arterial vessels in young children with FH. We chose the common carotid artery (CCA) because this vessel, which is close to the heart and rich in elastic fibers, is a representative site that enables evaluation of the “buffering” function of central arteries and contributes to the early stages of large-artery stiffening.9–11

Methods

Subjects

We performed this study in a homogeneous group of heterozygous FH male children (n = 30) and compared them with male normocholesterolemic controls (n = 27). Homozygous hypercholesterolemic children (n = 3) with documented major vascular lesions were excluded, because we focused on preclinical mechanical changes of the vessel wall. Normocholesterolemic controls (mean±SD age, 11.1±3.0 years) were normotensive (systolic/diastolic blood pressure, 112±10/55±7 mm Hg), nonobese (39±8 kg), and nondiabetic and had no clinical evidence of any disease.

Subjects with primary FH (mean±SD age, 11.1±2.0 years) were normotensive (systolic/diastolic blood pressure, 109±9/55±7 mm Hg), nonobese (40±6 kg), and nondiabetic and had no clinical evidence of cardiovascular, neurological, or renal diseases. The FH patients had class IIA hypercholesterolemia (Friederickson’s criteria). Diagnostic criteria for FH were (1) increased LDL cholesterol levels (>1.9 g/L), (2) eventual presence of xanthomas, and (3) a family history of hypercholesterolemia. Children with familial combined hyperlipoproteinemia, hypertriglyceridemia, familial chylomicronemia, dysbetalipoproteinemia, and secondary hyperlipoproteinemias were excluded from the present study.

All FH patients (n = 30) received dietary treatment, and 10 had taken cholesterol-lowering drugs for elevated LDL cholesterol levels, 5 took a bile acid sequestrant in doses of 4 to 8 g (cholestyramine), 4 were being treated with fenofibrate (lipanthy), and 1 patient received both cholestyramine and fenofibrate. The mean duration of treatment was 24±11 months (range, 6 to 36 months).

Laboratory Analysis

Plasma lipids were measured in venous blood samples obtained after an overnight fast. Serum total cholesterol and triglyceride values were measured by classic enzymatic methods. HDL cholesterol was measured by enzymatic methods after selective precipitation of LDL and VLDL by the phosphotungstic acid method.12,13 LDL cholesterol was calculated according to the classic formula of Friedewald et al:14

\[\text{LDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol} - (\text{triglycerides} / 5)\]

Protocol and Data Analysis

Examination of the subjects was performed at a controlled room temperature of 22±1°C. Blood pressure and heart rate were measured, after the subjects had been lying supine for 10 minutes, automatically by an oscilometric recorder (Dynamap model 8100, Critikon) on the left arm. Brachial systolic and diastolic blood pressures were used as an estimate of the carotid pressure at the moment of the echographic examination.

CCA Measurements

IMT Measurement

Noninvasive measurements were performed with a real-time, B-mode ultrasound measurement (Acuson XP 128). The right CCA was examined with a 7-MHz vascular probe as previously described.15,16 The IMT and lumen diameter measurements were performed in all subjects 1 to 2 cm proximal to the carotid bifurcation and along at least 1 cm of axial length. The same physician performed all measurements throughout the study (Y.A.). During scanning, the operator adjusted the sound beam perpendicular to the far wall of the vessel, thereby obtaining 2 parallel echogenic lines corresponding to the lumen intima-media and media-adventitia interfaces. The gain setting was adjusted to visualize 2D images for proximal and distal carotid walls: for each wall, 2 parallel line echoes were separated by a small, echo-free space. The IMT was measured between the 2 leading edges corresponding to the far wall of the CCA. Once these 2 parallel echogenic lines were clearly visible along at least 1.5 cm of the measured segment, the “frozen” end-diastolic (electrocardiographic R triggering) vessel image was transferred to a computer (Apple Macintosh 7100/80). Offline image analysis was then performed with an appropriate program (Iotec, IOQP System). This program is based on the analysis of gray-level densities and on specific tissue-recognition algorithms; it was used after a 3.63-fold magnification of the anatomic structure was examined. At first, the observer chose a region of interest that specifically included the far-wall IMT and drew a rectangle at least 1.5 cm long in the longitudinal axis of the vessel and at least 0.3 cm thick perpendicular to the wall. The computer located the 2 interfaces (lumen-intima and media-adventitia) by discriminating changes in gray levels inside the sample area and drew the 2 parallel lines representing these interfaces on the computer monitor. The average IMT obtained from the sample area represented the mean of at least 100 successive measurements of the distance between the 2 interfaces along 1.5 cm of artery.

Determination of Systolic and Diastolic CCA

Lumen Diameters

The sequence of B-mode images (50 frames/s) was stored by the computer for at least 5 cardiac cycles and then analyzed by frame (Iotec, IOQP). As for the IMT measurement, the proximal and distal walls were detected automatically by analyzing the mean gray-level profile of the frames. The relative displacement between gray-level profiles corresponding to consecutive frames was then measured. The diameter variations over at least 5 cardiac cycles as well as the synchronized electrocardiogram were visualized on the computer screen for visual agreement. The diastolic diameter was calculated as the mean of the minimal values of CCA lumen, corresponding to the R wave, for 5 consecutive cardiac cycles. In the same way, the systolic diameter was estimated as the mean of the maximal value of CCA lumen during the same cardiac cycles.

The following mechanical property parameters of the right CCA were measured or computed from echographic and pressure measurements: lumen diastolic diameter (dD), lumen systolic diameter (sD), absolute stroke change in diameter (∆dD = sD – ∆dD), relative stroke change in diameter (sD – dD/sD) or strain (ε), and end-diastolic IMT. The wall cross-sectional area (WCSA) was calculated as πR2, where R is the internal radius (Ri) plus IMT. WCSA is not influenced by blood pressure because of the incompressibility of the arterial mass,17 which remains constant during the whole cardiac cycle.

The relation between pressure changes (∆P) and volume changes (∆V) defines the compliance, C = ∆V/∆P. The cross-sectional compliance (CSC) was calculated from the formula

\[\text{CSC} = 2\pi sD (\Delta P / \Delta dD) \times (1 + \epsilon)\]

The incremental elastic modulus (E0, mm Hg), and the cross-sectional distensibility (CSD) was calculated from the pulsatile changes in diameters and pulsatile changes in pressure by using the formula

\[\text{CSD} = 2\pi sD (\Delta P / \Delta dD) \times (1 + \epsilon)\]

where PP is pulse pressure, defined by the stiffness of the carotid wall, was estimated by the formula

\[E0 = 3/2 \times \text{CSD} (1 - (1 - \gamma)^2)\]

where γ is the IMT/(Dd/2) ratio.19 Wall stress was calculated as the diastolic arterial pressure divided by γ (mm Hg).

Repeatability of Measurements

The examinations and all measurements (IMT and diameters) were performed by the same investigator in a blinded fashion, ie, without any information about the status of the subject (control or FH) during data acquisition and treatment. Series of paired measurements were compared and analyzed according to the recommendation of Bland and Altman.20 Repeatability of IMT and of systolic and diastolic diameters was investigated in 10 different subjects through calculation of a repeatability coefficient (RC),21 where

\[RC = \Sigma D^n / n\]

where n is the sample size and D is the difference between 2 measurements in a pair. This coefficient is the SD of the estimated difference between 2 repeated measurements. The RC values for intraobserver repeatability (comparison of 2 determinations separated by a 2-hour interval and obtained by the same observer)
Concerning IMT and diastolic and systolic diameters were 0.04, 0.2, and 0.15 mm, respectively, which were not statistically different from zero (Figure 1).

Assessment of Endothelial Function

Protocol

After at least 30 minutes of rest, arterial endothelial and smooth muscle function was studied with a high-resolution vascular ultrasound system as previously described. The right brachial artery was studied in all 30 FH and 27 control subjects. Changes in arterial diameter in response to reactive hyperemia (increased flow producing endothelium-dependent vasodilation) and to glyceryl trinitrate (GTN, an endothelium-independent vasodilator) were measured. The subject rested in the supine position for 10 minutes before the first scan and remained supine throughout the study. The target artery was scanned in a longitudinal section (for the brachial artery, 2 to 15 cm above the elbow), and the center of the vessel was identified when the clearest images of the anterior and posterior walls were obtained. The transmit zone was set to the level of the anterior vessel wall. Depth and gain settings were optimized to identify the lumen to vessel wall. Images were magnified with the resolution box function. The transmit zone was set to the level of the anterior vessel wall. Depth and gain settings were optimized to identify the lumen to vessel wall. Images were magnified with the resolution box function, leading to a television line width of ~0.065 mm. Machine settings were kept constant during each study. Arterial flow velocity was measured by mean of a pulsed-Doppler signal at a 60° angle to the vessel, with the range gate (1.5 mm) in the center of the artery. Flow increase was induced by inflation of a blood pressure cuff to 300 mm Hg. The cuff was released after 4 minutes, and the artery was scanned for 30 seconds before and for 90 seconds after cuff deflation, including a repeated flow velocity recording for 15 seconds after cuff deflation. Ten minutes later, a resting scan was recorded. GTN (400-μg spray) was then administered sublingually and the artery was scanned after 3 minutes.

Phantom studies reported in the literature and performed in our laboratory have confirmed that changes in diameter of as little as 0.1 mm can be detected accurately with this method. There is a low coefficient of variation for measurements of arterial diameter (inter-observer error) and a high correlation between consecutive control measurements within a study.

Data Analysis

Arterial diameters were measured from S-VHS videotape by 2 independent observers blinded to the scan sequence and the identity of the subject by using the same analysis device as for the CCA. Brachial diameters were measured from the anterior to the posterior interface between the media and adventitia (the “m line”) at a fixed distance from an anatomic marker. The mean diameter was calculated from 5 cardiac cycles incident with the R wave on the electrocardiogram. For the hyperemia scan, vessel diameter was measured 30 to 60 seconds after cuff release. Diameter changes were derived as percentage changes relative to the first scan. Baseline blood flow (measured during the first scan) was estimated by multiplying angle-corrected, pulsed-Doppler recordings of the flow velocity integral by heart rate and the square of the radius of the artery. Reactive hyperemia was calculated as the maximum flow measured during the first 15 seconds after cuff deflation divided by the baseline flow.

Statistical Analysis

Descriptive data are expressed as mean±SD. Comparison between groups was performed by 1-way ANOVA. Multivariable analysis was used to study the relationship between the E, age, mean blood pressure, and total cholesterol. The linear relationship between LDL cholesterol and the mechanical parameters of the CCA was studied by multivariate analysis. Statistical significance was considered for P<0.05.

Results

Table 1 shows anthropometric data and some biochemical characteristics in the 2 groups studied. There was no significant difference between the 2 groups in terms of age, weight, body surface area, blood pressure, and heart rate. Total and LDL cholesterol values were significantly higher in the FH than in the control group (P<0.0001). No subject from either group had atherosclerotic lesions as evidenced by careful

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<th>Table 1. Characteristics of FH and Control Subjects</th>
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BSA indicates body surface area; BMI, body mass index; SBP, DBP, systolic and diastolic blood pressures; PP, pulse pressure; and HR, heart rate. Values shown are mean±SD.

*P<0.0001.
analysis of B-mode images of the CCA walls. The subjects receiving treatment did not differ in age, height, and weight from the untreated subjects with FH (Table 2). Treated subjects had higher LDL and total cholesterol levels; however, carotid IMT and mechanical parameters did not significantly differ between treated and untreated subjects.

CCA Measurements
Table 3 reports anatomic and mechanical parameters of the CCA. WCSA was slightly (6%) but not significantly larger in FH than in controls (P=0.1). Systolic and diastolic carotid lumen diameters and IMT were not significantly different in the 2 groups. However, the systodiasstolic changes in carotid diameter (ΔD) were significantly lower in FH than in controls (by 20%, P=0.0003). CCA CSC and CSD values were significantly lower in the FH group (by 15% and 19%, respectively; P=0.02 and P=0.004). In parallel, the wall stiffness evaluated by Einc was larger in FH subjects than in controls (by 27%, P=0.003).

Brachial Artery Endothelial Function
There was no significant difference in resting diameters of the right brachial artery in control and FH subjects (3.0±0.4 versus 3.0±0.5 mm, respectively). The hyperemic response

| TABLE 2. Plasma Lipid Levels, Dimensions, and Mechanical Properties of the CCA in Treated and Untreated Subjects With FH |
|----------------------------------|-----------------|-----------------|
|                                  | Treated (n=10)  | Untreated (n=20) |
| Age, y                           | 11±2            | 11±3            |
| BMI, kg/m²                        | 31±2            | 31±2            |
| LDL cholesterol, mg/dL           | 250±66          | 215±63*         |
| Total cholesterol, mg/dL         | 301±53          | 250±55*         |
| IMT, mm                          | 0.51±0.03       | 0.52±0.03       |
| CSC, mm² - mm Hg⁻¹                | 0.14±0.02       | 0.13±0.03       |
| CSD, mm Hg⁻¹ · 10⁻²               | 0.67±0.10       | 0.60±0.10       |
| Einc, mm Hg · 10⁵                 | 1.6±0.4         | 1.8±0.6         |
| Wall stress, mm Hg · 10²          | 3.04±0.42       | 2.82±0.63       |

BMI indicates body mass index. Values shown are mean±SD. *P=0.05.

in the brachial artery, estimated as the maximal blood flow velocity (cm/s), was similar in FH and control subjects (143±25% versus 139±18%, NS). GTN induced (endothelium-independent) dilation of the brachial artery was similar in both groups (maximal diameter, 3.7±0.6 versus 3.6±0.4 mm in control and FH, respectively; NS). However, the flow-mediated dilation of the brachial artery (ie, dilation during the reactive hyperemic response given in percent values of the control diameter) was significantly impaired in the FH subjects (flow-mediated dilation of 9.0±3.1% versus 4.2±2.9%, P<0.001).

We did not find any correlation between Einc and IMT or plasma total or LDL cholesterol levels (Figure 2). In contrast, the flow-mediated dilation of the brachial artery was negatively correlated with the plasma LDL cholesterol level (r= −0.40, P=0.04; Figure 3).

| TABLE 3. Dimensions and Mechanical Properties of the CCA in Subjects With FH and Controls |
|----------------------------------|-----------------|-----------------|
|                                  | FH (n=30)       | Control (n=27)  |
| 6D, mm                           | 6.2±0.4         | 6.2±0.6         |
| dD, mm                           | 5.3±0.5         | 5.2±0.4         |
| ΔD, mm                           | 0.9±0.2‡        | 1.1±0.2         |
| ΔD/dD, %                         | 16±4‡           | 21±4            |
| WCSA, mm²                        | 9.5±1.1         | 9.0±1.2         |
| IMT, mm                          | 0.52±0.03       | 0.50±0.03       |
| CSC, mm² - mm Hg⁻¹               | 0.13±0.02*      | 0.16±0.05       |
| CSD, mm Hg⁻¹ · 10⁻²              | 0.62±0.15†      | 0.76±0.20       |
| Einc, mm Hg · 10⁵                | 1.74±0.50†      | 1.40±0.30       |
| Wall stress, mm Hg · 10²         | 2.90±0.60       | 2.81±0.50       |

See text for explanation of abbreviations. Values shown are mean±SD. *P<0.05; †P<0.01; ‡P<0.001.

Discussion
In this study, we have shown for the first time that the stiffness of the carotid wall was significantly increased in male children with heterozygous FH, independently of plasma LDL or total cholesterol levels. In the past, the mechanical properties of arteries were evaluated from the Moens-Korteweg equation, which usually assumes a thin
arterial wall. Thus, wall thickness was neglected in the calculation, and the results were presented mainly in terms of distensibility. During the last decade, noninvasive studies in various populations, mainly hypertensive subjects, have shown that wall thickness is important to consider. However, several limitations should be noted for the interpretation of the results. First, in the wall thickness measurements, it is difficult to differentiate between intima and media, so that only the combined intima-media thickness is determined. Second, the stiffness of the arterial wall is directly related to the degree of distension, ie, the level of blood pressure. Therefore, it is difficult to compare values obtained at different levels of blood pressure. In the present study, we highlight that for the same blood pressure and wall stress, children with hypercholesterolemia had a stiffer carotid arterial wall than did the healthy control population.

Structural changes of the CCA wall occur very early in atherosclerosis. Therefore, they might be responsible for changes in arterial stiffness. However, in the present study, we did not find evidence of any echographic atherosclerotic lesions. Furthermore, the young age of our FH subjects is not very compatible with an advanced sclerosis of the arterial wall.

Foam cells are likely to be present in early CCA alterations and are known to be mainly composed of soft material. Thus, it is difficult to attribute the arterial stiffening to accumulation of foam cells in the arterial wall. Owing to the coexistence of atherosclerosis and sclerosis, the latter is likely more involved in the alteration of arterial mechanical properties. This concept is supported by the absence of a correlation between CCA stiffness and plasma cholesterol and by the absence of a difference in wall thickness and mechanical characteristics of the CCA (compliance, distensibility, and $E_{\text{mac}}$) between treated and untreated subjects. However, the small number of treated subjects in the present study makes interpretation of this result difficult. Furthermore, the narrow range of LDL values could also statistically remove a correlation between the mechanical properties of the CCA and the plasma LDL concentration even if the overall relationship were strong. Alternatively, CCA stiffness may be related to LDL level but is cumulative over long periods of time and is not related to the current LDL level measured on the day that the echographic measurements were made. Additionally, we report herein apparently paradoxical higher values of LDL and total cholesterol in treated than in untreated subjects. This is likely due to the need for treatment of FH children with higher plasma lipid anomalies, whereas subjects with abnormal but lower cholesterol levels did not receive such treatment.

The endothelium, source of multiple vasoactive factors, is one of the major determinants of smooth muscle tone and thus, of the mechanical properties of the arterial wall. Endothelial function has been reported to be altered in children with FH. Our present results are in agreement with previous studies: the flow-mediated dilation of the brachial artery was higher in FH subjects (Figure 3), suggesting a link between LDL and impairment of the endothelium-dependent, flow-mediated dilation. In animal models, we have shown that an intact endothelium is required in vivo to achieve an adequate relationship between pulse pressure and diameter. Furthermore, NO donors are known to substantially alter the elasticity of large vessels, and their blockade in turn might favor arterial rigidity. The endothelium controls both smooth muscle tone and vascular wall remodeling. The mechanisms by which the endothelium controls vascular remodeling are not known, although several vasoactive molecules and growth factors have been implicated. NO produced by the endothelium is a likely candidate able to mediate vessel remodeling. Mechanical forces elicited by blood flow (shear stress) cause the acute release of NO and, after prolonged activation, induce endothelial NO synthase (eNOS) gene expression both in vitro and in vivo. NO is a potent vasodilator that inhibits extracellular matrix turnover and thus, could modify the mechanical properties of the arterial wall. In a high-flow rabbit model, we reported that pharmacological inhibition of NO release reduced the flow-dependent increase in carotid arterial diameter. In the same way, Rudic et al showed that in mice with targeted disruption of eNOS, the CCA did not remodel when subjected to a chronic increase in blood flow. In our present study, altered endothelium-dependent dilation observed in FH patients could be a consequence of altered eNOS function, which itself is responsible for alterations in arterial wall structure. The similar brachial artery diameter under rest (basal) conditions in both control subjects and hypercholesterolemic patients suggests that the endothelial dysfunction had no influence on the development of the brachial artery. However, markedly increased stiffness of the CCA could be due to altered extracellular matrix in FH patients.

In conclusion, we report that in children with FH, the CCA was stiffer than in control subjects matched for age and blood pressure. The stiffening of the CCA wall was not directly related to the plasma level of LDL or total cholesterol in FH children. Alterations in endothelial function and specifically, in flow-mediated arterial dilation, could account for altered vasomotor tone and/or arterial wall structure and therefore for properties of the large arteries.

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