Transthoracic Echocardiographic Assessment of Proximal Ascending Aorta Elasticity in Familial Heterozygous Hypercholesterolemia Patients

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Abstract

Background: Decreased elasticity of the aorta is associated with aging and several risk factors of atherosclerosis. The data regarding this phenomenon in patients with familial hypercholesterolemia are rather sparse.

Objectives: To evaluate non-invasively the elasticity of the proximal ascending aorta of 51 heterozygous FH patients compared to 42 normal age and gender-matched controls.

Methods: Aortic elasticity was estimated by transthoracic echocardiography using the "pressure-strain" elastic modulus and aortic strain formulas.

Results: The elastic modulus score was higher in the FH group than in the controls (1.12 $\pm$ 0.91 10^6 dynes/cm^2 vs. 0.65 $\pm$ 0.46 10^6 dynes/cm^2 respectively, P = 0.01). This was consistent in both the pediatric (0.5 $\pm$ 0.2 10^6 dynes/cm^2 vs. 0.4 $\pm$ 0.1 10^6 dynes/cm^2 respectively, P = 0.009) and adult subgroups (1.3 $\pm$ 1.0 10^6 dynes/cm^2 vs. 0.8 $\pm$ 0.5 10^6 dynes/cm^2 respectively, P = 0.0004). Aortic strain was significantly lower in patients with FH than in controls (6 $\pm$ 4% vs. 9 $\pm$ 5% respectively, P = 0.0002). These findings reflected decreased elasticity of the proximal ascending aorta in the FH patients. In multivariate analysis, age, serum cholesterol level and serum triglycerides level were the independent predictors of the elastic modulus score, whereas age was the predictor of aortic strain.

Conclusions: The elasticity of the proximal ascending aorta is decreased in heterozygous FH patients.

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Familial hypercholesterolemia is an autosomal dominant disorder characterized by an abnormally high serum level of low density lipoprotein due to congenital LDL receptor deficiency [1]. Heterozygous FH males have a probability higher than 50% of having a significant coronary artery disease by the sixth decade of life, compared to 30% in FH females [2]. Homozygous FH patients have a greater risk of premature coronary artery disease. In general, the aorta is one of the main targets of the atherosclerotic process, most frequently affecting the abdominal aorta. However, in homozygous FH, plaques affecting the aortic root are more common [3]. Beppu et al. [3] detected aortic valve calcification and atheromas of the proximal ascending aorta, leading to valvular and supravalvular aortic stenosis, in young homozygous FH patients.

FH = familial hypercholesterolemia
LDL = low density lipoprotein

Decreased aortic elasticity is known to be associated with advanced age, hypertension, menopause (in hypertensive women) and hypercholesterolemia [4–6]. The elasticity of the PAA can be assessed non-invasively by either echocardiography [5] or magnetic resonance imaging [7]. By indexing the aortic expansion during systole, aortic elasticity may be determined in terms of the observed distensibility. A strong correlation has been found between invasive and non-invasive methods of estimating aortic elasticity [8].

Only a few studies have investigated aortic elasticity in homogeneous groups of heterozygous FH patients [9,10]. The aim of the present study was to evaluate by transthoracic echocardiography the elasticity of the PAA in heterozygous FH patients compared to normal controls.

Patients and Methods

Study patients

The study group included 51 heterozygous FH patients (23 males, 28 females) who were under surveillance of the Lipid Clinic at Rabin Medical Center. The diagnosis of FH was based on the following clinical criteria: LDL-cholesterol level above the 90th percentile and the presence of xanthoma or a family history consistent with FH. All patients had been placed on a cholesterol-lowering diet. Thirty patients were receiving HMG-coenzyme A reductase inhibitors. Bile acid-binding resins were added in three patients and fibric acid derivatives in one.

The patients were divided by age into adult (> 18 years) and pediatric subgroups and were compared with 42 age-matched healthy volunteers who had no past history of hypercholesterolemia or other known risk factors of atherosclerosis. The levels of serum cholesterol were not available in the pediatric controls.

Echocardiography

All patients were studied by transthoracic color-Doppler echocardiography. A commercially available ultrasound system (SONOS 2000, Hewlett Packard, USA) was used. A cardiologist trained in echocardiography, who was blinded to the patient's diagnosis, evaluated every study. Supine blood pressure was measured in every patient at the beginning of the study.

PAA = proximal ascending aorta

Assessment of elasticity

The aortic sinotubular junction was traced in a 2D-parasternal long view. Its dimension was the distance between the trailing edge of the echogenic line in the near wall of the aorta to the leading edge on the far wall. Measurements were done in diastole (minimal diameter) (Aod) and systole (maximal diameter) (Aos). The timing of diastole and systole was correlated with the simultaneous ECG recording. Three cardiac cycles were averaged for analysis. The elasticity of the proximal aorta was estimated by two indices [6]:

- Peterson's "pressure-strain" elastic modulus (Ep):

  (Pulse pressure) x (Aod)/(Aos-Aod) 10^6 dynes/cm^2

  This formula expresses the magnitude of stress required to produce a given strain *in vitro*. *In vivo*, it reflects the arterial elastic properties when there is a linear stress-strain relationship during blood pressure variations.
- Percentage of change in sinotubular diameter between systole to diastole (aortic strain):

  (Aos-Aod) x 100/ Aos

  Decreased elasticity was associated with increased Ep value and decreased aortic strain value.

Statistical analysis

Descriptive baseline characteristics were summarized by frequencies and percentages or by mean values and standard deviations. Comparisons of continuous variables between groups were done with Student's unpaired two-tailed *t*-test. Frequency of proportions was compared by a chi-square test. A P value $\leqslant 0.05$ was considered significant. A multivariate analysis was formulated to predict Ep and aortic strain using the following independent variables: age, gender, systolic blood pressure, and serum level of cholesterol, LDL and triglycerides. Statistical analyses were done with the RS1 statistical package (Bolt, Beranek and Newman, 1993).

Variability

The reproducibility of the sinotubular diameter measurements was determined by having 10 randomly selected recordings from each group remeasured by a different observer (interobserver) and the same observer (intraobserver) on separate occasions. Variability was expressed as the standard deviation of the differences divided by the mean value.

Results

The adult and the pediatric FH subgroup included 36 patients (15 males, 21 females) and 15 patients (8 males, 7 females), respectively (P = NS regarding male to female ratio in FH vs. control and the various subgroups). The adult subgroup included 37 FH patients and 31 controls (age 43 $\pm$ 15 years vs. 38 $\pm$ 12 years, respectively, P = NS). The pediatric subgroup included 15 FH patients and 11 controls (age 9 $\pm$ 4 vs. 10 $\pm$ 5 years, respectively, P = NS). The characteristics of the two studied groups are shown in Table 1. Mean pretreatment serum cholesterol level was 364 $\pm$ 81 mg/dl in the whole FH group, 394 $\pm$ 69 mg/dl in the adult subgroup, and 285 $\pm$ 52 mg/dl in the pediatric subgroup. Serum cholesterol level was significantly lower in adult controls than in FH adults (180 $\pm$ 36 vs. 394 $\pm$ 69 mg/dl) (P = 0.001). Symptomatic coronary heart disease was present in only eight FH adults vs. none in adult controls (P = 0.007). Six FH patients had hypertension and one patient had non-insulin dependent diabetes mellitus (all adults). Both groups had similar rates of smoking.

Table 1. Characteristics of patients and control groups (adults and children)

	FH (n=51)	Control (n=42)	*P* value
Age (yr): Mean	33 $\pm$ 20	31 $\pm$ 16	NS
Range	2–70	4–65	NS
Gender (M/F)	23/28	21/21	NS
Systolic blood pressure (mmHg)	116 $\pm$ 21	114 $\pm$ 19	NS
Diastolic blood pressure (mmHg)	74 $\pm$ 12	73 $\pm$ 12	NS
Pulse pressure (mmHg)	42 $\pm$ 15	39 $\pm$ 10	NS
Aos (mm)*	25.2 $\pm$ 5.5	26.5 $\pm$ 5.4	NS
Aod (mm)**	23.8 $\pm$ 5.4	24.4 $\pm$ 5.4	NS
Aos-Aod (mm)	0.13 $\pm$ 0.08	0.22 $\pm$ 0.08	0.0001
Aortic valve calcification	17	4	0.001
Mitral annulus calcification	7	0	0.001
Coronary heart disease	8	0	0.007
Aortic regurgitation	16	3	0.004
Hypertension	6	0	0.02
Diabetes mellitus	1	0	NS
Smoking	2	2	NS

* Aos = sinotubular junction in systole

** Aod = sinotubular junction in diastole

Significant differences were found in the incidences of mitral annulus calcification (7 adult FH vs. none in the controls, P = 0.001), aortic valve calcification (17 adult FH patients vs. 4 adult controls, P = 0.001), and aortic regurgitation (16 FH patients: 15 minimal to mild and one moderate vs. 3 controls; all of them were minimal, P = 0.004). Three of the FH patients with aortic regurgitation were children, aged 3, 5 and 11 years (all of them in minimal grade), whereas all the controls with aortic regurgitation were adults. None of the FH patients had aortic valvular or supravalvular stenosis. Left ventricular dimension and systolic function were normal in both groups. Interobserver variability regarding the systolic and diastolic sinotubular dimensions were 2.6% and 2.8%, respectively. The intraobserver variability was 2.6% and 4.5%, respectively.

The Ep score of the whole FH group was higher than that of the controls: 1.12 $\pm$ 0.91 10^6 dynes/cm^2 vs. 0.65 $\pm$ 0.46 10^6 dynes/cm^2 (P = 0.01) [Figure 1]. This difference was present in both adult and pediatric subgroups [Table 2]. Smaller expansion of the sinotubular junction from diastole to systole in the FH group (P = 0.0001) was the cause of difference in Ep score between the two groups [Table 1]. Aortic strain was lower in the FH group than in the controls: 6 $\pm$ 4 vs. 9 $\pm$ 5% (P = 0.0002) [Figure 2], and lower in the adult and in the pediatric FH subgroups [Table 2].

Multivariate analysis (for the entire group) identified age (P = 0.004), serum level of cholesterol (P = 0.05) and triglycerides (P = 0.03) as independent predictors of Ep score in FH patients. Age was the only predictor of aortic strain in FH patients (P = 0.01).

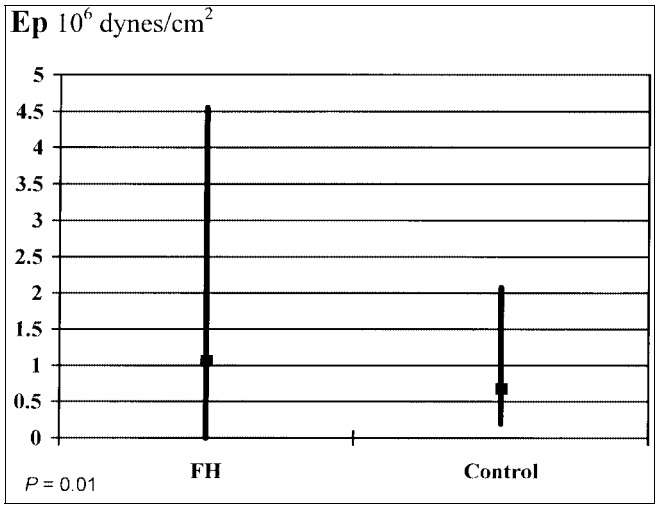

Figure 1. Ep score in FH and control groups (minimum, maximum and mean values)

Table 2. Elastic modulus (Ep) and aortic strain in the various subgroups

		Ep (10^6 dynes\cm^2)	*P* value	Aortic strain (%)	*P* value
Pediatric	FH	0.5±0.2		8±4	
group	Control	0.4±0.1	0.009	12±5	0.0002
Adult	FH	1.3±1.0		5±3	
group	Control	0.8±0.5	0.0004	9±5	0.0001
All	FH	1.1±0.9		6±4	
patients	Control	0.6±0.5	0.01	9±5	0.002

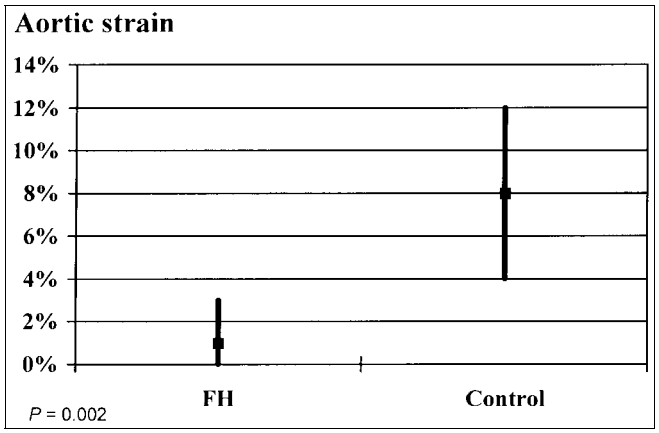

Figure 2. Aortic strain in FH and control groups (minimum, maximum and mean values)

Discussion

This is the first controlled study to evaluate the echocardiographic features of a large group of heterozygous FH patients, including a large group of children. The results show that the elasticity of the PAA is decreased in heterozygous FH patients since early childhood.

Familial hypercholesterolemia is a major independent risk factor of atherosclerotic cardiovascular disease. Atheromatous plaques in the aortic root are a typical finding, sometimes accounting for supravalvular aortic stenosis and ostial lesions of the coronary arteries [3]. Several factors are known to influence aortic elasticity, such as aging [11], hypertension [12], connective tissue abnormalities [13] and hypercholesterolemia [10].

The findings of our study are supported by previous studies that showed decreased aortic elasticity among FH adult patients [6,10]. The change in aortic elasticity in these studies appeared even when the intimal thickness was still normal or mildly increased [6]. Furthermore, the FH patients had a steeper decline in aortic elasticity with advanced age compared to the controls. The decreased elasticity was well correlated with the progression of atherosclerotic lesions [14,15]. Nevertheless, this issue is not consensual, as was shown by Dart et al. [5] who assessed the elasticity of the aortic arch by transthoracic echocardiography in adult patients with hypercholesterolemia and found that aortic elasticity was higher in asymptomatic patients with hypercholesterolemia than in age-matched controls.

One of the remarkable findings in the present study was that aortic elasticity in FH was decreased already in childhood. The association between hypercholesterolemia at a young age and changes in aortic elasticity is still controversial. Lehmann et al. [9] found better compliance of the aorta in 20 young heterozygous FH patients (mean age 15 ± 5.8 years) compared to controls. In contrast, Iannuzzi et al. [15] showed an increase in age-dependent aortic stiffness in 67 children with hypercholesterolemia (age 3–14 years). Recently, Leeson and colleagaues [16] studied brachial artery elasticity in 361 children aged 9–11 and showed a significant, inverse relation between serum cholesterol level (total cholesterol, LDL and apolipoprotein B respectively) and arterial elasticity. This indicates that arterial elasticity may be influenced by serum cholesterol level as early as the first decade of life.

A possible mechanism for the influence of hypercholesterolemia on aortic elasticity is via induction of endothelial dysfunction. The importance of the action of endothelial relaxing factor in the regulation of vascular tone is well established, and there is firm evidence of the induction of endothelial vasomotor dysfunction by hypercholesterolemia [17–20]. Controlled studies have shown improved coronary endothelial vasomotor function following aggressive medical treatment aimed at lowering LDL-cholesterol level [21,22]. Tomochika et al. [6] reported a regression in atherosclerotic lesions of the thoracic aorta with diet and cholesterol-lowering drugs in FH patients. Following treatment, the elasticity of the thoracic aorta was also improved. Animal studies have shown reduction in arterial elasticity even in the presence of fatty streaks, prior to other pathophysiologic changes [23]. Benzuly and co-workers [24] showed that improvement in endothelial vasomotor function following treatment preceded structural regression. These data indicate that in young patients, endothelial vasomotor dysfunction may be the mechanism affecting aortic elasticity before the appearance of overt atherosclerotic plaques.

Instead of the invasive measurement of aortic pressure required for the Ep calculation [8], we used the common non-invasive measurement of the brachial artery blood pressure. Despite its limitation, Imura et al. [25] have demonstrated that both methods are highly correlated for the calculation of Ep.

In conclusion, this study shows that heterozygous FH patients, of various ages, are at risk of decreased elasticity of the PAA. This can be easily detected non-invasively by transthoracic echocardiography. Echocardiography can be used from the early stages of life for the detection of this atherosclerotic manifestation.

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