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Original Article

Cardio-Ankle Vascular Index in Heterozygous Familial Hypercholesterolemia

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***Aim*: The cardio-ankle vascular index (CAVI) is a new non-invasive marker of arterial stiffness and atherosclerosis. The purpose of this study was to compare CAVI in patients with heterozygous familial hypercholesterolemia (FH) and in healthy controls.**
***Methods*: 82 FH subjects (27 males, 65 females), aged 53.7 ± 13.6 years without clinical symptoms of cardiovascular diseases and 359 healthy controls (121 males, 238 females), aged 43.9 ± 14.9 years, were examined. CAVI was measured using the system VaSera® 1500.**
***Results*: CAVI in FH patients was significantly higher (8.0 ± 1.4) than in healthy subjects (7.5 ± 1.3) $p = 0.002$; however, age, sex and BMI adjusted CAVI did not differ significantly ($p = 0.061$) between the FH group (7.5, CI: 7.3; 7.7) and control group (7.7, CI: 7.6; 7.7).**
***Conclusion*: The study showed no significant difference in CAVI between heterozygous FH and healthy controls.**

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Key words; Atherosclerosis, Cardio-ankle vascular index, Familial hypercholesterolemia, Statins, Ezetimibe

Introduction

Major causes of death in developed countries are cardiovascular and cerebrovascular diseases, which arise from the progress of atherosclerosis in certain arteries. Atherosclerosis is a chronic disease that develops over many years and usually does not cause symptoms, until its severity narrows the artery, or until it causes a sudden obstruction. A very important aspect of atherosclerosis is that its progression may be stopped or even reversed by clinical intervention. For example, aggressive lowering of elevated cholesterol levels leads to a reduction in both the physical extent of atherosclerosis and the incidence of coronary artery disease (CAD) and stroke[1-3]; therefore, it is very important to detect atherosclerotic changes early in order to prevent future clinical cardiovascular events more effectively. For this purpose, a simple, quantitative and non-invasive assessment of early stages of atherosclerosis is required. Several methods for the evaluation of

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Table 1. Diagnostic criteria for familial hypercholesterolemia[27]

Age	Total cholesterol (LDL-cholesterol) cut-off points (mmol/L)			
Age (years)	First-degree relative with FH	Second-degree relative with FH	Third-degree relative with FH	General population
< 20	5,7 (4,0)	5,9 (4,3)	6,2 (4,4)	7,0 (5,2)
20-29	6,2 (4,4)	6,5 (4,7)	6,7 (4,8)	7,5 (5,7)
30-39	7,0 (4,9)	7,2 (5,2)	7,5 (5,4)	8,8 (6,2)
40 +	7,5 (5,3)	7,8 (5,6)	8,0 (5,8)	9,3 (6,7)

A diagnosis of FH is made if cholesterol levels exceed the cut-off point. FH: familial hypercholesterolemia

arteriosclerosis have been introduced. Among them, high-resolution B-mode ultrasonography serves for the measurement of carotid intima-media thickness, a strong predictor of cardiovascular events[4-6]. Another widely used non-invasive method for the detection of atherosclerosis is the measurement of large artery stiffness. A very useful method for arterial stiffness evaluation is arterial pulse-wave velocity (PWV) measurement[7, 8]. PWV enables to detect arteriosclerosis in any part of the body and brachial-ankle PWV has been widely used to detect early stages of arteriosclerosis[9-11]. Brachial-ankle PWV has been shown to be a predictor of coronary artery disease and serves for the prognosis of acute coronary syndrome[10, 12]; however, there are several problems with its use in clinical practice. PWV measurement is rather technically difficult, its reproducibility is low and it is age-dependent and blood pressure-dependent; thus, the results are affected also by changes in BP during measurement[13, 14], which is why another simple quantitative index for the early diagnosis of atherosclerosis was required. Recently, a new method for the atherosclerosis index (cardio-ankle vascular index - CAVI) was introduced[14]. CAVI is adjusted for blood pressure based on stiffness parameter beta. The measurement of CAVI is not affected by changes in blood pressure during measurement[15], so CAVI is a pressure-independent index indicating the natural stiffness of the blood vessels, based on the stiffness parameter β[14, 16]. It is a marker suitable for atherosclerosis estimation in various arteries, including the femoral artery, aorta and tibial artery[17]. Several studies have shown the usefulness of CAVI for the detection of atherosclerosis[18-22]. The results of CAVI measurement have been reported in patients with various cardiovascular risk factors, such as obesity and metabolic syndrome[23], essential hypertension[20], diabetes mellitus[24, 25], and smoking[26]; however, no study has yet investigated CAVI in patients with inherent hyperlipoproteinemia, primarily in familial hypercholesterolemia (FH).

Aim

The aim of this study was to determine whether CAVI differs in patients with heterozygous FH as compared to healthy controls.

Methods

Patient Groups

The studied population consisted of 82 subjects with FH aged 18 and above from the Outpatients Department for lipid disorders, who underwent regular control examination between January 2010 and November 2010. Diagnostic criteria for FH were consistent with international criteria and were based on those of the US MEDPED program and publication of Williams *et al.*[27, 28]: FH was diagnosed when the cut-off values for total cholesterol as well as LDL-cholesterol exceeded the values given in **Table 1**. All FH patients were examined by molecular-biologic methods: firstly, gene for apolipoprotein B (p.Arg3500Gln mutation) was analyzed, and then analysis of the gene for LDL-receptor was performed in those patients, who had no mutation of the gene for apolipoprotein B. Mutation p.Arg3500Gln in the gene for apolipoprotein B was found in 20 patients (24,1%), and mutation in the gene for LDL-receptor in 36 patients (43%). Detailed information on the methods and procedures used for analysis of the LDL-receptor gene and the gene for apolipoprotein B were published recently[29, 30]. In all patients, the causes of secondary hypercholesterolemia (e.g. hypothyroidism, renal disease, and liver disease) were excluded.

All patients with heterozygous FH without arteriosclerotic signs (no clinical symptoms and no cardiovascular diseases in history) were included in this study. All patients with previous stroke or transient ischemic attack, previous angina pectoris or myocardial infarction, documented chronic ischemic heart disease, peripheral artery disease, cardiomyopathy or sig-

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nificant valvular disease, arrhythmia and also patients with renal or heart failure were excluded from the study. All FH patients were treated with hypolipidemic drugs (statins or combination statin + ezetimibe).

The control group consisted of 359 healthy subjects aged from 20 to 79 years. All subjects included in the control group were examined by a general practitioner and sent for CAVI examination if they fulfilled the following criteria: blood pressure <140/90 torr; glycemia <6.0 mmol/L; total cholesterol <5.0 mmol/L; personal history without cardiovascular diseases, hypertension, hyperlipidemia, diabetes mellitus, renal diseases and gout. All subjects in the control group had physiological ECG. All subjects in this study (FH group as well as control group) were Caucasian and of Slavic origin.

The study was approved by the ethics committee of St. Anne's Faculty Hospital Brno and written informed consent was obtained from the participants in the study at the beginning of the study. Informed consent was also obtained from all FH patients for genetic analysis.

Anthropometric Indices

Height and weight were measured by trained staff; BMI was calculated as weight (kg)/height squared (m^2).

Biomedical Markers

Blood pressure was measured twice (in a sitting position): once in the waiting room upon arrival and again after at least 10 minutes of rest, and the mean was calculated. Blood samples were taken in the morning after 8-10 hours of fasting, 1-2 weeks before CAVI measurement; they were sent to the laboratory for analysis within half an hour after collection. All laboratory tests were carried out in the same laboratory. Serum lipid and lipoprotein analyses were performed on an ADVIA 1650 analyzer (Siemens, Germany) with commercially available kits: total cholesterol and triglycerides were assayed by the enzymatic colorimetric method (Roche Diagnostic GmBH), HDL-cholesterol was assessed by the homogenous method for direct measurement without precipitation (Sekisui Medical, Tokyo), and LDL-cholesterol was calculated according to the Friedewald equation[31].

CAVI Measurement

CAVI was measured using the system VaSera® 1500 (Fukuda Denshi Co., Tokyo, Japan), adopting the oscillometric method for blood pressure measurement. It does not simultaneously measure blood pressure in 4 limbs but first measures at the right brachial and ankle and then at the left brachial and ankle. Thus, arteries on the right and left sides are alternately pressurized with the other side open. This procedure does not only reduce the burden on examinees but also enables more accurate measurement. The CAVI calculation is based on stiffness parameter β obtained by means of the Bramwell-Hill equation[14, 32]:

$CAVI = (\ln Ps/Pd) \times 2\rho/\Delta P \times PWV^2$, where Ps and Pd are systolic and diastolic blood pressures, respectively; PWV is the pulse wave velocity between the heart and ankle; ρ is blood density; and ΔP is pulse pressure.

The CAVI was measured by trained staff, with the participant resting in a supine position and the head held in a midline position. ECG and phonocardiography were monitored during the measurement. In order to limit the influence of diurnal variations, all subjects were always examined at the same time, 8:00-11:00 AM. The examination was conducted in a quiet room and at a stable temperature of 21-22℃.

Statistics

The characteristics of the subjects were described by the proportions for categorical variables and the mean (and SD) of continuous variables. Between-group comparisons of proportions and means were conducted by Fisher's exact test and the unpaired *t*-test. Spearman's rank correlation was computed to assess the relationship between CAVI and age or BMI. Analysis of covariance was used to adjust for age, sex, and BMI in the comparisons of CAVI and blood pressure. Statistical analyses were performed using SPSS 19.0.1 (IBM Corporation, 2010).

Results

Basic characteristics of the study populations and non-adjusted blood pressure and CAVI values are shown in **Table 2**. FH patients were older than healthy controls ($p<0.001$). FH patients have significantly higher systolic blood pressure, ($p=0.012$), diastolic blood pressure ($p=0.031$) and BMI ($p=0.016$). No statistically significant difference in the proportion of men/women was found ($p=1.000$). CAVI was significantly higher in the FH group than in the control group ($p=0,002$).

All FH patients were treated with hypolipidemic drugs - statins or combination statin with ezetimibe; the period from treatment onset to the CAVI measurement was 9.2 ± 4.2 years (mean ± SD). The generic names of the statins, mean dose and number of patients treated with particular drugs are shown in **Table 3**, plasma lipids in patients before treatment with

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Table 2. Baseline characteristics of patients with heterozygous familial hypercholesterolemia and control group

	Familial hypercholesterolemia ($N=82$)	Control group ($N=359$)	p^*
Male †	27 (32.9%)	121 (33.7%)	1.000
Age § (years)	53.7 ± 13.6	43.9 ± 14.9	< 0.001
BMI § (kg/m^2)	26.0 ± 3.9	24.8 ± 4.2	0.016
Systolic BP § (mmHg)	132.0 ± 12.8	127.3 ± 15.8	0.012
Diastolic BP § (mmHg)	80.4 ± 8.6	77.9 ± 9.7	0.031
CAVI §	8.0 ± 1.4	7.5 ± 1.3	0.002

CAVI: cardio-ankle vascular index; BP: blood pressure; BMI: body mass index
†Number and percentage of categorical variables; §mean ± SD of continuous variables;
*Fisher's exact test was used for testing the statistical significance of differences in categories, *T*-test was used to test the statistical significance of differences in the distribution of continuous variables.

Table 3. Summary of the treatment of patients with familial hypercholesterolemia (generic name of the statins, their dose, combination with ezetimibe)

	Number of patients treated by statin monotherapy	Dose of statins (mg)	Number of patients treated by combination of statin with ezetimibe 10 mg *N* (%)
Simvastatin	10	36.4 ± 16.7	8 (80)
Fluvastatin	3	80.0 ± 0.0	2 (67)
Atorvastatin	45	40.9 ± 20.2	27 (60)
Rosuvastatin	24	33.3 ± 9.43	5 (21)
Total	82	40.9 ± 20.1	42 (51)

The dose of statins is given as the mean ± SD

Table 4. Blood lipids in patients with FH before therapy and during therapy with statins at the time of CAVI examination

	Baseline (without statin treatment)	At the time of CAVI measurement (with statin treatment)	P
Total cholesterol (mmol/L)	9.55 ± 1.86	6.22 ± 1.51	< 0.001
LDL-cholesterol (mmol/L)	7.13 ± 1.78	4.05 ± 1.33	< 0.001
HDL-cholesterol (mmol/L)	1.65 ± 0.45	1.60 ± 0.42	0.366
Triglycerides (mmol/L)	1.69 ± 0.95	1.29 ± 0.80	< 0.001

Results are expressed as the mean ± SD; p-paired *t*-test on log-transformed data

statins and at the time of CAVI measurement are shown in **Table 4**. A positive correlation was found between the duration of treatment with statins/ezetimibe and CAVI value (r_s=0,344, p=0,004) (**Fig. 1**).

CAVI and blood pressure were adjusted for age, BMI and sex due to the statistically significant correlation of both CAVI and blood pressure with these descriptive factors. Adjusted values are shown in **Table 5**. Age-, sex- and BMI-adjusted CAVI became slightly, insignificantly (p=0,061) lower in FH patients than in the control group; adjusted systolic and diastolic blood pressure did not differ between the two groups.

We found a positive significant correlation between CAVI and age in both groups ($p<0.001$), and between CAVI and BMI in the control group ($p<0.001$) (**Fig. 2**).

Discussion

The aim of the present study was to compare CAVI in healthy subjects and in patients with heterozygous FH, who are at high risk of premature atherosclerosis and consequently of coronary heart disease.

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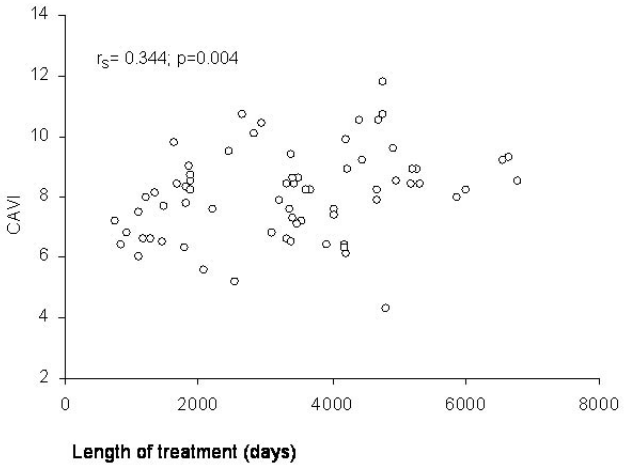

Fig. 1. Spearman's correlation of CAVI with length of treatment with statin/ezetimibe in heterozygous familial hypercholesterolemia group

CAVI: cardio-ankle vascular index; r_s: Spearman's rank correlation coefficient

No significant differences in CAVI were found in the group of 82 heterozygous FH patients treated with statins (or with combination statin and ezetimibe) when compared to healthy controls. FH is a genetic disorder presenting as premature atherosclerosis, primarily by coronary artery disease (CAD). It is an autosomal dominant disease caused by mutations in the LDL-receptor gene, or more rarely in the apolipoprotein B-100 gene[33, 34]. The phenotype of familial defective apolipoprotein B-100 is similar to that of patients with a mutation in the LDL-receptor gene and is not clinically distinguishable. Typical laboratory findings include very high levels of LDL-cholesterol (LDL-C); the main clinical symptom is premature atherosclerosis, primarily CAD[35]. Untreated FH heterozygotes may present with CAD at the age of 30-40 years and at the age of 50 years, 50% of men and 15% of women die of myocardial infarction[36]. The cumulative risk of fatal or non-fatal CAD is more than 50% at the age of 50 years in men and at least 30% in women aged 60 years[37, 38]. The progression of atherosclerosis and manifestation of cardiovascular disorders are therefore significantly accelerated in patients with FH in comparison to healthy population. The average age of HF patients in this study was 53.7 years; therefore, we expected CAVI, this very sensitive index of preclinical and clinical atherosclerosis, to be increased[20-22]; however, the values of CAVI did not significantly differ between the two studied groups after adjustment for age, BMI and gender. It has been demonstrated that high CAVI implies the progression of carotid and coronary arteriosclerosis[18, 19] and that CAVI might be more useful for the determination of coronary atherosclerosis probability than the assessment of carotid atherosclerosis by high-resolution B-mode ultrasonography[39]. We suppose that favourable CAVI values of FH patients in our study are the result of the highly restricted influence of cardiovascular risk factors. Atherosclerosis progress may be affected, except by age and gender, by other risk factors, such as increased BMI, hypertension, diabetes mellitus, increased LDL-cholesterol, low HDL-cholesterol or increased values of triglycerides. In our group with FH, values of blood pressure (after adjustment for age, gender and BMI) did not differ from the values in the control group and were within the physiological range. BMI was borderline (26 kg/m^2). Neither decreased HDL-cholesterol nor increased triglycerides were observed (**Table 4**) and diabetes mellitus was found only in two patients. The main risk factor was therefore represented by increased LDL-cholesterol; however, all patients with FH were treated long-term either with statins or with the combination of a statin and ezetimibe, which reduced plasmatic values of LDL-cholesterol by 45% (**Table 4**). Statins effectively reduce LDL-cholesterol plasma by the inhibition of HMG-CoA reductase, an enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis[40]. However, statins have also pleiotrophic, cholesterol-independent effects, such as increased nitric oxide bioactivity and the reduction of

Table 5. Adjusted means (95% confidence interval) of CAVI and blood pressure in patients with heterozygous familial hypercholesterolemia and control subjects

	Familial hypercholesterolemia (N=82)	Control group (N=359)	p*
CAVI	7.5 (7.3; 7.7)	7.7 (7.6; 7.7)	0.061
Systolic BP (mm Hg)	129.1 (126.5; 131.7)	127.9 (126.6; 129.3)	0.479
Diastolic BP (mm Hg)	78.6 (76.8; 80.3)	78.3 (77.4; 79.1)	0.782

Adjusted for age, sex, and body mass index by analysis of covariance. *Standard t-test was used to analyze the statistical significance of differences in distribution of continuous variables; CAVI: cardio-ankle vascular index; BP: blood pressure

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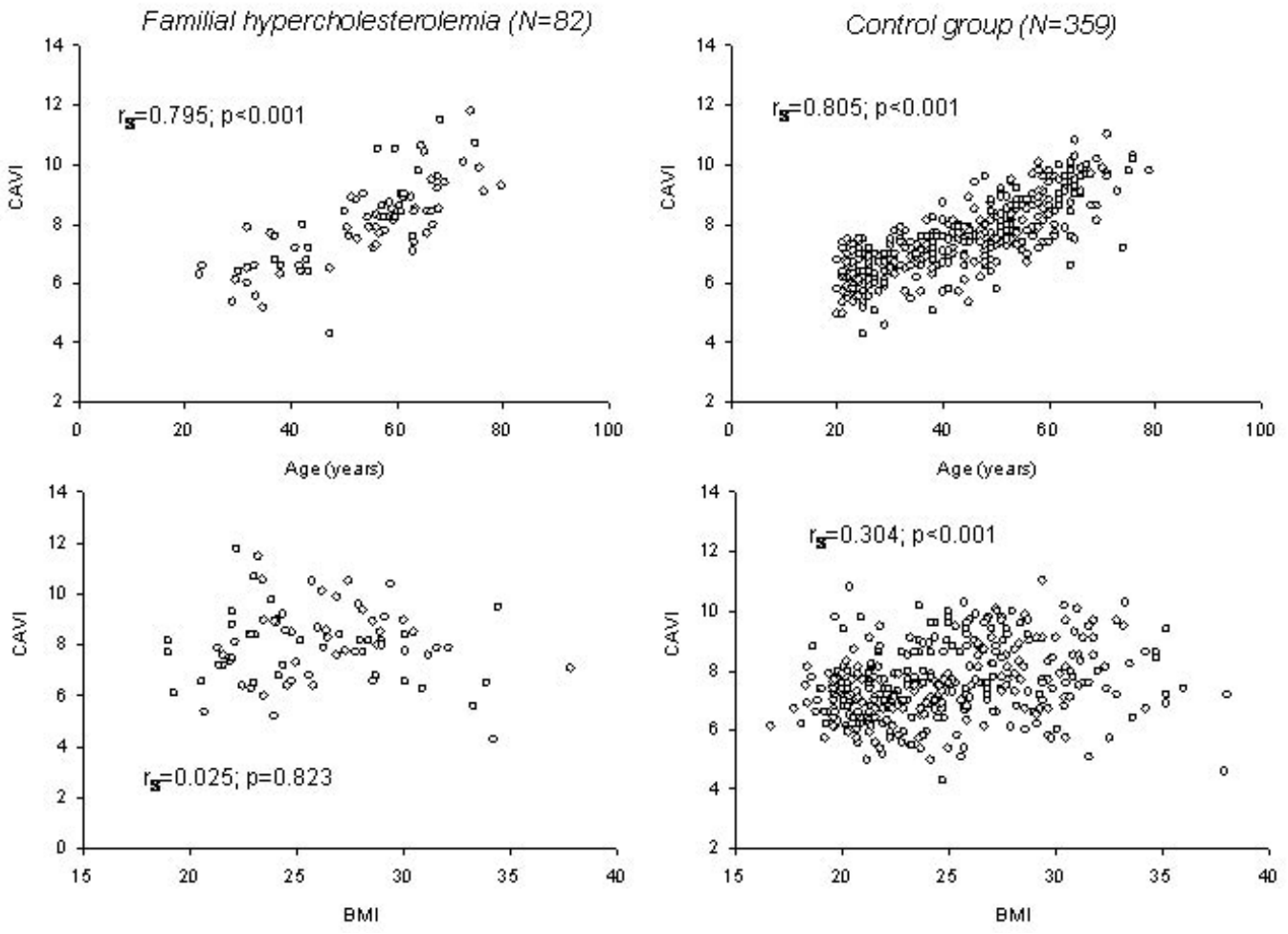

Fig. 2. Spearman's correlation of CAVI with age or BMI in heterozygous familial hypercholesterolemia group and in control group
CAVI: cardio-ankle vascular index; BMI: body mass index; r_s: Spearman's rank correlation coefficient

oxidative stress, which may contribute to the vasoprotective effects[41]. Thus, statins profoundly decrease cardiovascular risk and coronary mortality in patients with heterozygous FH and improve their clinical fate[42-44]. It has been also reported that fluvastatin improves arterial stiffness in patients with coronary artery disease and hyperlipidemia and that pitavastatin decreases CAVI after 12 months of treatment[24, 45]. All FH patients in our study used statins; moreover, 42% were treated with the combination of a statin and ezetimibe. Ezetimibe decreases the plasma level of cholesterol by limiting its absorption in the intestine. Treatment with ezetimibe decreases cholesterol level as well as CAVI[25]. LDL-lowering therapy was sufficient in our group of FH patients since average values of total cholesterol as well as LDL-cholesterol were close to the average values in the Czech population. According to the results of the Czech post-MONICA study, the average values of total cholesterol in the Czech Republic in 2001 were 5.88 ± 1.08 mmol/L in men and 5.82 ± 1.13 mmol/L in women, respectively[46]. Our results showed that, in FH patients with well-controlled risk factors, the progression of atherosclerosis measured by CAVI is not advanced as compared to healthy controls.

There are a few limitations of this study. First, the study was not designed as a case-control study; therefore, the controls were not age- and sex-matched. Nevertheless, the groups did not differ significantly in the distribution of men and women. As the differences in age and BMI are a concern, adjustment for age and BMI is a well-accepted statistical approach for overcoming differences between the study and control populations.

Secondly, it is not possible to evaluate the direct effect of treatment with statins/ezetimibe on CAVI in

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patients with FH, since treatment with hypolipidemic drugs was introduced many years earlier than the measurement of CAVI using VaSera® 1500. Moreover, it is not possible to measure CAVI in new FH patients before therapy, since practically all patients have been treated with statins prescribed by their general practitioners before they visit our department to verify the diagnosis of FH. The discontinuation of statins before CAVI measurement for a longer time is not possible for ethical reasons. The direct effect of treatment with pitavastatin as well as ezetimibe on CAVI reduction was recently reported in patients with diabetes mellitus without cardiovascular complications[24, 25].

Thirdly, blood lipid values were not available for the control group and therefore their comparison with the values of FH patients treated with statins was not possible. For an approximate comparison, data from the Czech post-MONICA study were used; blood lipids of a representative sample of the Czech population were examined in this study. Moreover, CAVI had a poor relationship with total cholesterol and LDL-cholesterol levels and no correlations among CAVI and the triglycerides and HDL-cholesterol levels were found[47]. In addition, the aim of this study was not to compare blood lipids of a healthy population and patients with FH treated with statins, but to assess CAVI values in these two groups. Since CAVI is quite a sensitive, non-invasive index of atherosclerosis progression, it might be of help for patients with FH where the risk of premature atherosclerosis development is high.

In conclusion, we demonstrated that there are no significant differences in CAVI between asymptomatic patients with heterozygous FH with well-controlled major risk factors and healthy controls; however, further studies using clinical long-term follow-up are required.

Disclosure

The authors declare no conflicts of interest.

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