The assessment of cardiac autonomic functions in adolescents with a family history of premature atherosclerosis

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OBJECTIVES: Subclinical atherosclerosis has been recently detected in adolescents with a family history of premature atherosclerosis. However, no studies in the literature have assessed the cardiac autonomic functions of these adolescents. The aim of this study was to evaluate the cardiac autonomic functions of adolescents with a family history of premature atherosclerosis compared with those of age- and gender-matched adolescents without a family history of atherosclerosis.

METHOD: We evaluated the cardiac autonomic functions of 36 adolescents with a family history of premature atherosclerosis (Group 1) and compared them with those of 31 age- and gender-matched adolescents whose parents did not have premature atherosclerosis (Group 2). Twenty-four-hour time domain (standard deviation of all normal sinus RR intervals [SDNN], standard deviation of the mean of normal RR intervals in each 5-minute segment [SDANN], root-mean-square differences in successive RR intervals) and frequency domain (very low frequency, low frequency, high frequency, low frequency/high frequency) parameters of heart rate variability were used for the evaluation of cardiac autonomic functions.

RESULTS: There were no differences in the time and frequency domain parameters of heart rate variability between the two groups. Heart rate was negatively correlated with SDNN ($r = -0.278$, $p = 0.035$), while age was significantly correlated with root-mean-square differences in successive RR intervals, high frequency, low frequency and low frequency/high frequency ($r = -0.264$, -0.370, 0.265 and 0.374, respectively; $p < 0.05$ for all).

CONCLUSION: We found that the cardiac autonomic functions of adolescents with a family history of premature atherosclerosis were not different compared with those of adolescents without a positive family history of premature atherosclerosis. It appears that subclinical atherosclerosis does not reach a critical value such that it can alter cardiac autonomic functions in adolescence.

KEYWORDS: Autonomic Dysfunction; Adolescent; Atherosclerosis.

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INTRODUCTION

Atherosclerosis (1) begins in childhood and atherosclerotic plaques (2) have been observed in coronary arteries during adolescence. A family history of premature atherosclerosis (3) creates an additive effect in this process and significantly increases the risk of developing atherosclerosis. Complementary to these findings, subclinical atherosclerosis in adolescents with a family history of premature atherosclerosis (4) has been recently demonstrated using noninvasive techniques. However, the effect of subclinical atherosclerosis on cardiac autonomic functions in these adolescents has not yet been evaluated.

Heart rate variability (HRV) analysis (5) is a useful tool for assessing cardiac autonomic functions. It has been used as a predictor of sudden cardiac death and as a marker of cardiovascular disease progression (6) in several high-risk populations. The main objective of this study was to evaluate the cardiac autonomic functions of adolescents with a family history of premature atherosclerosis compared with those of age- and gender-matched adolescents without a family history of premature atherosclerosis using HRV analysis.

MATERIALS AND METHODS

The coronary angiography records of Tepecik Training and Research Hospital collected between May 1, 2012 and

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May 1, 2013, were examined. We conducted phone interviews with patients who had undergone coronary angiography for atherosclerosis at an early age (males <45 years, females <55 years) during this period. The adolescent children of these patients were included in the study. The angiograms of the parents of the study participants were visually reviewed. Obstructive coronary artery disease (CAD) was defined as at least one epicardial coronary lesion>2 mm in length resulting in a>50% narrowing in diameter. Of the 59 patients who could be reached, five had no children and six declared that their children could not participate in the study for nonmedical reasons. The exclusion criteria were congenital heart disease, moderate-to-severe valvular heart disease, heart conduction disorders, branch block, hypertension, diabetes mellitus, asthma, liver or renal insufficiency, malignancy, smoking, or antiarrhythmic drug therapy. One adolescent with a secundum-type atrial septal defect and one with diabetes mellitus were excluded from the study. The remaining 36 adolescents (n = 25, males = 12) whose parents had CAD based on coronary angiography constituted Group 1; 31 adolescents (n = 23, males = 11) whose parents did not have CAD based on coronary angiography constituted Group 2.

Anthropometric measurements (weight, height, waist and hip circumferences) were performed using a standardized technique and the body mass index (BMI) was calculated by dividing the participant's weight in kilograms by the square of his/her height in meters. Systolic and diastolic blood pressures were measured twice by one investigator with the auscultation method using an appropriately sized cuff after the patient had been seated quietly with his or her back supported, feet on the floor and right arm supported for five minutes. The blood biochemistry records of the study participants in the last year, including complete blood count, serum urea, creatinine, liver enzymes, fasting blood glucose, lipid profile, uric acid, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were used.

Twenty-four-hour Holter recordings obtained from Group 1 and Group 2 were downloaded onto a computer and analyzed with a Holter program (Norav Medical, Version DL 800, 2006, Wiesbaden, Germany). All recordings were also examined visually and artifacts were deleted manually. All of the recordings had at least 22 hours of data after removing the artifacts. The HRV parameters were calculated using a computer and were statistically analyzed. The time and frequency domain HRV parameters used in this study were chosen according to the guidelines of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (7). The time domain parameters included the standard deviations of all normal sinus RR intervals over 24 hours (SDNN), standard deviations of the mean of normal RR intervals for each 5-minute segment (SDANN) and root-mean-square differences in successive RR intervals (RMSSD). Frequency domain parameters included low frequency (LF), high frequency (HF) and very low frequency (VLF) components and the LF/HF ratio. Frequency domain analysis was performed using a non-parametric Fast Fourier transform (FFT)-based method.

All the subjects were recorded under fairly similar conditions and in a fairly similar environment. They were asked not to consume tea, coffee, chocolate, or alcohol-containing substances for at least eight hours before and during the entire Holter recording period. They were asked to try and maintain normal behaviors and activities.

Ethics

The present study was a single-center study. All examinations were performed at the Department of Cardiology of Tepecik Training and Research Hospital. All subjects provided informed consent prior to inclusion in the study. The study protocol was approved by the Ethics Committee of Tepecik Training and Research Hospital.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). According to the Kolmogorov-Smirnov test, all of the continuous variables were normally distributed. To analyze the continuous data, a two-tailed independent samples *t*-test was used and the data were expressed as the mean ± standard deviation (SD). A chi-square test was used to analyze the categorical data and the data were expressed as percentages. To define correlations between age, heart rate and HRV measures, Pearson's correlation analysis was applied. *P*-values <0.05 were considered statistically significant.

RESULTS

There were no significant differences between Group 1 and Group 2 with regard to age, gender, BMI, waist circumference, systolic and diastolic blood pressures, fasting blood glucose, uric acid, lipid profile, ESR, CRP, hemoglobin or white blood cell counts (Table 1).

Basal heart rate was found to be higher in Group 1, but this difference did not reach significance ($p = 0.061$). Neither time nor frequency domain measures were found to be significantly different between the two groups (Table 2). There were no differences in HRV measures with regard to gender between the groups. Heart rate was negatively correlated with SDNN ($r = -0.278$, $p = 0.035$), while age was significantly correlated with RMSSD, HF, LF, and LF/HF ($r = -0.264$, -0.370, 0.265 and 0.374, respectively; $p<0.05$ for all) (Figure 1).

DISCUSSION

The major finding of this study was that the HRV parameters of adolescents with a family history of premature atherosclerosis are not different from those of adolescents without a family history of premature atherosclerosis. We initially hypothesized that if adolescents with a family history of premature atherosclerosis have subclinical atherosclerosis, as shown previously, their cardiac autonomic functions may be altered. However, our findings did not confirm this hypothesis. There may be several explanations for this finding. First, the degree of atherosclerosis in the adolescents with subclinical atherosclerosis may not reach a threshold such that cardiac autonomic functions are affected during the adolescent period. Because HRV has been shown to be deteriorated in adult patients with CAD and has been correlated with disease duration (8), it is logical to assume that cardiac automaticity is not yet affected in the early stages of atherosclerosis during adolescence. Second, the adolescents with a positive family history of atherosclerosis in our study may not have actually

Table 1 - Baseline characteristics and laboratory findings of the study groups.

Variables	Group 1 (n = 36)	Group 2 (n = 31))	*p*-value
Age, mean (years)	14.0 ± 1.9	14.8 ± 1.8	0.091
Gender (F) (%)	19 (52)	21(67)	0.112
BMI (kg/m^2)	21.5 ± 4.3	20.9 ± 3.0	0.529
Waist circumference (cm)	73.4 ± 12.5	72.0 ± 10.1	0.689
Systolic BP (mmHg)	106.8 ± 14.1	109.8 ± 10.5	0.342
Diastolic BP (mmHg)	65.2 ± 9.8	67.4 ± 9.8	0.378
Fasting glucose (mg/dL)	88.4 ± 10.2	87.5 ± 7	0.749
Uric acid (mg/dL)	4.3 ± 1.10	3.9 ± 1.07	0.326
Total cholesterol (mg/dL)	162.8 ± 25.0	151.4 ± 23.0	0.134
Triglycerides (mg/dL)	99.7 ± 19.4	82.2 ± 65.2	0.363
LDL-C (mg/dL)	93.7 ± 19.4	85.1 ± 21.3	0.187
HDL-C (mg/dL)	49 ± 8.6	49 ± 12.1	0.938
WBC (x10^3/μL)	7.1 ± 1.5	7.2 ± 1.8	0.798
Hemoglobin (g/dl)	13.6 ± 1.0	12.7 ± 1.7	0.062
ESR (mm/h)	7.0 ± 4.1	7.9 ± 3.2	0.556
CRP (mg/L)	0.5 ± 0.2	0.4 ± 0.1	0.721

BMI: body mass index; BP: blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; WBC: white blood cell count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

had subclinical atherosclerosis. Because we did not utilize noninvasive assessment tools for the evaluation of subclinical atherosclerosis in this group, we were unable to determine whether subclinical atherosclerosis was present. However, Celik et al. (4) demonstrated subclinical atherosclerosis in adolescents whose fathers had a history of premature CAD based on the carotid stiffness index, carotid intima-media thickness and pulse wave velocity.

The autonomic nervous system can be affected by the risk factors that cause CAD. The adolescents in Group 1 in our study had no risk factors other than a family history. However, elevation of inflammatory markers (4) leading to subclinical atherosclerosis was previously identified in a similar study population. Several studies evaluated the interaction of inflammation with the autonomic nervous system. In general, these studies (9-11) demonstrated significant associations between the elevated burdens of systemic inflammation and reduced mean levels of HRV. The initial step or trigger for this interaction may be either inflammation or autonomic nervous system dysfunction; however, this point is still debated. Banks et al. (12) and Goehler et al. (13) demonstrated the activation of sympathetic outflow secondary to elevated systemic inflammation in different studies. Additionally, middle-aged individuals with elevated inflammatory markers (14) were found to have lower HRV measures and elevated systemic inflammation has been hypothesized to result in deterioration of cardiac autonomic functions. However, several experimental and laboratory studies (15,16) have demonstrated that autonomic imbalance is the primary event leading to the activation of inflammation because the bone marrow and lymphoreticular system are innervated by autonomic nerves. In addition, sympathectomy, whether surgical or medical (17-18), alters and reduces the inflammatory reaction. We believe that our study is consistent with studies demonstrating that inflammation is the initial event leading to atherosclerosis. Because there was no deterioration of HRV measures in adolescents suspected to have subclinical atherosclerosis in our study. Based on these findings, it is plausible that the degree of inflammation and atherosclerosis are the determinants of deterioration in HRV. In adolescence, the threshold for the deterioration of HRV does not appear to be reached. We believe that comprehensive studies should be performed to investigate the interaction of inflammation and HRV in adolescence, especially among individuals with a family history of atherosclerosis.

Table 2 - Time and frequency domain parameters of the two groups.

Variables	Group 1 (n = 36)	Group 2 (n = 31)	*p*-value
SDNN (ms)	159.09 ± 32.72	162.35 ± 41.88	0.733
SDANN (ms)	108.53 ± 70.67	132.49 ± 91.48	0.251
RMSSD (ms)	77.24 ± 35.10	74.35 ± 40.24	0.763
VLF (ms^2)	288.37 ± 39.14	297.90 ± 62.58	0.472
LF (ms^2)	173.73 ± 32.01	186.92 ± 31.47	0.107
HF (ms^2)	149.0 ± 32.72	143.50 ± 34.40	0.521
LF/HF	1.23 ± 0.41	1.40 ± 0.48	0.147
HR (/min)	83.88 ± 8.81	79.66 ± 8.98	0.061

SDNN: standard deviation of all normal sinus RR intervals; SDANN: standard deviation of the mean of normal RR intervals in each 5-minute segment; RMSSD: root-mean-square differences in successive RR intervals; VLF: very low frequency; LF: low frequency; HF: high frequency; HR: heart rate. The data are shown as the mean ± SD.

HRV is a generally accepted tool for the assessment of cardiac autonomic functions. Reduction of HRV is a sign of cardiac autonomic imbalance and is associated with an increase in mortality. Although most HRV studies have been performed in adult populations, HRV has also been studied in children and adolescents. HRV is usually assessed with time and frequency domain analyses using short- and long-term recordings. The disadvantage of short-term recordings is their failure to detect long-term trends in diurnal influences on heart rate. Clinical studies in children and adolescents where good cooperation can be difficult predominantly utilize 24-hour time domain analysis. HRV studies in children and adolescents have often revealed that HRV measures changed with age and were related to gender. In contrast to adults, HRV measures tend to be increased in children and older adolescents (19-21). However, in our study, with increasing age, RMSSD and HF measures decreased in contrast to the trend of LF and LF/HF, reflecting decreased parasympathetic modulation. Our findings were consistent with HRV studies in adult populations, which may

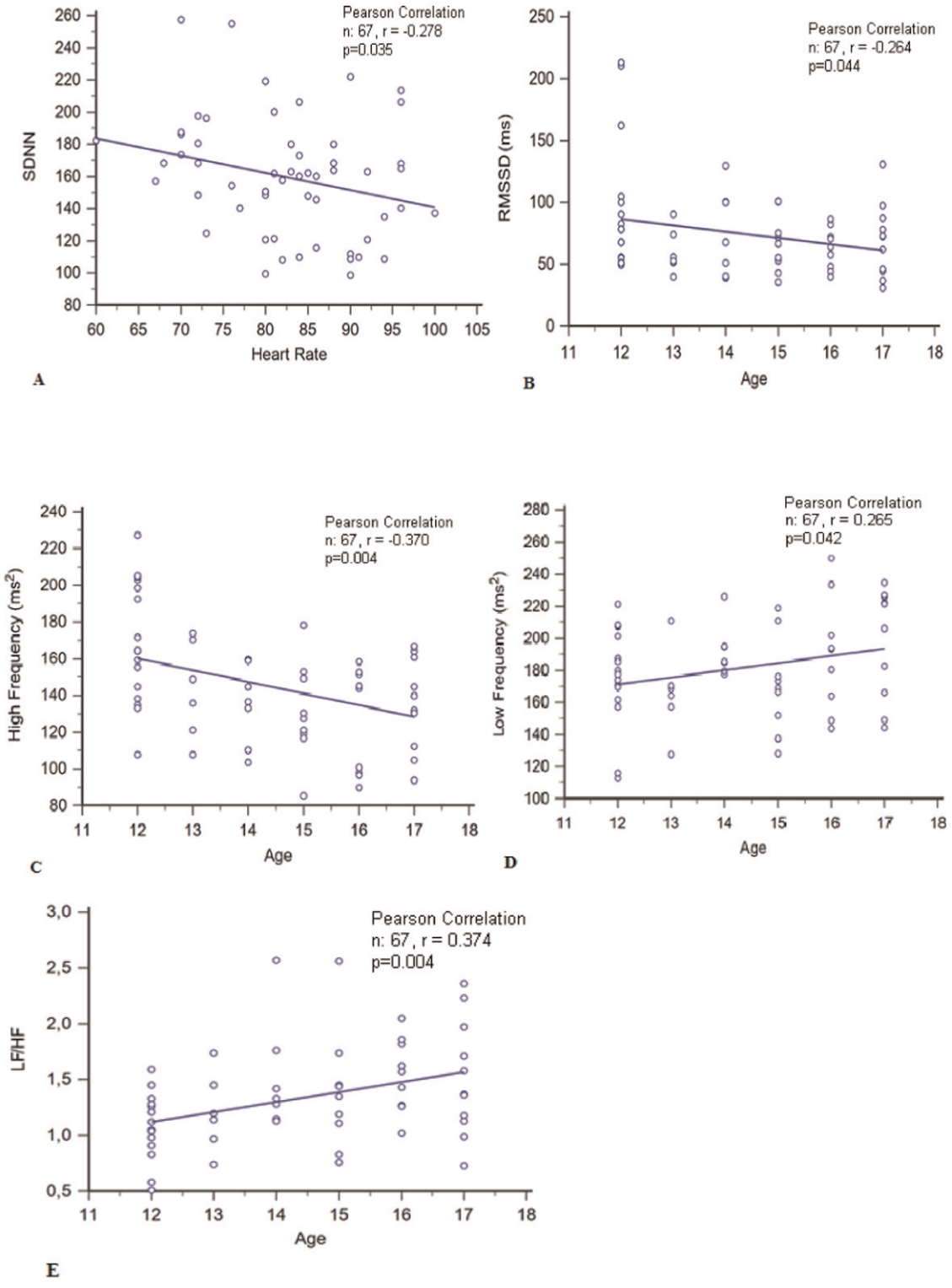

Figure 1 - Pearson correlation analysis of the following variables: heart rate and SDNN (A), age and RMSSD (B), age and HF (C), age and LF (D) and age and LF/HF (E). SDNN: standard deviation of all normal sinus RR intervals; RMSSD: root-mean-square differences in successive RR intervals; LF: low frequency; HF: high frequency.

be due to the lack of children in our study and the maturation of the autonomic nervous system during adolescence.

In adolescents, HRV was also evaluated in diseases known to affect cardiac autonomic functions in adulthood. Wawryk et al. (22) reported that adolescents with type 1 diabetes have decreased HRV measures compared with healthy controls. Additionally, poor glycemic control and a long duration of diabetes were found to be negatively associated with HRV measures (23-24). Obese adolescents (25) were found to have increased LF/HF values and lower

SDNN values, indicating an imbalance in the sympathetic activity of the heart. It has previously been shown that HRV is decreased in adult patients with CAD. However, until now, there have been no data available regarding whether subclinical atherosclerosis in adolescents alters HRV or the age range in which it begins to cause HRV deterioration. To our knowledge, this is the first study evaluating HRV in adolescents with a family history of premature atherosclerosis. Because subclinical atherosclerosis has been shown before in this population, we chose to investigate the HRV measures in this population.

The main limitation of our study is the small sample size. Because a small sample size results in low statistical power for equivalency testing, the negative results may simply be due to chance. Another limitation of our study is the fact that we accepted the study group as having subclinical atherosclerosis based on a recent study, as well as the lack of evaluation of subclinical atherosclerosis. Finally, we evaluated the inflammation level in the two groups based only on ESR and CRP levels and found no difference. The use of highly specific inflammatory markers for atherosclerosis, such as high-sensitivity CRP and homocysteine values, would be preferable.

In conclusion, the time and frequency domain HRV measures of adolescents with a family history of premature atherosclerosis were not different from those of adolescents without a family history of atherosclerosis. The level of subclinical atherosclerosis in adolescents does not reach a critical value that would result in deterioration of the cardiac autonomic functions during this stage. We believe that prospective studies with more participants should be conducted in adolescents and young adults to facilitate the observation of atherosclerosis maturation and the stage-by-stage effect of this process on cardiac autonomic functions.

AUTHOR CONTRIBUTIONS

Dursun H conceived the study, planned the study, performed data collection and wrote the manuscript. Kilicaslan B and Aydin M planned the study, performed data collection, performed statistical analysis and wrote the manuscript.

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