ORIGINAL ARTICLE

Evaluation of heart rate variability in patients with coronary artery ectasia and coronary artery disease

Koroner arter ektazisi ve koroner arter hastalığı olan hastalarda kalp hızı değişkenliğinin değerlendirilmesi

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ABSTRACT

Objective: The present study compared heart rate variability (HRV) parameters in patients with coronary artery ectasia (CAE) and coronary artery disease (CAD).

Methods: The study population consisted of 60 consecutive patients with CAE (14 women; mean age 51.63±7.44 years), 60 consecutive patients with CA (15 women; mean age 53.67±9.31 years), and 59 healthy individuals (13 women; mean age 52.85±8.19 years). Electrocardiograms, 24-hour Holter analyses, and routine biochemical tests were performed, and clinical characteristics were evaluated. Coronary angiography images were analyzed. Time-domain HRV parameters, including the standard deviation (SD) of normal-to-normal intervals (SDNN) and the root mean square of difference in successive normal-to-normal intervals (RMSSD) were evaluated, as were frequency-domain HRV parameters including low-frequency (LF), very low-frequency (VLF), high-frequency (HF), the proportion derived by dividing low- and high-frequency (LF/HF), and total power (TP).

Results: SDNN was lower in both the CAE and CAD groups, compared to the healthy group (140.85±44.21, 96.51±31.28, and 181.05±48.67, respectively). A significant difference in RMSSD values among the groups was determined (p=0.004). Significantly decreased VLF and HF values were found in the CAE group, compared with the healthy group (VLF p<0.001; HF, p=0.007). TP, VLF, and HF values were significantly lower (p<0.001, p<0.001, and p<0.001, respectively), but LF and LF/HF values were significantly higher (p<0.001 for both) in the CAD group than in the healthy group. TP values were significantly higher (p<0.001), and LF and LF/HF values were lower in the CAE group, compared with the CAD group (p<0.001 for both).

Conclusion: A decrease in vagal modulation or an increase in sympathetic activity of cardiac function, assessed by HRV analysis, is worse in patients with CAD than in patients with CAE.

ÖZET

Amaç: Bu çalışmada, koroner arter ektazisi (KAE) ve koroner arter hastalığı (KAH) olan hastaların kalp hızı değişkenliği (KHD) parametreleri karşılaştırıldı.

Yöntemler: Çalışma popülasyonu KAE'li ardışık 60 hasta (14 kadın, ortalama yaş 51.63±7.44 yıl), KAH'lı 60 hasta (15 kadın, ortalama yaş 53.67±9.31) ve sağlıklı 59 kişiden (13 kadın, ortalama yaş 52.85±8.19) oluşmaktaydı. Elektrokardiyogramlar (EKG) çekilip, 24 saatlik Holter EKG takıldı. Rutin biyokimyasal testleri yapıldı ve klinik özellikleri değerlendirildi. Koroner anjiyografi görüntüleri incelendi. Zamanla ilgili KHD parametrelerinden; tüm "normal-to-normal" (NN) intervallerinin standart sapma (SDNN), ardışık NN intervallerinin farkının kare kökü (RMSSD) ve frekansla ilgili KHD parametrelerinden düşük frekans (LF), çok düşük frekans (VLF), yüksek frekans (HF), düşük ve yüksek frekansın oranı (LF/HF) ve toplam güç (TP) hesaplandı.

Bulgular: SDNN, KAE ve KAH grubunda sağlıklı gruba göre düşüktü (sırasıyla, 140.85±44.21, 96.51±31.28, 181.05±48.67). Gruplar arasında RMSSD değerleri açısından istatistiksel olarak anlamlı fark bulundu (p=0.004). Sağlıklı grup ile karşılaştırıldığında, VLF ve HF değerleri KAE grubunda anlamlı olarak azalmıştı (VLF p<0.001; HF, p=0.007). KAH grubunda sağlıklı grup ile karşılaştırıldığında TP, VLF ve HF değerleri anlamlı olarak düşük (sırasıyla, p<0.001, p<0.001, p<0.001), LF ve LF/HF değerleri ise anlamlı olarak yüksekti (p<0.001, p<0.001). KAH grubu ile karşılaştırıldığında KAE grubunda, TP değerleri anlamlı olarak yüksek (p<0.001), LF ve LF/HF değerleri ise anlamlı olarak düşük bulundu (p<0.001, p<0.001).

Sonuç: Vagal modulasyonda azalma ve sempatik aktivitede artma ile kalp fonksiyonlarının değerlendirildiği KHD analizi KAH olan hastalarda KAE olan hastalara göre daha kötü sonuçlara sahiptir.

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Coronary artery ectasia (CAE) is defined as coronary artery dilatation with a diameter measuring 1.5 times or more that of the normal adjacent coronary artery. CAE is often viewed as a variant of obstructive coronary atherosclerosis. Exaggerated positive vascular remodeling due to inflammation and chronic overstimulation of the endothelium by nitric oxide are potential causative mechanisms.[1]

Heart rate variability (HRV) is the change in heart rate from beat to beat. HRV measurements can noninvasively provide information about the autonomic nervous system, including information regarding its vagal and sympathetic components.[2–4] Lowered HRV, as a parameter of the patient's autonomic function, has been shown to be another predictor of future cardiac events, cardiac death, arrhythmia, and all-cause mortality in patients with acute myocardial infarction. Lowered HRV is also related to coronary artery disease (CAD) and progression of coronary atherosclerosis.[5–9]

HRV is reduced in ischemic heart disease, regardless of previous myocardial infarction, and has been shown to be attenuated in patients with CAD. HRV may, therefore, be used for the early detection of myocardial ischemia.[10]

Changes in vagal modulation and sympathetic activity of cardiac function, as assessed by HRV analysis in patients with CAE and CAD, were investigated in the present study.

METHODS

Study population

The study population consisted of 60 consecutive patients with CAE (14 women; mean age 51.63±7.44 years), 60 consecutive patients with CAD (15 women; mean age 53.67±9.31 years), and 59 healthy individuals who had undergone coronary angiography (13 women; mean age 52.85±8.19 years). Exclusion criteria included acute coronary syndrome, congestive heart failure, 50% or more occlusive coronary artery lesions with CAE, valvular heart disease, pacemaker implantation, persistent atrial fibrillation, frequent atrial or ventricular premature beats, conduction defects, Wolff-Parkinson-White syndrome, peripheral vascular diseases, pericarditis, peripheral neuropathy, congenital heart disease, presence of diabetes mellitus, use of b-adrenergic blocking agents and digoxin, alcohol abuse, renal, hepatic, or thyroid disease, left ventricular hypertrophy, and left ventricular diastolic and systolic dysfunction. Electrocardiograms, 24-hour Holter analyses, recording analyses, and routine biochemical tests were performed, and clinical characteristics were evaluated. CAE was defined as nonobstructive lesion of the epicardial coronary arteries with a luminal dilation measuring 1.5 times that of a normal diameter. Coronary aneurysm was defined as a dilation exceeding 1.5 times that of a normal diameter. If no adjacent normal segment could be identified, mean diameters of coronary segments in a control group without heart disease served as normal values.[11–13] CAD group was defined as patients with 50% or more occlusive coronary artery lesions. For eccentric lesions, the projection with the highest degree of stenosis was used. Quantification of lesions was performed visually, as was quantification of left ventricular function. After coronary angiography, 59 healthy individuals with normal coronary arteries were selected for inclusion. Left ventricular ejection fraction was measured using modified Simpson's rule. Mean of 3 measurements of the technically best cardiac cycles was recorded. Severity of stenosis was determined by visual estimation in 2 or more orthogonal views. Angiographic findings were assessed by experienced cardiologists. Operators reading angiograms were unaware of the results of laboratory analyses. Number, location, and severity of lesions in each arterial segment were recorded.

Abbreviations:

ANOVA	*Analysis of variance*
CAD	*Coronary artery disease*
CAE	*Coronary artery ectasia*
HF	*High-frequency*
HRV	*Heart rate variability*
LF	*Low-frequency*
LF/HF	*Proportion derived by dividing low- and high-frequency*
NCA	*Normal coronary arteries*
RMSSD	*Root mean square of difference in successive normal-to-normal intervals*
SDNN	*Standard deviation of normal-to-normal intervals*
TP	*Total power*
VLF	*Very low-frequency*

Heart rate variability analysis

HRV analysis was performed with 24-hour Holter recording according to Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology guidelines.[14] Holter analysis was performed on a DMS 300-4A system (DM Software, Stateline, NV, USA) and independently analyzed by 2 cardiologists. Arrhythmia was defined as occurrence of atrial or ventricular premature

contractions, ventricular couplets, atrial tachycardia, or paroxysmal atrial fibrillation. Short-term spectral analysis of HRV was performed with records taken at 5-minute intervals. HRV analysis was performed using Fourier method. After RR-tachogram was obtained, time-domain HRV parameters including SD of normal-to-normal intervals (SDNN) and root mean square of difference in successive normal-to-normal intervals (RMSSD) were measured, as were frequency-domain parameters including low-frequency (LF), very low-frequency (VLF), high-frequency (HF), the proportion derived by dividing low- and high-frequency (LF/HF), and total power (TP).

Statistical analysis

Statistical analysis was performed with SPSS software, version 13.0 (SPSS Inc., Chicago, IL, USA). Parametric values were expressed as mean±SD, and categorical parameters were presented as percentages. Kolmogorov-Smirnov test was used to evaluate the normality of distribution of all continuous variables. Comparison among multiple groups was performed with one-way analysis of variance (ANOVA), with Bonferroni correction test for continuous variables. Kruskal-Wallis test was used to compare the groups for parameters that were not distributed normally and for ordinal variables. If the p value was <0.05 according to Kruskal-Wallis test, Conover multiple comparison test was used to find the group causing the difference. For multiple regressions, factors with p<0.05 in one-way ANOVA and Kruskal-Wallis test were selected. Standardized β-regression coefficients and their significance from multinomial logistic regression analysis are reported. A two-tailed p-value of 0.05 was considered statistically significant.

RESULTS

Sixty consecutive CAE patients (46 men, mean age: 51.6±7.4 years), 60 consecutive CAD patients (45 men, mean age: 53.6±9.3 years), and 59 patients with normal coronary arteries (NCA; 46 men, mean age: 52.8±8.1 years) were included. Baseline demographic and clinical characteristics were similar among groups. Significant statistical differences were not found regarding sex, hypertension, hyperlipidemia, family history, smoking, height, weight, body mass index, ejection fraction, and use of drugs. Neither were statistically significant differences present among groups regarding hematological and biochemical parameters including fasting blood glucose, HbA1c, urea, creatinine, hematocrit, white blood cell, neutrophil, lymphocyte, neutrophil lymphocyte ratio, thrombocyte, triglyceride, total cholesterol, high-density lipoprotein, low-density lipoprotein, sodium, potassium, magnesium, and calcium (Table 1). Maximum, average, and minimum heart rate observed in the 24-hour period did not differ among groups. Incidence of arrhythmias was higher in patients with CAD, compared to other groups (CAE: 18 [30%], CAD: 30 [50%], NCA: 6 [10.2%]; p0 <0.001, p1 [CAE-CAD] = 0.040, p2 [CEA-NCA] = 0.014, p3 [CAD-NCA] = 0.001; Table 2). In the CAE group, 5 patients had premature atrial contractions, 5 had premature ventricular contractions, 3 had both, 3 had supraventricular tachycardia, and 2 had paroxysmal atrial fibrillation. In the CAD group, 9 patients had premature atrial contractions, 8 had premature ventricular contractions, 4 had both, 6 had supraventricular tachycardia, and 3 had paroxysmal atrial fibrillation. In the NCA group, 3 patients had premature atrial contractions, 2 had premature ventricular contractions, and 1 had supraventricular tachycardia. No significant difference in type of arrhythmias among the groups was found (p=0.652).

Heart rate variability parameters

SDNN was significantly different among the groups. SDNN was found to be lower in the CAD and CAE groups, compared to the NCA group (CAE: 140.85±44.21 vs NCA: 181.05±48.67, p<0.001; CAD: 96.51±31.28 vs NCA: 181.05±48.67, p<0.001). A significant difference in RMSSD was also determined among the groups (p=0.004). RMSSD was found to be lower in the CAD group, compared to the CAE and NCA groups. However, a significant difference was found between the CAD and NCA groups (p=0.006).

Regarding frequency-dependent measurements, TP, VLF, LF/HF, HF, and LF were significantly different among the groups. TP, VLF, and HF values were decreased (pTP [CAD-NCA] <0.001, pVLF [CAD-NCA] <0.001, pHF [CAD-NCA] <0.001), while LF and LF/HF were significantly increased in the CAD group, compared to the NCA group (pLF [CAD-NCA] <0.001, pLF/HF [CAD-NCA] <0.001). No significant difference in VLF was found between the CAD and CAE groups. VLF and HF values were significantly decreased in the CAE group, compared to the NCA

Table 1. Demographic characteristics of all groups

	CAE (n=60)	CAD (n=60)	NCA (n=59)	*p*
Mean age (year)	51.73±8.16	53.67±9.73	52.85±8.20	.478
Sex (men)	46 (76.6%)	45 (75%)	46 (78%)	.929
Hypertension	24 (40%)	28 (46.7%)	24 (40.6%)	.719
Hyperlipidemia	30 (50%)	34 (56.7%)	28 (47.5%)	.583
Family history	12 (20%)	20 (33.3%)	10 (16.6%)	.080
Smoking	23(38.3%)	33 (55%)	25 (42.4%)	.161
Height (cm)	166.60±7.52	168.71±7.49	167.91±8.01	.316
Weight (kg)	75.49±9.65	75.31±10.15	74.85±12.60	.947
Body mass index	27.30±3.49	26.27+4.04	26.39±4.00	.285
Ejection fraction (median; IQR)	64.0; 5.0	62.5; 5.0	64.0; 5.0	.518
Aspirin	16 (26.7%)	20 (33.3%)	13 (22%)	.380
Statin	10 (16.7)	12 (20%)	5 (8.5%)	.196
Diuretic	12 (20%)	14 (23.3%)	11 (18.6%)	.809
ACE/ARB	20 (33.3%)	22 (36.7%)	15 (25.4%)	.402
Fasting blood glucose (median; IQR)	97.0; 14.5	99.5; 11.7	97.0; 15.0	.449
HbA1c (median; IQR)	5.80; 0.76	5.96; 0.84	5.80; 0.76	.142
Urea (median; IQR)	30.0; 10.0	33.0; 9.5	32.0; 14.0	.431
Creatinine	0.76±0.13	0.82±0.14	0.76±0.14	.067
Hematocrit (median; IQR)	44.0; 5.7	42.4; 6.5	42.3; 5.5	.104
White blood cell (median; IQR)	6.7; 2.7	7.6; 3.1	7.0; 2.6	.363
Neutrophil (median; IQR)	3.8; 1.8	4.6; 2.2	4.0; 2.1	.078
Lymphocyte	2.15±0.59	2.10±0.74	2.11±0.63	.915
NLR (median; IQR)	2.2; 0.9	2.3; 1.4	2.1; 1.0	.268
Thrombocyte (median; IQR)	248000; 62000	220000; 100500	246000; 68000	.286
Triglyceride	142.65±83.13	158.98±56.65	128.94±71.66	.074
Total cholesterol	188.91±41.68	192.30±43.36	181.67±40.17	.369
High-density lipoprotein	46.58±11.67	43.86±13.10	47.50±10.44	.218
Low-density lipoprotein	117.60±37.03	121.56±40.97	107.79±32.40	.116
Ca	9.49±0.44	9.46±0.55	9.50±0.56	.917
Na (median; IQR)	140.0; 2.7	140.0; 3.0	140.0; 3.0	.918
Mg	1.96±0.14	1.93±0.26	1.93±0.17	.587
K	4.46±0.32	4.48±0.42	4.47±0.40	.973

CAE: Coronary artery ectasia; CAD: Coronary artery disease; NCA: Normal coronary arteries; ACE/ARB: Angiotensin-converting enzyme/Angiotensin-receptor blocker; NLR: Neutrophil/lymphocyte ratio; IQR: Interquartile range; p represents significance value of all groups.

group (VLF [CAE-NCA] <0.001, pHF [CAE-NCA] = 0.007). However, LF and LF/HF values were significantly increased in the CAE group, compared to the NCA group (pLF [CAE-NCA] <0.001, pLF/HF [CAE-NCA] <0.001). No difference was observed among other frequency-dependent parameters. SDNN and TP were significantly decreased (pSDNN [CAD-CAE] <0.001, pTP [CAD-CAE] <0.001), while LF and LF/HF were significantly increased in the CAD group, compared to the CAE group (pLF [CAD-CAE] <0.001, pLF/HF [CAD-CAE] <0.001). RMSDD, VLF, and HF values were not significantly different

Table 2. Heart rate variability parameters of all groups

	CAE (n=60)	CAD (n=60)	NCA (n=59)	*p*
Maximum heart rate (median; IQR)	131.0; 61.7	129.5; 48.0	138.0; 66.0	.536
Average heart rate	74.86±13.24	76.05±11.33	78.66±12.28	.231
Minimum heart rate	57.05±12.15	58.18± 9.61	55.28±7.47	.281
Arrhythmias	18 (30%)	30 (50%)	6 (10.2%)	<.001[a]
SDNN	140.85±44.21	96.51±31.28	181.05±48.67	<.001[b]
RMSSD (median; IQR)	24.0; 39.0	19.0; 31.0	33.0; 57.0	.004[c]
Total power (median; IQR)	2285.0; 2183.7	1750.0; 885.0	2890.0; 2580.0	<.001[d]
Very low-frequency (median; IQR)	225.0; 248.0	115.5; 267.5	320.0; 373.0	<.001[e]
Low-frequency/High-frequency (median; IQR)	1.0; 1.2	2.2; 2.4	0.5; 0.7	<.001[f]
High-frequency (median; IQR)	795.0; 949.5	650.0; 846.0	950.0; 1700.0	<.001[g]
Low-frequency (median; IQR)	785.0; 955.0	1510.0; 2182.5	450.0; 280.0	<.001[h]

CAE: Coronary artery ectasia; CAD: Coronary artery disease; NCA: Normal coronary arteries; SDNN: Standard deviation of all normal-to-normal intervals; RMSSD: root mean square of difference in successive normal-to-normal intervals; p represents significance value of all groups.
[a]p (CAE-CAD) = 0.040, p (CAE-NCA) = 0.014, p (CAD-NCA) <0.001.
[b]p (CAE-CAD) <0.001, p (CAE-NCA) <0.001, p (CAD-NCA) <0.001.
[c]p (CAE-CAD) = 0.777, p (CAE-NCA) = 0.062, p (CAD-NCA) = 0.006.
[d]p (CAE-CAD) <0.001, p (CAE-NCA) = 0.740, p (CAD-NCA) <0.001.
[e]p (CAE-CAD) = 0.622, p (CAE-NCA) <0.001, p (CAD-NCA) <0.001.
[f]p (CAE-CAD) <0.001, p (CAE-NCA) <0.001, p (CAD-NCA) <0.001.
[g]p (CAE-CAD) = 0.654, p (CAE-NCA) = 0.007, p (CAD-NCA) <0.001.
[h]p (CAE-CAD) <0.001, p (CAE-NCA) <0.001, p (CAD-NCA) <0.001.

among the CAD and CAE groups (p=0.777, p=0.622, p=0.654; Table 2).

All significant (p<0.05) parameters in patients with CAE and CAD in the ANOVA and Kruskal-Wallis test analyses (SDNN, RMSSD, TP, VLF, LF/HF, HF, LF, and arrhythmia) were selected in the multinomial logistic regression model. Multinomial logistic regression analysis showed that both low RMSSD (p<0.001) and high LF (p<0.001) were independently correlated with CAE in the first model. In addition, low RMSSD (p<0.001), high LF (p<0.001), and arrhythmia (p=0.003) were correlated with CAE in the second model (Table 3). Otherwise, multinomial logistic regression analysis showed that low SDNN (p<0.001), low TP (p=0.034), high TP (p=0.039), and low LF (p=0.030) were independently correlated with CAD in the first model. In addition, low SDNN (p<0.001), high TP (p=0.023), and arrhythmia (p<0.001) were correlated with CAD in the second model (Table 4).

Coronary angiographic characteristics of CAE and CAD patients

The study population consisted of 60 patients with CAD and 60 patients with CAE; 26.7% had ectasia in 1 vessel, 30% had ectasia in 2 vessels, and 43.3% had ectasia in 3 vessels. In the CAD group, 50% had uniarterial and 50% had multi-arterial disease.

DISCUSSION

The present study is, to the best of our knowledge, the first to compare CAD, CAE, and healthy groups using HRV parameters. Primary findings were, first, that HRV parameters were higher in patients with CAE, indicating lower sympathetic activity, compared to the CAD group, and second, that the incidence of arrhythmias was higher in patients with CAD.

The most common cause of CAE is CAD. The angiographic incidence of CAE ranges from 0.3% to 5.3%. Atheromatous ulcerations found in the ectatic segments suggest that atherosclerosis is the most common cause of CAE. Perfusion defects have been observed in the myocardial regions that sustain ectatic arteries in patients with CAE.[1] Turbulent blood flow in ectatic segments and loss of laminar flow cause an increase in red blood cell aggregation and thrombogeneity. Distal embolization of the thrombus is the major cause of the correlation between CAE and mi-

Table 3. Factors associated with coronary artery ectasia

Coronary artery ectasia	Model 1			Model 2		
Variables	β	Std. Error	*p*	β	Std. Error	*p*
Standard deviations of all normal-to-normal intervals						
Low (<102 ms)	1.119	.660	.090	1.413	.721	.050
High (>180 ms)	-.860	.600	.151	-.962	.651	.141
Normal (102–180 ms)	0[b]	–	–	0[b]	–	–
RMSSD						
Low (<15 ms)	21.012	.597	.001	20.958	.641	.001
High (<39 ms)	.747	.507	.141	.838	.550	.128
Normal (15–39 ms)	0[b]	–	–	0[b]	–	–
Total power						
Low (<2448 ms^2)	.000	.554	.999	-.358	.616	.562
High (<4484 ms^2)	.772	.752	.305	-1.207	.847	.154
Normal (2448–4484 ms^2)	0b	–	–	0[b]	–	–
Low-frequency						
Low (<754 ms^2)	-.822	.598	.170	-.711	.640	.267
High (>1586 ms^2)	20.201	.766	.001	20.945	.797	.001
Normal (754–1586 ms^2)	0[b]	–	–	0[b]	–	–
High-frequency						
Low (<772 ms^2)	.852	.702	.225	.970	.763	.204
High (>1178 ms^2)	.403	.659	.541	.889	.730	.223
Normal (772–1178 ms^2)	0[b]	–	–	0b	–	–
Low-frequency/High-frequency						
Low (<1.5)	-.853	1.021	.404	-.324	1.145	.777
High (>2)	-.218	1.339	.871	.916	1.472	.534
Normal (1.5–2)	0[b]	–	–	0[b]	–	–
Arrhythmia						
Yes	–	–	–	1.982	.676	.003
No	–	–	–	0b	–	–

RMSSD: Root mean square of difference in successive normal-to-normal intervals.

crovascular perfusion defects. The metabolic extent of myocardial ischemia has been found to correlate with diameter and angiographic severity of impaired blood flow in the proximal segment of the left anterior descending coronary artery.[15] Other causes include inflammatory diseases and collagen or connective tissue disorders.[16–18]

Iellamo et al. found that exercise training increases baroreflex sensitivity and heart rate variability in patients with CAD.[19] In an animal study, Hull et al. showed that the presence of depressed vagal reflexes and enhanced sympathetic activation is associated with a greater risk for life-threatening arrhythmias during myocardial ischemia.[20]

Turker et al. found that the incidence of arrhythmias was significantly higher in patients with CAE.[21] Karakaya et al. reported that isolated CAE is associated with prolonged QT interval and increased QT dispersion. Microvascular dysfunction and/or ischemia may be the mechanisms responsible.[22] Microembolisms with consecutive disturbance of coronary perfusion may account for ventricular arrhythmias in patients with CAE.[15] In the present study, incidence of arrhythmias was significantly higher in patients

Table 4. Factors associated with coronary artery disease

Coronary artery ectasia	Model 1			Model 2		
Variables	β	Std. Error	*p*	β	Std. Error	*p*
Standard deviation of all normal-to-normal intervals						
Low (<102 ms)	2.505	.748	.001	2.904	.843	.001
High (>180 ms)	-19.202	6190.707	.998	-19.350	5954.143	.997
Normal (102–180 ms)	0[b]	–	–	0[b]	–	–
RMSSD						
Low (<15 ms)	21.235	.000	–	21.218	.000	–
High (<39 ms)	.773	.719	.283	.753	.814	.355
Normal (15–39 ms)	0[b]	–	–	0[b]	–	–
Total power						
Low (<2448 ms^2)	1.724	.815	.034	1.391	.930	.135
High (<4484 ms^2)	-3.133	1.513	.039	-3.868	1.698	.023
Normal (2448–4484 ms^2)	0[b]	–	–	0[b]	–	–
Low-frequency						
Low (<754 ms^2)	-1.746	.804	.030	-1.573	.914	.085
High (>1586 ms^2)	22.044	.000	–	22.556	.000	–
Normal (754–1586 ms^2)	0[b]	–	–	0[b]	–	–
High-frequency						
Low (<772 ms^2)	1.598	.880	.069	1.600	.983	.103
High (>1178 ms^2)	-.551	.930	.554	.402	1.060	.705
Normal (772–1178 ms^2)	0[b]	–	–	0[b]	–	–
Low-frequency/High-frequency						
Low (<1.5)	-1.954	1.173	.096	-.938	1.353	.488
High (>2)	-1.182	1.449	.415	.886	1.677	.597
Normal (1.5–2)	0[b]	–	–	0[b]	–	–
Arrhythmia						
Yes	–	–	–	3.724	.858	.001
No	–	–	–	0b	–	–

RMSSD: Root mean square of difference in successive normal-to-normal intervals.

with CAD, compared to patients with CAE.

Decrease in vagal modulation or increase in sympathetic activity of cardiac function evaluated by HRV analysis in patients with CAD has been associated with increased risk of arrhythmia and sudden cardiac death.[23,24] Decreases in HRV are also a reported predictor of mortality in CAD patients.[25–27] Turker et al. found that that HRV was significantly lower in CAE patients, compared to those without CAE. These researchers observed significant reductions in time-domain indices, with the exception of the RMSSD in the CAE group. In the present study, RMSSD was lower in CAE patients than in healthy patients, but differences between the groups were not statistically significant, suggesting that HRV reduction in CAE patients was caused by changes in both autonomic and vagal tone.[21] Long-term indices, including SDNN, represent a general measurement of autonomic nervous system balance in time-domain analyses, whereas short-term indices such as RMSSD predominantly reflect parasympathetic activity.[28,29]

HRV parameters among patients with CAD, CAE, and NCA were investigated in the present study. A comparison of CAD and CAE group time-domain pa-

rameters revealed a statistically significant decrease in SDNN. No difference in RMSSD was observed between the CAD and CAE groups, though RMSSD was lower in the CAD group, compared to the CAE group. SDNN was decreased in both the CAE and CAD groups, though the CAD group demonstrated the lowest SDNN values. SDNN is the most frequently used time-domain parameter. Schwartz et al. used SDNN measurements to estimate total cardiac mortality after myocardial infarction.[30] Huikuri et al. found significant correlations between SDNN and the progression of coronary atherosclerosis.[24] In addition, Kurtoğlu et al. also found HRV values diminished in patients with mitral annular calcification, with or without CAD. Time-domain parameters including SDNN, the SD of 5-minute mean RR intervals (SDANN), and the mean of the SD of all normal-to-normal RR intervals for all 5-minute segments (SDNN index) were found to be decreased in the group with mitral annular calcification.[31] Topal E. et al. found that short-term trimetazidine therapy improved HRV parameters and endothelial products such as endothelin-1 and nitric oxide, as well as anginal symptoms in patients with slow coronary artery flow. These patients showed an improvement in HRV parameters that correlated with endothelin-1 and nitric oxide levels.[32] Akyel et al. found that HRV was reduced in diabetic patients, indicating that these patients had both endothelial dysfunction and autonomic dysfunction.[33]

In analysis of frequency-dependent parameters, an increase in TP, VLF, and HF reflects parasympathetic activity, whereas an increase in LF or LF/HF reflects sympathetic activity.[19] In the present study, TP, VLF, and HF values in frequency-dependent parameters were significantly decreased in the CAD group, compared to the NCA group. These values were also decreased in the CAE group, compared to the NCA group, though a significant difference was found between VLF and HF values. No significant difference in VLF and HF was found between the CAD and CAE groups, with TP being the exception. LF and LF/HF ratios were increased in the CAD group, compared to the others. An increase in LF, a decrease in HF, and an increase in LF/HF values has been demonstrated in many ischemic heart disease studies, including the present. SDNN and TP values were significantly decreased, and LF and LF/HF values were increased in the CAD group, compared to the CAE group, indicative of sympathetic activity.

The lack of correlation in the CAE group can be explained by insufficient sample size, and additional studies with larger sample sizes are needed.

In conclusion, CAE causes myocardial perfusion defects and microvascular dysfunction, as does CAD. Ultimately, these lead to changes in the neural control of the heart and the development of autonomic imbalances. A decrease in vagal modulation or an increase in sympathetic cardiac activity, assessed by HRV analysis, leads to worse outcome in patients with CAD than in patients with CAE.

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