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Association between cardiac autonomic nervous dysfunction and the severity of coronary lesions in patients with stable coronary artery disease

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Abstract

Objective: Autonomic dysfunction is recognized in patients with coronary artery disease (CAD) and is related to worse cardiovascular outcome. This study aimed to evaluate cardiac autonomic nervous function by heart rate recovery (HRR) and heart rate variability (HRV), and demonstrate their relationship with the severity of coronary lesions in patients with stable CAD (SCAD).

Methods: Consecutive patients without CAD (controls, n = 65) and those with SCAD (n = 63) were included in this study. Patients with SCAD were further divided into single- or two-/three-vessel disease, as well as $<$70% or $\geq$70% stenosis subgroups. The association between HRR/HRV and coronary lesions was analysed.

Results: HRR and HRV values were significantly lower in the SCAD group compared with the control group. Multivariate logistic regression analysis showed that abnormal HRR and HRV were risk factors of SCAD. Moreover, delayed HRR was a risk factor of the severity of coronary lesions.

Conclusions: Our results show that autonomic function is impaired in patients with SCAD and delayed HRR is closely related to the severity of coronary lesions.

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Introduction

Patients with stable coronary artery disease (SCAD) suffer from chronic myocardial ischaemia and hypoxia, which might result in autonomic regulation imbalance and dysfunction.[1,2] Heart rate recovery (HRR) and heart rate variability (HRV) are widely used methods to assess cardiac autonomic function.[3,4] Abnormal HRR reflects vagal activity withdrawing after exercise and can be used to predict the severity of coronary artery disease (CAD).[1] HRV reflects autonomic responses to environmental and external stimuli, which can reflect sympathetic and vagal modulation of the sinus node.[5] Previous studies have shown that delayed HRR or reduced HRV in patients with CAD are related to worse cardiovascular outcome in these patients.[6,7] However, little is known regarding the status of autonomic nervous function by using combined assessment of HRR and HRV and their relationship with the severity of coronary lesions in patients with SCAD. Therefore, the present study compared HRR and HRV parameters between hospitalized patients with SCAD and non-CAD patients. We examined the association between HRR and HRV for assessing autonomic nervous function with the severity of coronary lesions (number of coronary artery lesions and the degree of coronary artery stenosis) in patients with SCAD.

Methods

Study population

Consecutive patients who were hospitalized because of chest pain during May 2016 to April 2017were included in this retrospective study. Patients were diagnosed with no CAD (controls) or SCAD according to coronary artery angiography (CAG) results. Patients were treated according to the European Society of Cardiology 2013 guideline on the management of SCAD.[8] Patients with SCAD were divided into the single-vessel group ($n = 36$) and two-/three-vessel group ($n = 27$). Patients with SCAD were also divided into the mild coronary stenosis ($<70\%$) group ($n = 25$) and severe coronary stenosis ($\geq 70\%$) group ($n = 38$) according to the degree of coronary artery stenosis. Gensini scores was calculated for every patient.[9] All of the patients underwent 24-hour Holter monitoring and the treadmill exercise test (TET), and all of them achieved the submaximal heart rate goal $[(220 - \text{age}) \times 0.85]$ before CAG. Patients with $\geq 50\%$ stenosis in the left main stem, peripheral vascular occlusive disease, hyperthyroidism, uncontrolled hypertension, decompensated heart failure, Mobitz II second or third degree atrioventricular block, complete left bundle branch block, Wolff–Parkinson–White syndrome, atrial fibrillation, atrial flutter, valvular heart disease, cardiac pacemaker implantation, a history of acute myocardial infarction, acute pericarditis or myocarditis, severe hepatic, and renal dysfunction were excluded.

Ethics committee review was not necessary because this study was a retrospective analysis. Informed consent was waived because this study involved analysis of existing medical records.

CAG and assessment

All of the patients received multi-position selective CAG with local anaesthesia

under continuous electrocardiographic monitoring. A narrowing of $\geq$50% of main branch stenosis was defined as CAD. The degree of coronary artery stenosis was evaluated according to the consensus opinion of two experienced interventional cardiologists.

TET and HRR analysis

The TET was performed on a GET2100 treadmill machine equipped with CASE6.5 software (General Electric Company, Boston, MA, USA) with continuous electrocardiographic monitoring according to the American College of Cardiology/American Heart Association 2002 guideline update for exercise testing.[10] The symptom-limited Bruce's protocol was used.[3] Blood pressure was measured and recorded at rest, at the end of each stress stage, at peak stress, and at the recovery stage until 6 minutes after exercise, or when the ST segment returned to the baseline level. Exercise was stopped at the time of the submaximal heart rate goal. HRR was calculated by subtracting the heart rate values at the 1st to 5th minutes of the recovery phase from the peak heart rate (HRR1−HRR5). HRR1 value $\leq$24 beats per minute[11] and HRR2 value $\leq$42 beats per minute[12] were defined as abnormal. Exercise testing was terminated prematurely for the following reasons: chest pain, fatigue, dyspnoea, severe arrhythmia, blood pressure $\geq$250/120 mmHg; or systolic blood pressure was repeatedly decreased more than 10 mmHg accompanied by hypoperfusion with development of significant electrocardiographic abnormalities, including $\geq$2 mm of ST-segment depression or $\geq$1 mm of ST-segment elevation.

Twenty-four-hour Holter monitoring and HRV analysis

Twenty-four-hour Holter monitoring was performed by a GE Seer Light recording box (General Electric Company) and HRV parameters were analysed by the MARS Software system (General Electric Company). HRV was defined as the beat-to-beat variation in time of consecutive heart beats expressed in normal sinus rhythm on electrocardiogram recordings, ranging from a few minutes to 24 hours. HRV parameters were based on the standards according the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[13] Time domain HRV parameters included the standard deviation of NN intervals (SDNN), standard deviation of all 5-minute mean NN intervals (SDANN), root mean square of successive differences (RMSSD), and the proportion derived by dividing the number of interval differences of successive NN intervals greater than 50 ms by the total number of NN intervals (pNN50). Frequency domain HRV parameters included very-low-frequency power (VLF, 0.003–0.04 Hz), low-frequency power (LF, 0.04–0.15 Hz), high-frequency power (HF, 0.15–0.40 Hz), and the LF/HF ratio.

Statistical analysis

Continuous data are presented as mean $\pm$ standard deviation. Normal distribution of continuous variables was determined using the Kolmogorov–Smirnov test. Continuous variables with a normal distribution were assessed by the Student's *t*-test. Non-normally distributed data were tested by the two-tailed Mann–Whitney U test. The chi-square test was used to compare categorical variables as percentages. The risk factors for SCAD and severity of coronary lesions were determined by multivariate logistic regression analysis. Spearman correlation analysis was performed between HRR and HRV parameters in patients with SCAD. *P* values less than 0.05 were considered statistically significant. All statistical

analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Clinical features of patients with SCAD and controls

A total of 128 patients were included in the study. The clinical characteristics of patients in the control (n = 65; age, 60 ± 6 years; male/total, 28/65 [43.1%]) and SCAD (n = 63; age, 62 ± 6 years; male/total, 36/63 [57.1%]) groups are shown in Table 1. There were no significant differences in sex, age, incidence of smoking, left ventricular ejection fraction, heart rate before treadmill exercise, peak heart, incidence of diabetes mellitus, and dyslipidaemia between the two groups. The Gensini score, percentages of abnormal HRR1 and HRR2, incidence of hypertension, aspirin, statins, and beta-blocker use were significantly higher in the SCAD group compared with the control group (all $P < 0.05$). HRR1 to HRR5 values and the values of HRV parameters (SDNN, RMSSD, pNN50, VLF, LF, and HF) were significantly lower in the SCAD group than in the control group (all $P < 0.05$, Table 1). Multivariate logistic regression analysis showed that a high Gensini score, HRR1 ≤24 bpm, delayed HRR2 and HRR3, and reduced HRV (RMSSD, pNN50, VLF, LF, HF) were risk factors of SCAD after adjusting for sex, age, and beta-blocker use (all $P < 0.05$, Table 2).

Clinical features of patients with SCAD and single-vessel or two-/three-vessel lesions

A total of 17 stents were implanted in 11 patients with SCAD. Sex, age, left ventricular ejection fraction, peak HR, hypertension, diabetes mellitus, beta-blocker use, and HRV parameters, were similar between the single-vessel and two-/three-vessel disease groups. The Gensini score, heart rate before treadmill exercise, percentage of abnormal HRR2, and incidence of smokers were significantly higher, while HRR2, HRR3, and HRR5 values were significantly lower in the two-/three-vessel lesion group compared with the single-vessel lesion group (all $P < 0.05$, Table 3). Multivariate logistic regression analysis showed that a high Gensini score (hazard ratio [HR] = 1.302, 95% confidence interval [CI] 1.110–1.527, $P = 0.001$), HRR2 ≤42 bpm (HR = 4.047, 95% CI 1.262–12.983, $P = 0.019$), and delayed HRR5 (HR = 1.059, 95% CI 1.001–1.121, $P = 0.047$) were risk factors of multiple coronary artery lesions in patients with SCAD after adjusting for sex, age, and beta-blocker use (all $P < 0.05$, Table 4).

Clinical features of patients with SCAD and coronary stenosis <70% and coronary stenosis ≥70%

The clinical characteristic and HRV parameters were similar between the coronary stenosis <70% and coronary stenosis ≥70% groups. The Gensini score was significantly higher, while HRR2, HRR4, and HRR5 values were significantly lower in the coronary stenosis ≥70% group compared with the coronary stenosis <70% group (all $P < 0.05$, Table 5). Multivariate logistic regression analysis showed that a high Gensini score (HR = 1.328, 95% CI 1.131–1.559, $P = 0.001$) and delayed HRR5 (HR = 1.062, 95% CI 1.002–1.124, $P = 0.043$) were risk factors of severe coronary artery stenosis in patients with SCAD after adjusting for sex, age, and beta-blocker use (both $P < 0.05$, Table 6).

Spearman correlation analysis of HRR and HRV parameters in SCAD

Spearman correlation analysis between HRR and HRV parameters showed that

Table 1. Clinical characteristics of the control and SCAD groups

	Control group (n = 65)	SCAD group (n = 63)	*P* value
Age (years)	60.34 ± 6.08	61.86 ± 6.09	0.161
Male sex (n, %)	28/65 (43.1%)	36/63 (57.1%)	0.112
Smoker (n, %)	17/65 (26.2%)	23/63 (36.5%)	0.206
BMI (kg/m^2)	24.15 ± 3.33	24.40 ± 3.36	0.679
Hypertension (n, %)	32/65 (49.2%)	47/63 (74.6%)	0.004
DM (n, %)	6/65 (9.2%)	6/63 (9.5%)	0.995
Dyslipidaemia (n, %)	52/65 (80.0%)	54/63 (85.7%)	0.392
Cr (μM)	66.55 ± 14.43	71.57 ± 14.42	0.051
CHOL (mM)	4.48 ± 0.89	4.60 ± 1.20	0.983
TG (mM)	1.67 ± 0.90	1.84 ± 1.34	0.717
LDL-c (mM)	2.70 ± 0.85	2.87 ± 1.07	0.502
HDL-c (mM)	1.10 ± 0.35	1.04 ± 0.26	0.399
Random blood glucose (mM)	5.73 ± 1.56	5.93 ± 1.77	0.359
HBA1c (%)	5.77 ± 0.82	5.85 ± 0.74	0.600
hs-CRP(mg/L)	2.84 ± 2.00	5.98 ± 15.58	0.337
TNI (μg/L)	0.005 ± 0.01	0.267 ± 1.77	0.578
BNP (pM)	36.00 ± 37.03	41.54 ± 38.90	0.483
Ejection fraction (%)	62.28 ± 6.30	61.19 ± 5.92	0.317
Gensini score	1.76 ± 3.05	18.96 ± 20.05	0.000
Heart rate before Ex (bpm)	78.15 ± 12.42	82.29 ± 12.12	0.172
Peak heart rate (bpm)	139.23 ± 7.78	137.78 ± 6.35	0.602
HRR1 (bpm)	29.02 ± 10.48	24.21 ± 8.16	0.005
HRR1 ≤24 bpm (n, %)	24/65 (36.9%)	37/63 (58.7%)	0.014
HRR2 (bpm)	48.34 ± 10.81	42.14 ± 10.96	0.002
HRR2 ≤42 bpm (n, %)	20/65 (30.8%)	34/63 (54.0%)	0.008
HRR3 (bpm)	53.51 ± 10.62	47.00 ± 10.73	0.001
HRR4 (bpm)	55.22 ± 9.81	49.52 ± 10.27	0.002
HRR5 (bpm)	56.34 ± 9.87	51.22 ± 10.96	0.006
SDNN (ms)	126.42 ± 29.90	115.57 ± 26.41	0.032
SDANN (ms)	112.74 ± 29.77	104.86 ± 26.92	0.119
RMSSD (ms)	27.60 ± 8.97	22.11 ± 6.03	0.000
pNN50 (%)	6.71 ± 6.43	3.45 ± 3.30	0.000
VLF (ms)	28.49 ± 7.37	24.43 ± 5.83	0.001
LF (ms)	16.15 ± 5.32	13.69 ± 4.03	0.006
HF (ms)	11.34 ± 4.03	8.93 ± 2.52	0.000
LF/HF	1.47 ± 0.34	1.56 ± 0.35	0.118
Medication			
Aspirin use (n, %)	32/65 (49.2%)	58/63 (92.1%)	0.000
Statin use (n, %)	37/65 (56.9%)	59/63 (93.7%)	0.000
Beta-blocker use (n, %)	17/65 (26.2%)	37/63 (58.7%)	0.000
ACEI use (n, %)	8/65 (12.3%)	14/63 (22.2%)	0.137
ARBs use (n, %)	13/65 (20%)	18/63 (28.6%)	0.258
CCB use (n, %)	25/65 (38.5%)	27/63 (42.9%)	0.613
Diuretic use (n, %)	3/65 (4.6%)	7/63 (11.1%)	0.299

Values are expressed as n (%) or mean ± SD. Abbreviations: control, non-coronary artery disease; SCAD, stable coronary artery disease; BMI, body mass index; DM, diabetes mellitus; Cr, creatinine; CHOL, cholesterol; TG, triglycerides; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; HBA1c, glycosylated haemoglobin; hs-CRP, high-sensitivity C-reactive protein; TNI, troponin I; BNP, brain natriuretic peptide; Ex, treadmill exercise; HRR, heart rate recovery; HRRn, heart rate recovery at n minutes post-exercise; SDNN, standard deviation of NN intervals; SDANN, standard deviation of all 5,minute mean NN intervals; RMSSD, root mean square of successive differences; pNN50, the proportion derived by dividing the number of interval differences of successive NN intervals greater than 50 ms by the total number of NN intervals; VLF, very-low-frequency power; LF, low-frequency power; HF, high-frequency power; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Table 2. Multivariate logistic regression results for the risk of SCAD.

	B	SE	Wald	*P* value	HR	95% CI
Hypertension (n, %)	0.787	0.437	3.242	0.072	2.196	0.933–5.171
Gensini score	0.406	0.076	28.480	0.000	1.501	1.293–1.743
HRR1 (bpm)	0.047	0.024	3.854	0.050	1.048	1.000–1.099
HRR1 $\leq$24 bpm (n, %)	0.857	0.408	4.415	0.036	2.356	1.059–5.238
HRR2 (bpm)	0.045	0.021	4.530	0.033	1.046	1.004–1.091
HRR2 $\leq$42 bpm (n, %)	0.754	0.412	3.342	0.068	2.126	0.947–4.771
HRR3 (bpm)	0.050	0.021	5.378	0.020	1.052	1.008–1.096
HRR4 (bpm)	0.042	0.023	3.437	0.064	1.044	0.998–1.092
HRR5 (bpm)	0.027	0.021	1.626	0.202	1.028	0.985–1.071
SDNN (ms)	0.011	0.007	2.061	0.151	1.011	0.996–1.026
RMSSD (ms)	0.098	0.033	8.781	0.003	1.104	1.034–1.178
pNN50 (ms)	0.144	0.055	6.845	0.009	1.155	1.036–1.285
VLF (ms)	0.095	0.034	7.953	0.005	1.100	1.029–1.175
LF (ms)	0.113	0.048	5.575	0.018	1.236	1.019–1.23
HF (ms)	0.212	0.075	8.062	0.005	1.236	1.067–1.431

Abbreviations: SCAD, stable coronary artery disease; HR, hazard ratio; CI, confidence interval; HRR, heart rate recovery; HRRn, heart rate recovery at n minutes post-exercise; SDNN, standard deviation of NN intervals; RMSSD, root mean square of successive differences; pNN50, the proportion derived by dividing the number of interval differences of successive NN intervals greater than 50 ms by the total number of NN intervals; VLF, very-low-frequency power; LF, low-frequency power; HF, high-frequency power.

Table 3. Clinical characteristic of the single-vessel SCAD group and two- or three-vessel SCAD group

	Single-vessel (n = 36)	Two/three-vessel (n = 27)	*P* value
Age (year)	61.17 $\pm$ 5.44	62.78 $\pm$ 6.87	0.303
Male sex (n, %)	18/36 (50%)	18/27 (66.7%)	0.186
Smoker (n, %)	9/36 (25%)	14/27 (51.9%)	0.028
BMI (kg/m^2)	24.78 $\pm$ 3.64	23.88 $\pm$ 2.92	0.293
Hypertension (n, %)	25/36 (69.4%)	22/27 (81.5%)	0.277
DM (n, %)	1/36 (2.8%)	5/27 (18.5%)	0.094
Dyslipidaemia (n, %)	30/36 (83.3%)	24/27 (88.9%)	0.795
Cr (μM)	70.88 $\pm$ 16.44	72.49 $\pm$ 11.43	0.650
CHOL (mM)	4.52 $\pm$ 0.94	4.70 $\pm$ 1.49	0.906
TG (mM)	1.58 $\pm$ 0.93	2.19 $\pm$ 1.68	0.089
LDL-c (mM)	2.83 $\pm$ 0.82	2.91 $\pm$ 1.35	0.546
HDL-c (mM)	1.05 $\pm$ 0.27	1.02 $\pm$ 0.23	0.597
Ejection fraction (%)	60.53 $\pm$ 5.42	62.07 $\pm$ 6.53	0.275
Gensini score	9.07 $\pm$ 5.07	32.15 $\pm$ 24.66	0.000
Heart rate before Ex (bpm)	79.5 $\pm$ 9.93	86 $\pm$ 13.88	0.034
Peak heart rate (bpm)	138 $\pm$ 5.79	137.48 $\pm$ 7.14	0.751
HRR1 (bpm)	25.11 $\pm$ 7.49	23 $\pm$ 8.97	0.313
HRR1 $\leq$24 bpm (n, %)	18/36 (50.0%)	19/27 (70.4%)	0.104
HRR2 (bpm)	44.53 $\pm$ 9.78	38.96 $\pm$ 11.79	0.045
HRR2 $\leq$42 bpm (n, %)	14/36 (38.9%)	20/27 (74.1%)	0.006

(continued)

Table 3. Continued.

	Single-vessel (n = 36)	Two/three-vessel (n = 27)	*P* value
HRR3 (bpm)	49.31 ± 9.88	43.93 ± 11.22	0.019
HRR4 (bpm)	51.56 ± 9.74	46.82 ± 10.51	0.069
HRR5 (bpm)	54.11 ± 10.10	47.37 ± 11.05	0.011
SDNN (ms)	117.86 ± 26.97	112.52 ± 25.84	0.431
SDANN (ms)	107.28 ± 27.03	101.63 ± 26.94	0.414
RMSSD (ms)	23.17 ± 7.26	20.70 ± 3.47	0.081
pNN50 (%)	4.12 ± 4.03	2.57 ± 1.62	0.457
VLF (ms)	24.26 ± 5.90	24.65 ± 5.83	0.453
LF (ms)	13.61 ± 4.32	13.80 ± 3.69	0.857
HF (ms)	9.25 ± 2.85	8.51 ± 1.98	0.248
Beta-blocker use (n, %)	21/36 (58.3%)	16/27 (59.2%)	0.941

Values are expressed as n (%) or mean ± SD. Abbreviations: SCAD, stable coronary artery disease; BMI, body mass index; DM, diabetes mellitus; Cr, creatinine; CHOL, cholesterol; TG, triglycerides; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; Ex, treadmill exercise; HRR, heart rate recovery; HRRn, heart rate recovery at n minutes post-exercise; SDNN, standard deviation of NN intervals; SDANN, standard deviation of all 5-minute mean NN intervals; RMSSD, root mean square of successive differences; pNN50, the proportion derived by dividing the number of interval differences of successive NN intervals greater than 50 ms by the total number of NN intervals; VLF, very-low-frequency power; LF, low-frequency power; HF, high-frequency power.

Table 4. Multivariate logistic regression results for the risk of coronary lesions in SCAD

	B	SE	Wald	*P* value	HR	95% CI
Smoker (n, %)	1.325	0.708	3.503	0.061	3.763	0.939–15.072
Gensini score	0.264	0.081	10.488	0.001	1.302	1.110–1.527
Heart rate before Ex (bpm)	0.051	0.026	3.854	0.050	1.053	1.000–1.107
HRR2 (bpm)	0.042	0.027	2.331	0.127	1.043	0.988–1.100
HRR2 ≤42 bpm (n, %)	1.398	0.595	5.526	0.019	4.047	1.262–12.983
HRR3 (bpm)	0.046	0.028	2.713	0.100	1.047	0.991–1.106
HRR5 (bpm)	0.057	0.029	3.950	0.047	1.059	1.001–1.121

Abbreviations: SCAD, stable coronary artery disease; HR, hazard ratio; CI, confidence interval; Ex, treadmill exercise; HRR, heart rate recovery; HRRn, heart rate recovery at n minutes post-exercise.

the percentage of abnormal HRR1 was negatively correlated with RMSSD values ($r = -0.276$, $P = 0.028$) and pNN50 values ($r = -0.252$, $P = 0.046$). HRR5 values were positively correlated with RMSSD values ($r = 0.271$, $P = 0.032$) and pNN50 values ($r = 0.251$, $P = 0.047$). HRR2 values were also positively correlated with RMSSD values ($r = 0.259$, $P = 0.041$) and HRR3 values were positively correlated with SDNN values ($r = 0.271$, $P = 0.031$) in patients with SCAD (Table 7).

Discussion

The main finding of the present study is that abnormal HRR and HRV were closely related to development of SCAD, which suggested the presence of autonomic dysfunction in patients with SCAD. Moreover, reduced HRR, but not HRV changes, were related to the severity of coronary artery lesions in patients with SCAD. To the best of our knowledge, this is the first report to assess autonomic dysfunction

Table 5. Clinical characteristics of the coronary stenosis <70% SCAD group and coronary stenosis ≥70% SCAD group.

	Stenosis <70% (n = 25)	Stenosis ≥70% (n = 38)	*P* value
Age (years)	61.96 ± 6.02	61.79 ± 6.22	0.914
Male sex (n, %)	12/25 (48.0%)	24/38 (63.2%)	0.234
Smoker (n, %)	8/25 (32.0%)	15/38 (39.5%)	0.547
BMI (kg/m^2)	24.90 ± 4.08	24.06 ± 2.80	0.377
Hypertension (n, %)	18/25 (72.0%)	29/38 (76.3%)	0.700
DM (n, %)	1/25 (4.0%)	5/38 (13.2%)	0.440
Dyslipidaemia (n, %)	20/25 (80.0%)	34/38 (89.5%)	0.494
Cr (μM)	72.84 ± 17.44	70.73 ± 12.22	0.574
CHOL (mM)	4.55 ± 1.04	4.63 ± 1.31	0.773
TG (mM)	1.51 ± 0.61	2.05 ± 1.61	0.407
LDL-c (mM)	2.85 ± 0.89	2.88 ± 1.18	0.768
HDL-c (mM)	1.10 ±0.28	1.00 ± 0.23	0.136
Ejection fraction (%)	61.04 ± 5.83	61.29 ± 6.06	0.795
Gensini score	7.66 ± 5.01	26.40 ± 22.68	0.000
Heart rate before Ex (bpm)	79.32 ± 11.65	84.24 ± 12.18	0.116
Peak heart rate (bpm)	138 ± 6.20	137.63 ± 6.53	0.824
HRR1 (bpm)	26.08 ± 7.93	22.97 ± 8.18	0.141
HRR1 ≤24 bpm (n, %)	13/25 (52.0%)	24/38 (63.2%)	0.379
HRR2 (bpm)	45.68 ± 8.38	39.82 ± 11.90	0.037
HRR2 ≤42 bpm (n, %)	10/25 (40.0%)	24/38 (63.2%)	0.071
HRR3 (bpm)	50.20 ± 8.78	44.90 ± 11.46	0.054
HRR4 (bpm)	52.92 ± 9.39	47.29 ± 10.33	0.032
HRR5 (bpm)	55.16 ± 10.23	48.63 ± 10.77	0.019
SDNN (ms)	118.92 ± 18.79	113.37 ± 30.46	0.375
SDANN(ms)	108.12 ± 19.60	102.71 ± 30.87	0.398
RMSSD (ms)	23.28 ± 7.79	21.34 ± 4.47	0.267
pNN50 (%)	4.29 ± 4.78	2.91 ± 2.10	0.806
VLF (ms)	24.58±6.00	24.33 ± 5.79	0.869
LF (ms)	13.92 ± 4.55	13.54 ± 3.71	0.721
HF (ms)	9.39 ± 2.95	8.63 ± 2.19	0.255
LF/HF	1.51 ± 0.30	1.60 ± 0.38	0.304
Beta-blocker use (n, %)	14/25 (56.0%)	23/38 (60.5%)	0.721

Values are expressed as n (%) or mean ± SD. Abbreviations: SCAD, stable coronary artery disease; BMI, body mass index; DM, diabetes mellitus; Cr, creatinine; CHOL, cholesterol; TG, triglycerides; LDL,c, low-density lipoprotein cholesterol; HDL,c, high-density lipoprotein cholesterol; Ex, treadmill exercise; HRR, heart rate recovery; HRRn, heart rate recovery at n minutes post-exercise; SDNN, standard deviation of NN intervals; SDANN, standard deviation of all 5,minute mean NN intervals; RMSSD, root mean square of successive differences; pNN50, the proportion derived by dividing the number of interval differences of successive NN intervals greater than 50 ms by the total number of NN intervals; VLF, very-low-frequency power; LF, low-frequency power; HF, high-frequency power.

and its relationship with severity of coronary lesions in patients with SCAD and combined HRR and HRV analysis.

HRR and HRV are known sensitive parameters that reflect changes in autonomic nervous function. Delayed HRR after the TET is considered a marker of reduced parasympathetic activity.[6] Decreased vagal and increased sympathetic modulation of the sinus node may be

Table 6. Multivariate logistic regression results for the risk of coronary artery stenosis in SCAD

	B	S.E.	Wald	*P* value	HR	95% CI
Gensini score	0.284	0.082	12.023	0.001	1.328	1.131–1.559
HRR2 (bpm)	0.049	0.028	3.103	0.078	1.050	0.994–1.110
HRR4 (bpm)	0.056	0.032	3.052	0.081	1.126	0.993–1.126
HRR5 (bpm)	0.059	0.029	4.087	0.043	1.062	1.002–1.124

Abbreviations: SCAD, stable coronary artery disease; HR, hazard ratio; CI, confidence interval; HRR, heart rate recovery; HRRn, heart rate recovery at n minutes post-exercise.

Table 7. Spearman correlation analysis between HRR and HRV parameters in SCAD

	SDNN	SDANN	RMSSD	pNN50	VLF	LF	HF	LF/HF
HRR1	0.193	0.168	0.154	0.130	0.237	0.203	0.192	0.045
HRR1 $\leq$24 bpm	−0.239	−0.223	−0.276*	−0.252*	−0.246	−0.194	−0.229	0.044
HRR2	0.226	0.177	0.259*	0.245	0.236	0.161	0.235	−0.044
HRR2 $\leq$42 bpm	−0.119	−0.090	−0.171	−0.158	−0.109	−0.060	−0.170	0.107
HRR3	0.271*	0.245	0.231	0.223	0.186	0.145	0.247	−0.082
HRR4	0.159	0.129	0.220	0.218	0.161	0.095	0.183	−0.086
HRR5	0.228	0.202	0.271*	0.251*	0.153	0.102	0.238	−0.165

Abbreviations: HRR, heart rate recovery; HRV, heart rate variability; SCAD, stable coronary artery disease; SDNN, standard deviation of NN intervals; SDANN, standard deviation of all 5-minute mean NN intervals; RMSSD, root mean square of successive differences; pNN50, the proportion derived by dividing the number of interval differences of successive NN intervals greater than 50 ms by the total number of NN intervals; VLF, very-low-frequency power; LF, low-frequency power; HF, high-frequency power; HRRn, heart rate recovery at n minutes post-exercise. Statistical significance is shown as $*P < 0.05$.

reflected by reduced HRV.[5] Our study showed that HRR1 to HRR5 values and HRV parameter (SDNN, RMSSD, pNN50, VLF, LF, and HF) values were lower in patients with SCAD compared with controls. Multivariate regression analysis demonstrated that abnormal HRR1, delayed HRR2 to HRR3, and reduced HRV (RMSSD, pNN50, VLF, LF, and HF) were risk factors of SCAD after adjusting for sex, age, and beta-blocker use. These findings indicated that sympathetic and vagal function was impaired in patients with SCAD. Furthermore, our study showed that HRR values were lower in the two-/three-vessel SCAD group and in the coronary stenosis $\geq$70% SCAD group. This finding indicated that parasympathetic function was impaired in proportion with increasing severity of coronary lesions in patients with SCAD. However, HRV values were similar in patients with SCAD and single- or multiple-vessel lesions between the coronary stenosis $<$70% and $\geq$70% groups. This finding suggested that HRV parameters could not be used to predict the severity of coronary artery lesions. These findings are in line with previous reports. Ghaffari and colleagues observed that abnormal HRR was associated with the severity of coronary artery stenosis in patients with CAD.[1] However, another study showed that abnormal HRR predicted the presence of CAD, but not the severity of coronary lesions.[14] Previous studies[15,16] have also shown that HRV can be used as a method for detecting myocardial ischaemia in subjects without known

CAD, and reduced LF, HF, SDNN, RMSSD were predictive of obstructive CAD. Kotecha et al.[2] reported that 5-minute HRV could predict obstructive angiographic coronary disease. Beta-blockers enhance vagal tone during daily activities. Previous studies have shown that HRR and HRV parameters can be significantly affected by beta-blocker use.[17,18] Multiple logistic regression analysis in our study showed that HRR and HRV values were different between the control and SCAD groups and between the two subgroups of patients with SCAD after adjusting for sex, age, and beta-blocker use. Therefore, the differences in HRR and HRV parameters between the various groups were unlikely to be due to beta-blocker use in our study.

Notably, we found that delayed HRR and reduced HRV were related to SCAD, while low HRR values were associated with severe coronary lesions in patients with SCAD. Therefore, assessing HRR and HRV is important for patients who are suspected as having SCAD. Patients with abnormal HRR and HRV values have an increased risk of SCAD, while abnormal HRR could be used to speculate the severity of coronary lesions. Therefore, patients with abnormal HRR and HRV are suitable candidates for CAG to confirm the diagnosis of SCAD. Recently, ORBITA investigators reported the placebo effect of percutaneous coronary intervention (PCI) in patients with stable angina.[19] Whether patients with SCAD and severely impaired autonomic nervous function might benefit more from PCI s compared with patients with SCAD and only mildly impaired autonomic nervous function remains unknown. The FAME 2 study suggested that PCI of lesions with reduced fractional flow reserve improved long-term outcome and was economically attractive compared with optimal medical therapy alone.[20,21] Whether autonomic nervous system dysfunction is improved post-PCI and whether improvement of autonomic nervous system function serves as a major determinant for outcome post-PCI in patients with SCAD remain unknown. Future clinical trials evaluating the real-world efficacy of PCI in patients with SCAD and various degrees of autonomic nervous system dysfunction are warranted.

Study limitations

There are some limitations in this study. First, the present study results were derived from a small patient cohort based on a single-centre database. The number of our patient population was limited because some of the patients with a serious condition in SCAD could not perform the TET. Our results need to be validated by a larger patient cohort from a multicentre database. Second, because of the small number of patients, we did not observe the predictive value of abnormal HRR and HRV in the prognosis of patients with SCAD. A long follow-up period is required to observe the prognostic value of autonomic nervous dysfunction in patients with SCAD.

Conclusions

Our study shows that autonomic nervous function is abnormal in patients with SCAD as reflected by reduced HRR and HRV. The severity of coronary lesions is associated with lower HRR values, but not changes in HRV. Therefore, CAG is should be indicated for patients who are suspected of having abnormal HRR and HRV, while negative CAG results might be found in patients with normal HRR and HRV.

Author contributions

Ye Gu conceived and designed the study. Yafei Chen and Yijun Yu performed the statistical analyses, wrote the first draft, and revised the

manuscript. Wusong Zou, Mingjing Zhang, and Yuting Wang analysed the data and revised the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declare that there is no conflict of interest

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