ORIGINAL RESEARCH

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Heart rate variability and turbulence to determine true coronary artery disease in patients with ST segment depression without angina during exercise stress testing

Abstract

Purpose: ST segment depression without angina during an exercise stress test causes diagnostic problems, particularly in non-diabetic patients. Heart rate variability (HRV) and heart rate turbulence (HRT) are used to evaluate the changes in cardiac autonomic functions and are also both decreased in patients with coronary artery disease. The aim of this study was determine the values of HRV and HRT that discriminate true coronary artery disease from false positive stress test results.

Methods: Ninety non-diabetic patients who underwent diagnostic coronary angiography (CA) due to suspected coronary artery disease after ST segment depression without angina during an exercise stress test were enrolled in the study. Prior to CA, 24 hour ambulatory electrocardiogram recordings were taken and HRV and HRT parameters were calculated.

Results: Patients were divided into three groups according to the severity of their coronary lesions: (group 1 normal, group 2 non-obstructive and group 3 obstructive. There were no differences among the groups with regards to age, sex, medical history, medications, systolic and diastolic blood pressures, body mass index, fasting glucose, anemia and thyroid status, lipid profile and creatinine clearance. HRV parameters and turbulence slope (TS) were significantly lower while turbulence onset (TO) was significantly higher in group 3 than groups 1 and 2. According to the cut-off values calculated using ROC analysis, SDNN $\leq$ 69.63 msec, TO $>$ 0.14%, and TS $\leq$ 2.78 msec/RR have high diagnostic accuracy for predicting obstructive coronary artery disease.

Conclusion: HRV and HRT parameters may provide additional information for discriminating between patients who do and do not truly need CA.

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Coronary angiography continues to be used as the gold standard method for diagnosis of coronary artery disease (CAD). Noninvasive stress test procedures are important auxiliary diagnostic tools that provide additional information about the likelihood of obstructive CAD and help distinguish which patients should receive coronary angiography, particularly in patients with an intermediate risk for CAD. The diagnostic accuracy of these tests depends on the pretest probability of CAD, which is determined by age, gender and symptoms [1]. For patients with a low pretest probability of having CAD, the exercise stress test has the drawback of a high false-positive rate of ST-segment depression [2]. Although not suggested by current guidelines, a substantial number of exercise stress tests are performed on patients with a low to intermediate risk [1]. Overall, 25% of patients undergoing coronary angiography may have normal or slightly abnormal studies [3]; moreover, ST segment depression without angina during an exercise stress test causes diagnostic problems, particularly in non-diabetic patients.

Heart rate variability (HRV) analysis has been used as a predictor of sudden cardiac death and as a useful tool for assessing autonomic cardiac functions [4]. Clinical studies have shown that reduced HRV correlates with an increased risk of cardiac mortality [5]. Heart rate turbulence (HRT), which reflects the response of heart rate to a premature ventricular beat (PVB), has been introduced as a new noninvasive tool for cardiac risk stratification. HRT is one of the strongest independent cardiac risk predictors after myocardial infarction [6]. Both HRV and HRT are known to be blunted in CAD [7,8].

The aim of this study was to determine which values of HRV and HRT discriminate true coronary artery disease from false positive stress test results.

Materials and Methods

Study Population

Ninety non-diabetic patients with suspected coronary artery disease, because of ST segment depression without angina during an exercise stress test, and who were to receive diagnostic coronary angiography, were enrolled to the study. An exercise stress test was performed on patients suffering from chest pain and with low to intermediate pretest probability. Only the patients having ST segment depression without angina during an exercise stress test were included in the study. Patients with known coronary artery disease, significant valvular heart disease, congenital heart disease, atrial fibrillation, heart conduction disorders, branch block, an implanted pacemaker, diabetes mellitus, prior cerebrovascular accident, chronic obstructive

pulmonary disease, severe liver or renal insufficiency, acute or chronic inflammatory disease or malignancy were excluded from the study. Smokers, patients who were referred from another center, who experienced chest pain, ST segment elevation or malignant ventricular arrhythmias during the test, terminated early due to various reasons, developed an abnormal blood pressure response, had pathologies which may cause ST segment depression such as anemia, cardiomyopathy, digitalis use, hypokalemia, left ventricular hypertrophy or mitral valve prolapse were also excluded from the study.

The present study was a single center study. All examinations were performed at the cardiology clinic. All subjects gave their informed consent and the study protocol was approved by the ethics committee at our institution.

Exercise Stress Test

Patients were recruited from the stress test laboratory of our outpatient clinic. Data from patients who had eaten food within 3 hours of the test were not used. Treadmill exercise tests (Marquette 2000 Treadmill, GE Medical Systems, Milwaukee, USA) were performed using the Bruce protocol. ST segment depression was defined as 0.1 mV or greater horizontal or downsloping ST segment depression at 80 msec after the J point.

Heart Rate Variability Analysis

Twenty-four hour Holter recordings taken from both the patient and control groups were downloaded onto a computer and analyzed with a Holter program (Reynolds Medical Pathfinder Software, Version V8.255, Hedford, England). All recordings were also examined visually and artifacts were deleted manually. All of the recordings had at least 22 hours of data once the artifacts were deleted. HRV parameters were calculated and statistically analyzed. Both the time- and frequency-domain parameters of HRV were determined through analysis of the entire 24 hour recordings. The time-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 Pacemaker and Electrophysiology [9], and included mean RR intervals (RR), percentage of differences between adjacent NN intervals that are >50 msec (pNN50), standard deviation of all normal RR intervals (SDNN), standard deviation of the mean of normal RR intervals at each 5 minute segment (SDANN), and root mean squared differences of successive RR intervals (RMSSD). The frequency-domain HRV parameters used in this study were chosen according to the same guidelines [9], and included vari-

ance of all NN intervals (total power: approximately ≤ 0.4 Hz), power in the very low frequency range (VLF: 0.003-0.04 Hz), power in the low frequency range (LF: 0.04-0.15 Hz), and power in the high frequency range (HF: 0.15-0.4 Hz).

All recordings were made under similar conditions and in a similar environment. The patients and the control subjects were asked not to consume tea, coffee, chocolate or alcohol-containing substances for at least eight hours before and during the entire Holter recording. They were asked not to engage in extraordinary behavior or activity and to try to have as ordinary a day as possible. None of the subjects were involved in competitive sporting activities.

Heart Rate Turbulence Analysis

HRT parameters, turbulence onset (TO) and turbulence slope (TS) were calculated automatically by a computer program (HRT View, Version 0.60–0.1 Software Programme, Munich, Germany). Abnormal data that occurred between five sinus beats before and 15 sinus beats after a PVB, as well as visually identified artifacts that the program accepted as a normal PVB,

were excluded from analysis. TO, an indicator of early sinus acceleration after PVB, was defined as the difference between the mean duration of the first two sinus beats following a PVB and the mean duration of the last two sinus beats preceding a PVB, divided by the mean duration of the last two sinus beats preceding the PVB [10]. TS is an indicator of late sinus deceleration after PVB and is defined as the maximum positive slope of a regression line assessed over any sequence of five subsequent RR intervals within the first 20 sinus rhythm intervals after PVB [11].

Coronary Angiography

Elective diagnostic coronary angiography (Artis zee, Siemens, Germany) was performed on all subjects. Coronary angiograms were evaluated by two experts and the mean values were used to assess the severity of stenosis. Obstructive coronary artery disease was defined as stenosis that obstructed 50% or more of the diameter of a major epicardial or branch vessel that was more than 2.0 mm in diameter. Modified Gensini scores were

TABLE 1. Demographic characteristics of the study groups

Variables	Group 1 n=30 number (%)	Group 2 n=30 number (%)	Group 3 n=30 number (%)	P value	P value Group 3 vs. 1	P value Group 3 vs. 2
Age (years)	57±8	57±9	61±10	0.139	0.249	0.264
Male	14 (47)	16 (53)	21 (70)	0.171	0.067	0.184
Hypertension	14 (47)	15 (50)	17 (57)	0.733	0.438	0.605
Dyslipidemia	6 (20)	6 (20)	6 (20)	1.000	1.000	1.000
β blocker	10 (33)	11 (37)	13 (43)	0.718	0.426	0.589
RAS blocker	10 (33)	8 (27)	15 (50)	0.155	0.190	0.063
CC blocker	4 (13)	4 (13)	7 (23)	0.487	0.317	0.317
Acetylsalicylic acid	9 (30)	12 (40)	17 (57)	0.107	0.037	0.196
Statin	4 (13)	4 (13)	8 (27)	0.296	1.000	0.197
Systolic blood pressure (mmHg)	130 [120-135]	128 [115-145]	130 [120-143]	0.937	0.715	0.851
Diastolic blood pressure (mmHg)	80 [75-80]	80 [75-90]	80 [75-88]	0.758	0.469	0.589
Body mass index (kg/m ²)	28±3	27±3	28±6	0.921	1.000	1.000
Fasting glucose (mg/dl)	96 [89-96]	90 [87-99]	98 [91-111]	0.152	0.079	0.120
Hemoglobin (g/dl)	12.5±1.3	12.8±1.3	13.2±1.3	0.086	0.082	0.776
TSH (μIU/ml)	1.67 [1.16-2.21]	1.13 [0.70-1.73]	1.23 [0.67-1.64]	0.250	0.092	0.413
Total cholesterol (mg/dl)	192±35	205±48	189±30	0.251	1.000	0.342
LDL-cholesterol (mg/dl)	126±29	142±47	125±38	0.176	1.000	0.311
HDL- cholesterol (mg/dl)	47 [41-48]	48 [38-61]	49 [41-70]	0.987	0.879	0.906
Triglyceride (mg/dl)	145±66	149±70	136±67	0.759	1.000	1.000
Creatinine clearance (ml/min/1.73 m ²)	112±27	98±26	87±39	0.082	0.078	0.902

RAS rennin angiotensin aldosteron; CC calcium channel; TSH thyroid stimulating hormone; LDL low density lipoprotein; HDL high density lipoprotein.

Data are shown as n (%), mean±SD, median [interquartile range].

TABLE 2. Comparison of the demographic characteristics between group 3 and combined groups 1+2

	Group 1 + 2 n=60 number (%)	Group 3 n=30 number (%)	P value
Age (years)	57±9	61±10	0.050
Male	30 (50)	21 (70)	0.071
Hypertension	29 (48)	17 (57)	0.456
Dyslipidemia	12 (20)	6 (20)	1.000
β blocker	21 (35)	13 (43)	0.442
RAS blocker	18 (30)	15 (50)	0.063
CC blocker	8 (13)	7 (23)	0.230
Acetylsalicylic acid	21 (35)	17 (57)	0.050
Statin	8 (13)	8 (27)	0.119
Systolic blood pressure (mmHg)	125 [120-138]	130 [120-143]	0.749
Diastolic blood pressure (mmHg)	80 [75-85]	80 [75-88]	0.465
Body mass index (kg/m ²)	28±3	28±6	0.878
Fasting glucose (mg/dl)	93 [87-102]	98 [91-111]	0.055
Hemoglobin (g/dl)	12.7±1.3	13.2±1.3	0.054
TSH (μIU/ml)	1.29 [0.92-2.04]	1.23 [0.67-1.64]	0.149
Total cholesterol (mg/dl)	198±42	189±30	0.260
LDL-cholesterol (mg/dl)	134±40	125±38	0.336
HDL- cholesterol (mg/dl)	47 [41-55]	49 [41-70]	0.876
Triglyceride (mg/dl)	147±68	136±67	0.478
Creatinine clearance (ml/min/1.73 m ²)	105±27	87±39	0.060

RAS rennin angiotensin aldosterone; CC calcium channel; TSH thyroid stimulating hormone; LDL low density lipoprotein; HDL high density lipoprotein.

Data are shown as n (%), mean±SD, median [interquartile range].

calculated for each patient as defined previously [12]. Patients were evaluated and treated according to the current guidelines.

Statistical Analysis

Statistical analysis was performed using commercial software (SPSS 19.0, Chicago, IL, USA; MedCalc 11.3, Mariakerke, Belgium). For normally distributed variables, mean and ±SD are listed. Otherwise, median values are given. The differences in variables among the groups were assessed using either an one-way ANOVA or Kruskal-Wallis analysis of variance, with multiple comparisons made using Bonferroni's test in case of global statistical significance (as indicated), whereas proportions were compared using chi-square test. Multivariate analysis of covariance (MANCOVA) was used to compare the HRV and HRT parameters among groups; age, systolic and diastolic blood pressures, body mass index, hemoglobin, and serum creatinine clearance were accepted as covariates. Correlations were determined using Spearman's test. A receiver operating characteristic (ROC) curve was constructed for HRV and HRT pa-

rameters to test the effectiveness of various cutoff points in predicting obstructive and non-obstructive CAD. The area under the ROC curve and the sensitivity and specificity of the most appropriate cut-off points of HRV and HRT parameters for predicting CAD were calculated. *P* values below 0.05 were considered statistically significant.

Results

Patients were divided into three groups according to the severity of their coronary lesions: group 1 normal, group 2 non-obstructive, and group 3 obstructive. There were no differences among the groups with regard to age, sex, medical history, medications, systolic and diastolic blood pressures, body mass index, fasting glucose, anemia and thyroid status, lipid profile and and creatinine clearance (Table 1). When group 3 was compared with group 1 and 2, significant differences were found only in use of acetylsalicylic acid: the number of patients receiving acetylsalicylic acid was significantly higher in group 3 than group 1 (30% *vs.* 57%). There were no any other signifi-

TABLE 3. Heart rate variability and turbulence parameters of the study groups

Variables	Group 1 n=30	Group 2 n=30	Group 3 n=30	P value	Adjusted P value**
RR (msec)	876±103	884±122	852±94	0.489	0.622
SDNN (msec)	125±35	118±28*	93±34*	<0.001	<0.001
SDANN (msec)	113±46	99±33	95±24	0.123	0.263
pNN50 (%)	13 [5-17]	8 [2-15]	2 [1-4]*,†	<0.001	0.022
RMSSD (msec)	37 [26-50]	27 [19-47]	23 [18-27]*,‡	0.001	0.129
Total power (msec ²)	3427 [2584-5202]	2715 [1468-3150]	2262 [1657-2595]*,§	0.002	0.085
VLF (msec ²)	2207±1248	1714±1015	1542±869	0.051	0.004
LF (msec ²)	720 [517-1789]	381 [102-632]	346 [295-493]*	<0.001	0.001
HF (msec ²)	264 [147-504]	134 [44-256]	83 [48-140]*,‡	<0.001	0.027
TO (%)	-3.85±4.24	-1.25±2.87§	1.89±2.17*,†	<0.001	0.001
TS (msec/RR)	9.25 [4.31-12.25]	6.02 [3.25-11.69]	2.08 [1.63-2.58]*,¶	<0.001	0.001

RR RR interval; SDNN standard deviation of all normal RR intervals; SDANN standard deviation of mean of normal RR intervals at each 5 minute segment; pNN50 percentage of differences between adjacent NN intervals that are >50 msec; RMSSD root mean squared differences of successive RR intervals; VLF very low frequency component of the spectral HRV analysis; LF low frequency component of the spectral HRV analysis; HF high frequency component of the spectral HRV analysis; TO turbulence onset; TS turbulence slope.

* $P<0.001$ vs group 1, † $P=0.001$ vs group 2, ‡ $P<0.05$ vs. group 2, § $P<0.01$ vs. group 1, ¶ $P<0.001$ vs. group 2.

**Adjusted P values for age, systolic and diastolic blood pressure, body mass index, hemoglobin, and creatinine clearance.

Data are shown as mean±SD, median [interquartile range].

cant differences between group 3 and group 1 (Table 1). When data from group 1 and group 2 were combined and compared with data from group 3 (group 3 *vs.* group 1+2), the significance of the P values did not change (Table 2). Gensini scores were 0 for group 1, 3 [3-5] for group 2, and 32 [18-45] for group 3 ($P<0.001$).

Most of the time- and frequency-domain HRV parameters were significantly different among the three groups. SDNN was significantly lower in group 2 and group 3 than group 1 ($P<0.001$). LF was lower in group 3 than group 1 ($P<0.001$). pNN50, RMSSD, total power, and HF were lower in group 3 than group 1 and group 2 (Table 3). TO was significantly higher and TS was significantly lower in group 3 than groups 1 and 2 (Table 3). TO was higher in group 2 than in group 1 ($P<0.01$). After adjusting the HRV and HRT parameters for possible confounding factors like age, systolic and diastolic blood pressure, body mass index, hemoglobin, and creatinine clearance, only SDNN, pNN50, LF, HF, TO, and TS remained significantly different (Table 3). When data from group 1 and group 2 were combined and compared with data from group 3 (group 3 *vs.* group 1+2), the significance of the P values did not change (Table 4). The value for PVB was not different between groups 2 and 3, but was significantly higher than group 1 ($P<0.001$) (Group 1, 5.0 [5.0-6.0], group 2, 8.0 [6.0-18.0], and group 3, 8.5 [6.0-25.0]).

The Gensini score had a strong correlation with SDNN, pNN50, RMSSD, total power, LF, HF, TO and TS (Table 5). According to the cut-off values calculated using ROC analysis, all of the HRV and HRT parameters had significant diagnostic accuracy but only SDNN≤69.63 msec, TO>0.14%, and TS≤2.78 msec/RR had high diagnostic accuracy for predicting obstructive CAD (Table 6). Only SDNN≤75.84 msec, TO>-2.27%, and LF≤943 msec² had significant diagnostic accuracy for predicting non-obstructive CAD (Table 7). Positive and negative predictive values of any combination of SDNN, TO and TS for predicting obstructive CAD are given in Table 8.

Discussion

The major finding of the present study is that HRV and HRT parameters are blunted in patients with CAD and that this finding is even more pronounced in those with obstructive CAD.

Noninvasive stress test procedures, such as exercise ECG, stress echocardiography, and radionuclide stress studies, are widely used for the diagnosis of CAD in clinical cardiological practice. Exercise treadmill ECG is one of the most frequent noninvasive modalities used to assess patients with suspected cardiovascular disease [13]. The diagnostic accuracy of this test mainly depends on the pretest probability of CAD. Meta-analysis of 147 published reports involving 24074 patients with

TABLE 4. Comparison of the HRV and HRT parameters between group 3 and combined groups 1+2

	Group 1 + 2 n=60	Group 3 n=30	P value
RR (msec)	880±112	852±94	0.246
SDNN (msec)	121±31	93±34	<0.001
SDANN (msec)	106±40	95±24	0.170
pNN50 (%)	7 [3-16]	2 [1-4]	<0.001
RMSSD (msec)	30 [22-47]	23 [18-27]	<0.001
Total power (msec ²)	2873 [1968-4202]	2262 [1657-2595]	<0.001
VLF (msec ²)	1965±1156	1542±869	0.086
LF (msec ²)	603 [343-774]	346 [295-493]	0.001
HF (msec ²)	224 [85-357]	83 [48-140]	<0.001
TO (%)	-2.53±3.81	1.89±2.17	<0.001
TS (msec/RR)	7.12 [4.36-12.61]	2.08 [1.63-2.58]	<0.001

RR RR interval; SDNN standard deviation of all normal RR intervals; SDANN standard deviation of mean of normal RR intervals at each 5 minute segment; pNN50 percentage of differences between adjacent NN intervals that are >50 msec; RMSSD root mean squared differences of successive RR intervals; VLF very low frequency component of the spectral HRV analysis; LF low frequency component of the spectral HRV analysis; HF high frequency component of the spectral HRV analysis; TO turbulence onset; TS turbulence slope.

Data are shown as mean±SD, median [interquartile range].

TABLE 5. Correlations between Gensini score and heart rate variability and turbulence parameters

	SDNN	pNN50	RMSSD	TP	LF	HF	TO	TS
Correlation coefficient	-0.628	-0.372	-0.349	-0.357	-0.394	-0.392	0.603	-0.613
P value	<0.001	<0.001	0.001	0.001	<0.001	<0.001	<0.001	<0.001

SDNN standard deviation of all normal RR intervals; pNN50 percentage of differences between adjacent NN intervals that are >50 msec; RMSSD root mean squared differences of successive RR intervals; TP total power; LF low frequency component of the spectral HRV analysis; HF high frequency component of the spectral HRV analysis; TO turbulence onset; TS turbulence slope.

TABLE 6. Comparison of the diagnostic accuracy of HRV and HRT parameters for obstructive coronary artery disease

	Cut-off value	AUC	95% CI of AUC	Sensitivity	Specificity	P value [§]
SDNN	≤69.63	0.796	0.698-0.847	0.833	0.767	<0.001
pNN50	≤4.13	0.775	0.675-0.857	0.800	0.667	<0.001
RMSSD	≤25.91	0.737	0.634-0.824	0.767	0.633	<0.001
TP	≤2472	0.731	0.624-0.821	0.862	0.667	<0.001
LF	≤593	0.720	0.613-0.881	0.897	0.509	<0.001
HF	≤160	0.765	0.651-0.842	0.931	0.544	<0.001
TO	>0.14	0.871	0.783-0.932	0.900	0.783	<0.001
TS	≤2.78	0.904	0.824-0.956	0.733	0.933	<0.001

SDNN standard deviation of all normal RR intervals; pNN50 percentage of differences between adjacent NN intervals that are >50 msec; RMSSD root mean squared differences of successive RR intervals; TP total power; LF low frequency component of the spectral HRV analysis; HF high frequency component of the spectral HRV analysis; TO turbulence onset; TS turbulence slope.; AUC Area Under the Receiver Operating Characteristic Curve.

[§] Significant level of AUC

TABLE 7. Comparison of the diagnostic accuracy of HRV and HRT parameters for non-obstructive coronary artery disease

	Cut-off value	AUC	95% CI of AUC	Sensitivity	Specificity	P value [§]
SDNN	≤75.84	0.839	0.721-0.921	0.733	0.967	<0.001
pNN50	≤10.3	0.526	0.392-0.656	0.633	0.567	0.733
RMSSD	≤25.43	0.548	0.414-0.677	0.467	0.733	0.522
TP	≤5043	0.564	0.426-0.695	0.893	0.310	0.402
LF	≤943	0.666	0.529-0.786	0.964	0.310	0.021
HF	≤256	0.591	0.452-0.719	0.750	0.483	0.231
TO	>-2.27	0.672	0.539-0.788	0.700	0.667	0.013
TS	≤6.85	0.608	0.474-0.732	0.600	0.700	0.138

SDNN standard deviation of all normal RR intervals; pNN50 percentage of differences between adjacent NN intervals that are >50 msec; RMSSD root mean squared differences of successive RR intervals; TP total power; LF low frequency component of the spectral HRV analysis; HF high frequency component of the spectral HRV analysis; TO turbulence onset; TS turbulence slope.; AUC Area Under the Receiver Operating Characteristic Curve.

[§] Significant level of AUC

coronary angiography showed that exercise ECG has a lot of variability in sensitivity and specificity (mean sensitivity was approximately 68%, and specificity was 77%) [13]. Froelicher *et al.* studied 814 consecutive patients who presented with angina pectoris and found that a 1 mm horizontal or downsloping ST depression on exercise ECG has a sensitivity of 45% and specificity of 85% for obstructive CAD [14].

Although current guidelines recommend stress tests only for patients with intermediate pretest probability, in clinical practice a considerable number of patients who underwent exercise ECG had a low to intermediate pretest probability [1]. Using the exercise ECG in patients with low to intermediate pretest probability decreases the specificity of the test and may thus cause false positive results. Due to workload, technical difficulties and personal preferences, clinicians sometimes use exercise ECG results to determine if coronary angiography is necessary. For this reason, proper interpretation of exercise ECG becomes important. Interpretation of exercise ECG depends on the occurrence of ischemic chest pain, abnormalities in exercise capacity, systolic blood pressure, heart rate response

to exercise and electrocardiographic changes. The most important electrocardiographic changes are ST depression and elevation. Development of ST segment depression accompanied by angina during exercise strongly support obstructive CAD; However, when ST segment depression with the absence of angina is seen on exercise ECG, other diagnostic parameters may reveal conflicting results, particularly in non-diabetic patients. Unfortunately, most of these patients are referred for diagnostic catheter angiography in order to identify possible CAD. It is obvious that additional, noninvasive diagnostic methods are needed in order to avoid unnecessary coronary angiography in such patients. HRV and HRT are both known to be blunted in CAD, so we hypothesized that HRV and HRT can be used to discriminate between patients with and without a high probability of having CAD [7,8]. In the present study, and consistent with previous findings, HRV and HRT were found to be impaired in patients with CAD. Moreover, the cut-off values were calculated with reasonable sensitivity and specificity for SDNN, TO and TS to predict the presence of obstructive CAD.

Previous studies examining the relationship between CAD and HRV and HRT usually include patients with myocardial infarction and investigate the predictive value of these parameters for survival after myocardial infarction and as well as for sudden death [15-18]. Sestito *et al.* found that $TO > -0.26\%$, $TS < 2.12$ msec/RR, and SD of all RR intervals < 96.3 msec had similar predictive powers for discriminating between patients with CAD and normals (positive predictive value 86.7%, negative predictive value 64.4%) [8]. Cygankiewicz *et al.* concluded that $TO \geq -0.37\%$ and $TS \leq 4.25$ msec/RR can be considered abnormal in the CAD population [19]. There has been little work on obstructive CAD. Sedziwy *et al.* and Klecha *et al.*

TABLE 8. Comparison of the diagnostic accuracy of any combination of SDNN, TO and TS for obstructive coronary artery disease

SDNN (msec)	TO (%)	TS (msec/RR)	PPV (%)	NPV (%)
≤69.63	>0.14	>2.78	82.8	92.0
≤69.63	≤0.14	≤2.78	86.4	83.8
>69.63	>0.14	≤2.78	84.6	87.5
≤69.63	>0.14	≤2.78	86.4	83.8

SDNN standard deviation of all normal RR intervals; TO turbulence onset; TS turbulence slope; PPV positive predictive value; NPV negative predictive value.

both showed that successful myocardial revascularization by means of the coronary arteries leads to an increase in HRV [20,21]. Goernig *et al.* demonstrated that TO, but not HRV, was significantly higher in patients with restenosis after percutaneous coronary revascularization. Using a threshold of a TO of <0%, restenosis was predicted in 83.4% of patients [22]. Santangali *et al.* found that HRV parameters were lower in obstructive CAD compared with controls and that myocardial revascularization lead to improvement in HRV [23]. Lin *et al.* found that TO was higher and TS was lower in CAD, and that percutaneous myocardial revascularization caused improvement in HRT. They also concluded that HRT correlated with the severity of the coronary lesions [24]. In our study $SDNN \leq 69.63$ msec and $TS \leq 2.78$ msec/RR were found to have the highest positive predictive value (86.4%) and $SDNN > 69.63$ msec and $TO \leq 0.14\%$ had the highest negative predictive value (92.0%) for discriminating the obstructive CAD. Although larger studies are needed in order to confirm these results, these cut-off values may be useful for discriminating the patients who do and do not truly require coronary angiography.

Non-coronary causes of ST segment depression during an exercise ECG is an important consideration is assessing patients. Anemia, cardiomyopathy, digitalis use, hypokalemia, intraventricular conduction disturbance, preexcitation syndrome, supraventricular tachyarrhythmias, left ventricular hypertrophy, mitral valve prolapse, severe aortic stenosis, severe aortic or mitral regurgitation, severe hypertension, glucose load, sudden excessive exercise, hyperventilation and severe hypoxia must be excluded during the interpretation of an exercise ECG [13]. In our study, patients who had these pathologies were excluded from the study, but unfortunately, the oxygen status could not be evaluated to rule out other confounding conditions. There are also other ways to rule out false positive ST depression; a hyperventilation test can be used to rule out this type of false positive, but is no longer recommended for routine use before standard testing [25].

The main limitation of our study is the small sample size: resulting in low statistical power for equivalency testing, and so negative results may be simply due to chance. One of the most important limitations of our study is that we used the deletion method and not the interpolation methods for the study. Non-invasive risk predictors of arrhythmias such as HRV and HRT can cause false positive results especially in a middle-aged healthy population (1-37% for SDNN, 19% for TO, 5% for TS) [26]. The false positive rates of the patients in this study with normal coronary arteries are 3% for SDNN, 17% for TO,

and 3% for TS. The incidence of these false positive results is similar to previous findings.

In conclusion, HRV and HRT parameters are blunted in patients with CAD. The decrease in these parameters is more pronounced in those with obstructive CAD. HRV and HRT parameters may provide additional information for discriminating between patients who do and do not truly require coronary angiography in order to reduce unnecessary testing. Studies with a larger number of patients and further prospective studies are needed before HRV and HRT may be accepted as a useful tool for the diagnosis of obstructive CAD in patients with ST segment depression without angina during exercise stress testing.

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