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Original Article

The effects of clinical and angiographic aspects of coronary artery disease on the cardiac autonomic function: a single-center prospective cohort study

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Abstract: Background: Autonomic malfunction is linked to elevated cardiovascular morbidity and mortality. Various patient characteristics can alter the cardiac autonomic function therefore, using a prospective observational study, we aimed to assess the effects of different clinical and angiographic factors of coronary artery disease (CAD) patients on the cardiac autonomic function evaluated by heart rate variability (HRV) measurement. Methods and Patients: 100 patients undergoing coronary angiography when clinically indicated were enrolled. A short-term 5-minute HRV measurement was performed by CheckMyheart™ handheld HRV device manufactured by DailyCare BioMedical Inc, Taiwan. HRV data were fed to CheckMyheart™ 5-min HRV analysis software and interpreted based on the standard methods for HRV measurement as discussed in the Task Force of the European Society of Cardiology (ESC) and The North American Society of Pacing and Electrophysiology (NAPSE). Coronary angiography was done with an emphasis on SYNTAX (SX) score calculation. Results: The mean age of the recruited patients was 56.89±10.75 years with 85% of them were males and the mean SX score 13.11±8.52. Multivariate regression analysis of the different patient clinical and angiographic characteristics affecting HRV showed that CAD type either single or multi-vessel and SX score were the major independent variables affecting HRV in patients with CAD. Conclusion: The complexity of CAD measured by SX score was the main independent predictor affecting the cardiac autonomic function estimated by HRV measurement.

Keywords: Coronary artery disease, heart rate variability, cardiac autonomic function, SYNTAX score

Introduction

Cardiac autonomic dysfunction is usually linked to an increased cardiovascular morbidity and mortality risk [1]. Previous studies confirmed that low heart rate variability (HRV) is an independent risk factor for sudden cardiac death (SCD) in coronary artery disease (CAD) [2], previous myocardial infarction (MI) [3], and congestive heart failure patients [4]. It is also an independent predictor of increased cardiovascular risk in diabetic and hypertensive patients [5, 6]. CAD and exercise-induced angina are linked to a state of sympathetic overstimulation [7], Myocardial ischemia is the stimulus of that state of sympathetic overstimulation. HRV measurement is a non-invasive method that can reflect the activity of the autonomic nervous system (ANS) and detect any imbalance between its components (sympathetic and parasympathetic systems) [8, 9]. While SYNTAX (SX) Score is one of the models which was designed to quantify the anatomical complexity of coronary lesions in patients with left main or three-vessel disease CAD and it is now well established to be an independent predictor of long-term major adverse car-diovascular and cerebrovascular events (MACCE) (Death, Myocardial infarction, Revascularization and Cerebrovascular accidents) in patients treated with PCI [10-14].

Several patient characteristics can affect the cardiac autonomic function therefore, this study aimed to determine the effects of different clinical and angiographic factors assessed by SX Score measurement on the cardiac autonomic function evaluated by HRV assessment among CAD patients.

Patients and methods

Study population

The study was designed as a single-center prospective cohort study included 100 patients.

Inclusion criteria: Clinical indication for coronary angiography (CA): 1. Subjective symptoms of ischemia or post-acute coronary syndrome (ACS). 2. Objective evidence of ischemia by a stress test or a viability study.

Exclusion criteria: 1. Subjects with contraindication to receive contrast media. 2. Patients who have atrial fibrillation, multiple premature beats, or receiving anti-arrhythmic drugs for any indication. 3. Patients who had previous percutaneous coronary interventions (PCI) or Coronary Artery Bypass Graft (CABG).

Informed consent was acquired from all patients. The ethical committee of the hospital approved the study protocol.

Clinical evaluation

Full history, clinical examination, routine laboratory investigations including (hemoglobin %, creatinine level), a standard 12 lead electrocardiogram (ECG), and a 2D transthoracic echocardiography (TTE) were acquired from all patients.

Coronary angiographic data

Coronary angiographic data was recorded with emphasis on CAD type whether single or multiple CAD and SYNTAX (SX) score calculation using SX score calculator software.

Heart rate variability measurement

5-minute (short-term) HRV assessment was done before CA using CheckMyheart™ handheld HRV device manufactured by DailyCare BioMedical Inc, Taiwan. Data were fed to CheckMyheart™ 5-min HRV analysis software using the standard methods for HRV measurement based on the Task Force of the ESC and the NASPE with an emphasis on HRV time-domain parameters (mean time, SDNN, and RMSSD) (illustrated in **Table 1A**) and HRV frequency-domain parameters (low frequency (LF), high frequency (HF) and LF/HF ratio) (illustrated in **Table 1B**).

Table 1A. Summary of the used time-domain measures of HRV

Variable	Unit	Description
Mean time	ms	Time average of RR interval
SDNN	ms	Standard deviation of all normal to normal (NN) intervals
RMSSD	ms	Square root of the mean of the sum of the square of differences between adjacent NN interval

Ms = millisecond.

Table 1B. Summary of the used frequency-domain measures of HRV

Variable	Units	Description	Frequency range
LF	ms^2	Low-frequency power	0.04-0.15 Hz
HF	ms^2	High-frequency power	0.15-0.4 Hz
LF/HF		Ratio between low to high-frequency power	

ms^2 = millisecond square.

Statistical analysis of the data

Statistical analysis was done using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Number and percent were used to describe qualitative data. Mean and standard deviation (SD) were used to describe quantitative data.

A significant level was set at 5% (p-value ≤0.05).

Statistical tests used: 1. Chi-square test for categorical variables comparing different groups. 2. Fisher's Exact correction for chi-square if >20% of the cells have expected count <5. 3. Mann-Whitney test for abnormally distributed quantitative variables comparing two groups. 4. Kruskal Wallis test for abnormally distributed quantitative variables comparing between more than two groups. 5. Wilcoxon signed ranks test for abnormally distributed quantitative variables, to compare two periods. 6. Friedman test for abnormally distributed quantitative variables, to compare between more than two periods or stages. Spearman coefficient to correlate between two distributed abnormally quantitative variables. 7. Multivariate logistic regression analysis to detect the most independent/affecting factors for HRV parameters.

Results

Baseline patient demographic and clinical data

The mean age of the enrolled patients was 56.89±10.75 years, 85% of them were males. (Demographic and clinical data illustrated in **Table 2**).

Coronary angiographic data

Multi-vessel CAD was encountered in 42 (42%) patients while single-vessel CAD was found in 58 (58%) patients with a mean SX score of 13.11±8.52 (illustrated in **Table 2**).

Table 2. Baseline patient demographic, clinical, and angiographic data (n=100)

1. Demographic data	
Age (years)	56.89±10.75
Male Sex	85 (85%)
2. Risk Factors	
Diabetes Mellitus	41 (41%)
Hypertension	47 (47%)
Smoking	79 (79%)
Family history of CAD	11 (11%)
Dyslipidemia	8 (8%)
Others	4 (4%)
3. Indication For Coronary Angiography	
Typical ischemic symptoms	6 (6%)
Positive stress test	8 (8%)
Post-ACS	86 (86%)
4. Clinical Data	
Mean heart rate (beats/minute)	77.95±11.79
Mean LVEF (%)	54.03±11.08
5. Coronary Angiographic Data	
Single-Vessel CAD	58 (58%)
Mean SX score	13.11±8.52
TIMI III distal flow	65 (65%)

Results are shown in % and numbers of patients.

HRV parameters

The relation between HRV time and frequency domain parameters and different patient characteristics was illustrated in **Tables 3**, **4**.

The correlation between HRV time domain parameters and patient characteristics revealed that there was a statistically significant positive correlation between mean time, SDNN, and RMSSD and LVEF (r=0.370, P=0.001),

Table 3. Relation between the mean value of HRV time-domain parameters and different patient characteristics

Patient characteristics	Number of patients	Mean Time (ms)	U	P	SDNN (ms)	U	P	RMSSD (ms)	U	P
Gender										
Male	85	685.01±47.60	614.0	0.820	11.94±3.32	609.50	0.787	7.12±1.95	603.0	0.738
Female	15	685.67±43.62			11.63±3.66			7.45±2.63		
Age (years)										
<65	76	695.14±44.03	382.50*	<0.001*	12.60±3.29	447.50*	<0.001*	7.41±2.07	640.0*	0.028*
≥ 65	24	653.33±41.54			9.67±2.51			6.39±1.83		
HTN										
No	53	692.57±36.80	1067.5	0.218	12.35±3.02	1037.0	0.149	7.60±1.83	891.0*	0.014*
Yes	47	676.70±55.23			11.38±3.67			6.68±2.19		
DM										
No	59	698.39±36.35	757.0*	<0.001*	12.77±3.17	768.0*	0.002*	7.60±1.91	823.50*	0.007*
Yes	41	666.0±53.62			10.64±3.26			6.55±2.11		
FH										
No	89	686.42±46.04	444.0	0.616	11.96±3.27	403.50	0.343	7.25±2.03	388.0	0.262
Yes	11	674.55±53.9			11.39±4.16			6.48±2.20		
Smoking										
No	21	681.43±51.68	788.0	0.725	11.43±3.60	512.0	0.516	7.13±2.56	797.50	0.786
Yes	79	686.09±45.75			12.02±3.30			7.18±1.91		
Dyslipidemia										
No	92	685.50±45.98	366.50	0.985	11.90±3.24	329.0	0.620	7.16±2.03	341.0	0.731
Yes	8	680.63±59.07			11.8± 4.78			7.25±2.46		
LVEF										
≤45	34	662.79±50.17	681.0*	0.001*	10.88±3.24	842.0*	0.041*	6.34±1.71	709.0*	0.003*
>45	66	696.6±40.82			12.42±3.32			7.59±2.09		
ACS	86	683.27±48.39			9.30± 2.13			7.14±2.07		
Non-ACS	14	696.43±34.94	527.50	0.459	11.82±2.77	596.0	0.952	7.36±1.98	564.50	0.709
Type of CAD										
MVD	42	650.26±39.31	289.0*	<0.001*	9.30±2.13	259.50*	<0.001*	5.60±1.64	299.0*	<0.001
SVD	58	710.34±33.95			13.78±2.78			8.30±1.50		
TIMI										
0 + I	27	670.19±38.24	695.0*	0.024*	10.93±2.99	4.0	0.133	6.58±1.83	759.0	0.078
II + III	73	690.63±48.70			12.25±3.43			7.38±2.10		

Drug history (Beta-blockers)										
No	17	694.41±36.09	647.50	0.594	11.74±2.69	685.50	0.854	7.35±2.0	659.0	0.668
Yes	83	683.2±48.69			11.93±3.49			7.13±2.07		

U, P: U and *P* values for Mann Whitney test for comparing between the two groups. *: Statistically significant at P≤0.05.

Table 4. Relation between the mean value of HRV frequency-domain parameters and different patient characteristics

Patient characteristics	Number of patients	LF	U	P	HF	U	P	LF/HF	U	P
Gender										
Male	85	42.0±6.53	578.0	0.565	11.60±3.38	597.50	0.699	3.79±0.72	597.50	0.698
Female	15	43.53±8.41			11.93±4.18			3.88±0.76		
Age (years)										
<65	76	43.13±6.76	599.0*	0.011*	12.09±3.55	606.0*	0.013*	3.73±0.72	650.0*	0.033*
≥ 65	24	39.38±6.29			10.26±2.95			4.01±0.71		
HTN										
No	53	43.24±6.32	1015.50	0.111	12.36±3.15	950.0*	0.041*	3.62±0.61	885.0*	0.012*
Yes	47	41.10±7.23			10.84±3.70			4.01±0.79		
DM										
No	59	43.68±6.40	836.0*	0.009*	12.44±3.20	820.0*	0.006*	3.62±0.61	810.50*	0.005*
Yes	41	40.15±6.93			10.52±3.60			4.06±0.80		
FH										
No	89	42.54±6.87	366.50	0.174	11.85±3.49	342.0	0.104	3.75±0.71	300.50*	0.036*
Yes	11	39.68±6.03			10.0±3.15			4.18±0.77		
Smoking										
No	21	42.48±8.25	822.0	0.949	11.57±4.04	827.0	0.983	3.92±0.78	749.50	0.496
Yes	79	42.16±6.44			11.67±3.36			3.77±0.71		
Dyslipidemia										
No	92	42.30±6.84	340.50	0.726	11.72±3.47	333.0	0.656	3.78±0.71	284.0	0.283
Yes	8	41.38±6.84			10.90±3.81			4.06±0.84		
LVEF										
≤45	34	39.38±6.25	707.0*	0.002*	10.87±3.33	895.0	0.098	3.81±0.78	1084.0	0.781
>45	66	43.70±6.67			12.05±3.52			3.80±0.70		
ACS	86	42.15±6.88	550.0	0.605	11.72±3.56	559.50	0.672	3.78±0.73	512.50	0.371
Non-ACS	14	42.75±6.59			11.21±3.12			3.95±0.73		
Type of CAD										
MVD	42	36.76±5.12	222.0*	<0.001*	8.48±2.37	113.50*	<0.001*	4.46±0.64	108.0*	<0.001*

SVD	58	46.19±4.88			13.95±2.07			3.32±0.27		
TIMI										
0 + I	27	39.76±5.94	731.0*	0.048*	10.89±3.19	818.0	0.193	3.81±0.73	964.50	0.870
II + III	73	43.14±6.93			11.93±3.57			3.79±0.73		
Drug history (Beta-blockers)										
No	17	43.09±6.49	626.0	0.465	11.50±3.14	686.50	0.861	3.88±0.69	634.0	0.509
Yes	83	42.05±6.90			11.68±3.57			3.78±0.73		

U, P: U and *P* values for Mann Whitney test for comparing between the two groups. *: Statistically significant at P≤0.05.

(r=0.282, P=0.004), and (r=0.288, P=0.004) respectively while there was a statistically significant negative correlation between them and SX score as well as age (r=-0.686, P=0.001), (r=-0.435, P=0.001), (r=-0.637, P=0.001), (r=-0.416, P=0.001) (r=-0.673, P=0.001) and (r=-0.233, P=0.019) respectively (illustrated in **Table 5**).

Table 5. Correlation between different HRV time-domain parameters and patient characteristics (n=100)

Patient Characteristics	Mean time		SDNN		RMSSD	
	r_s	p	r_s	p	r_s	P
Age (years)	-0.435*	<0.001*	-0.416*	<0.001*	-0.233*	0.019*
LVEF	0.370*	<0.001*	0.282*	0.004*	0.288*	0.004*
SYNTAX score	-0.686*	<0.001*	-0.637*	<0.001*	-0.673*	<0.001*
TIMI flow	0.151	0.133	0.085	0.398	0.121	0.229

r_s: Spearman coefficient. *: Statistically significant at P≤0.05.

While the correlation between HRV frequency domain parameters and patient characteristics showed that there was a statistically significant negative correlation between LF and HF with SX score and age (r=-0.709, P=0.001), (r=-0.251, P=0.012) and (r=-0.699, P≤0.001), (r=-0.259, P=0.009) respectively while there was a statistically significant positive correlation between LF/HF ratio with SX score and age (r=0.630, P≤0.001), (r=0.227, P=0.023) (illustrated in **Table 6**).

Table 6. Correlation between different HRV frequency-domain parameters and patient characteristics (n=100)

Patient Characteristics	LF		HF		LF/HF	
	r_s	p	r_s	p	r_s	p
Age (years)	-0.251*	0.012*	-0.259*	0.009*	0.227*	0.023*
LVEF	0.288*	0.004*	0.154	0.127	0.008	0.935
SYNTAX score	-0.709	<0.001*	-0.699*	<0.001*	0.630*	<0.001*
TIMI flow	0.122	0.227	0.042	0.680	0.071	0.483

r_s: Spearman coefficient. *: Statistically significant at P≤0.05.

Multivariate regression analysis of patient factors affecting mean time, SDNN, and RMSSD revealed that age, LVEF, CAD type, and SX score were the most powerful independent factors that affect the HRV time-domain parameters (illustrated in **Table 7**).

Table 7. Multivariate linear analysis logistic regression of patient characteristics affecting HRV time-domain parameters

A. Multivariate linear analysis logistic regression of patient characteristics affecting mean time

Patient characteristics	B	SE	Sig.	95% CI	
				LL	UL
Age	-1.512	0.210	<0.001*	-1.929	-1.096
DM	-3.505	4.758	0.463	-12.954	5.944
LVEF	1.458	0.220	<0.001*	1.022	1.894
Type of CAD	32.184	5.821	<0.001*	20.624	43.744
SYNTAX score	-2.275	0.390	<0.001*	-3.050	-1.500
TIMI flow	-2.759	2.010	0.173	-6.750	1.232

B. Multivariate linear analysis logistic regression of patient characteristics affecting SDNN

Patient characteristics	B	SE	Sig.	95% CI	
				LL	UL
Age	-0.121	0.018	<0.001*	-0.156	-0.086
DM	-0.236	0.397	0.554	-1.023	0.552
LVEF	0.081	0.018	<0.001*	0.044	0.117
Type of CAD	3.102	0.470	<0.001*	2.170	4.035
SYNTAX score	-0.097	0.030	0.001*	-0.156	-0.039

C. Multivariate linear analysis logistic regression of patient characteristics affecting RMSSD

Patient characteristics	B	SE	Sig.	95% CI	
				LL	UL
Age	-0.033	0.013	0.009*	-0.058	-0.008
DM	0.228	0.301	0.450	-0.369	0.826
LVEF	0.054	0.014	<0.001*	0.026	0.082
Type of CAD	1.891	0.336	<0.001*	1.223	2.559
SYNTAX score	-0.064	0.022	0.004*	-0.107	-0.021

B: Unstandardized Coefficients, OR: Odds ratio, CI: Confidence interval, LL: Lower limit, UL: Upper Limit. *: Statistically significant at P≤0.05.

Multivariate regression analysis of patient factors affecting LF, HF, and LF/HF ratio revealed that CAD type and SX score were the most powerful independent factors affecting the HRV frequency-domain parameters (illustrated in **Table 8**).

Table 8. Multivariate linear analysis logistic regression of patient characteristics affecting HRV frequency-domain parameters

A. Multivariate linear analysis logistic regression of patient characteristics affecting LF

Patient Characteristics	B	SE	Sig.	95% CI	
				LL	UL
Age	-0.119	0.039	0.003*	-0.195	-0.042
DM	0.346	0.875	0.694	-1.392	2.084
LVEF	0.130	0.040	0.002*	0.050	0.210
Type of CAD	6.156	1.071	<0.001*	4.030	8.282
TIMI (before)	-0.048	0.370	0.897	-0.782	0.686
SYNTAX score	-0.303	0.072	<0.001*	-0.446	-0.161

B. Multivariate linear analysis logistic regression of patient characteristics affecting HF

Patient Characteristics	B	SE	Sig.	95% CI	
				LL	UL
Age	-0.052	0.018	0.004*	-0.087	-0.016
HTN	-0.083	0.403	0.837	-0.883	0.717
DM	0.096	0.424	0.821	-0.746	0.939
Type of CAD	3.723	0.467	<0.001*	2.795	4.651
Syntax	-0.160	0.028	<0.001*	-0.216	-0.105

C. Multivariate linear analysis logistic regression of patient characteristics affecting HF/LF ratio

Patient Characteristics	B	SE	Sig.	95% CI	
				LL	UL
Age	0.006	0.004	0.132	-0.002	0.014
HTN	0.091	0.086	0.296	-0.081	0.262
DM	0.020	0.091	0.827	-0.161	0.201
FH	0.054	0.135	0.690	-0.214	0.322
Type of CAD	-0.761	0.102	<0.001*	-0.963	-0.559
Syntax	0.032	0.006	<0.001*	0.020	0.044

B: Unstandardized Coefficients, OR: Odds ratio, CI: Confidence interval, LL: Lower limit, UL: Upper Limit. *: Statistically significant at P≤0.05.

Discussion

Our study included 100 patients undergoing CA with a broad spectrum of patient selection including patients with various indications for intervention such as patients with typical anginal symptoms or positive stress testing also, post-ACS patients either unstable angina or post-MI angina patients with or without a viability study. On the contrary to all previous studies [1], in our study, the complexity of CAD was quantified using SX score [15]. Multivariate linear regression analysis of the various patient factors that can affect HRV showed that the CAD type either single or multi-vessel and SX score were the main independent variables to affecting cardiac autonomic malfunction assessed by HRV parameters in CAD patients.

Previous studies addressed the link between CAD and autonomic dysfunction, Airaksinen et al [2], evaluated vagal cardiac function in CAD patients by measuring HRV range during deep breathing suggesting that CAD was associated with vagal cardiac function impairment independently of the NYHA class, medications, diseased coronary arteries location, previous MI, and left ventricular function indices. Hayano et al [16], analyzed the RR interval variability under controlled respiration in patients referred for CA demonstrating that CAD was associated with vagal dominant impairment in cardiac autonomic function and the reduction in the vagal cardiac function correlated with the angiographic severity independently from previous MI, diseased coronary artery location, and left ventricular function. Huikuri et al [17], proved that reduced autonomic responses to sleep-wake rhythm could suggest that the cardiac autonomic function modulation by central nervous system stimuli was impaired in CAD patients in comparison to age-matched individuals with no evidence of CAD. Wennerblom et al [18], investigated whether uncomplicated chronic CAD could cause changes in HRV and if so, whether the HRV pattern different from that was described in AMI patients. The study involved 65 patients with angina who had no previous MI or other diseases and not receiving drugs affecting sinus rhythm. Time and frequency-domains of HRV were measured and results were compared with 33 age-matched healthy subjects revealing that uncomplicated CAD even without previous AMI was associated with reduced HRV parameters. Kotecha et al [19], conducted (The Alternative Risk Markers in Coronary Artery Disease (ARM-CAD) study), a prospective multicenter observational study to assess the feasibility of a bedside (5-minute) HRV test to be used as a predictor of CAD presence recruiting 470 consecutive patients undergoing elective CA regardless the co-morbidities. The study concluded that lower HRV was highly predictive of angiographic CAD irrespective of other risk factors and it can be clinically used as a risk predictor for CAD in sinus rhythm patients. Simula et al [20], performed quantitative coronary angiography (QCA), myocardial Tc-99m sestamibi (MIBI) perfusion imaging, and HRV to study the correlation between cardiac autonomic function and the extent and distribution of coronary atherosclerosis in 30 asymptomatic patients with high familial risk of CAD yet no evident myocardial ischemia. The study concluded that the severity and extent of coronary atherosclerosis were related to a change in cardiac autonomic regulation to sympathetic predominance in patients without subjective or objective evidence of ischemia. Feng et al [21], assessed the correlation between CAD and cardiac autonomic dysfunction using HRV among 236 patients with stable angina. Unlike our study where the SX score was calculated, Gensini score was used to quantify CAD severity. The study concluded that HRV analysis among CAD patients may predict CAD severity, screening of high-risk population and determine prognosis. Li et al [22], studied if HRV could predict the presence of angiographic CAD beyond Framingham risk in 514 patients presenting with stable angina concluding that low HRV can be used as a predictive non-invasive method for CAD in patients with stable angina, independent from the traditional risk factors and Framingham risk.

Study limitations

Our study was a single-center prospective study that involved a relatively small number of patients.

Study recommendations

Large-scale studies are required to validate the patient characteristics linked to reduce HRV in CAD patients and to further confirm the usefulness of HRV as a prognostic factor for CAD patients.

Conclusion

In single-center prospective study studying the effects of different patient characteristics affecting cardiac autonomic dysfunction in CAD patients, the complexity of CAD measured by SX score was the main independent predictor affecting the cardiac autonomic function estimated by HRV measurement.

Disclosure of conflict of interest

None.

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References

[1] Feng J, Wang A, Gao C, Zhang J, Chen Z, Hou L, Luo C, Jiang Y and Pan J. Altered heart rate variability depend on the characteristics of coronary lesions in stable angina pectoris. Anatol J Cardiol 2015; 15: 496-501.

[2] Airaksinen K, Ikäheimo M, Linnaluoto M, Niemelä M and Takkunen J. Impaired vagal heart rate control in coronary artery disease. Heart 1987; 58: 592-597.

[3] Chattipakorn N, Incharoen T, Kanlop N and Chattipakorn S. Heart rate variability in myocardial infarction and heart failure. Int J Cardiol 2007; 120: 289-296.

[4] Musialik-Łydka A, Sredniawa B and Pasyk S. Heart rate variability in heart failure. Kardiol Pol 2003; 58: 10-16.

[5] Tarvainen MP, Laitinen TP, Lipponen JA, Cornforth DJ and Jelinek HF. Cardiac autonomic dysfunction in type 2 diabetes-effect of hyperglycemia and disease duration. Front Endocrinol 2014; 5: 130.

[6] Huikuri HV, Ylitalo A, Pikkujämsä SM, Ikäheimo MJ, Airaksinen KJ, Rantala AO, Lilja M and Kesäniemi YA. Heart rate variability in systemic hypertension. Am J Cardiol 1996; 77: 1073-1077.

[7] Gomes ME, Aengevaeren WR, Lenders JW, Verheugt FW, Smits P and Tack CJ. Improving myocardial perfusion by percutaneous coronary intervention reduces central sympathetic activity in stable angina. Clin Cardiol 2010; 33: E16-E21.

[8] Sztajzel J. Heart rate variability: a noninvasive electrocardiographic method to measure the autonomic nervous system. Swiss Med Wkly 2004; 134: 514-522.

[9] Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of pacing and electrophysiology. Circulation 1996; 93: 1043-1065.

[10] Mohr FW, Morice MC, Kappetein AP, Feldman TE, Ståhle E, Colombo A, Mack MJ, Holmes DR Jr, Morel MA, Van Dyck N, Houle VM, Dawkins KD and Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013; 381: 629-638.

[11] Mohr FW, Rastan AJ, Serruys PW, Kappetein AP, Holmes DR, Pomar JL, Westaby S, Leadley K, Dawkins KD and Mack MJ. Complex coronary anatomy in coronary artery bypass graft surgery: impact of complex coronary anatomy in modern bypass surgery? Lessons learned from the SYNTAX trial after two years. J Thorac Cardiovasc Surg 2011; 141: 130-140.

[12] Généreux P, Palmerini T, Caixeta A, Cristea E, Mehran R, Sanchez R, Lazar D, Jankovic I, Corral MD, Dressler O, Fahy MP, Parise H, Lansky AJ and Stone GW. SYNTAX score reproducibility and variability between interventional cardiologists, core laboratory technicians, and quantitative coronary measurements. Circ Cardiovasc Interv 2011; 4: 553-561.

[13] Papadopoulou SL, Girasis C, Dharampal A, Farooq V, Onuma Y, Rossi A, Morel MA, Krestin GP, Serruys PW, de Feyter PJ and Garcia Garcia HM. CT-SYNTAX score: a feasibility and reproducibility study. JACC Cardiovasc Imaging 2013; 6: 413-415.

[14] Généreux P, Palmerini T, Caixeta A, Rosner G, Green P, Dressler O, Xu K, Parise H, Mehran R and Serruys PW. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (synergy between PCI with taxus and cardiac surgery) score. J Am Coll Cardiol 2012; 59: 2165-2174.

[15] Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME and Mohr FW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005; 1: 219-227.

[16] Hayano J, Sakakibara Y, Yamada M, Ohte N, Fujinami T, Yokoyama K, Watanabe Y and Takata K. Decreased magnitude of heart rate spectral components in coronary artery disease. Its relation to angiographic severity. Circulation 1990; 81: 1217-1224.

[17] Huikuri HV, Niemelä M, Ojala S, Rantala A, Ikäheimo M and Airaksinen K. Circadian rhythms of frequency domain measures of heart rate variability in healthy subjects and patients with coronary artery disease. Effects of arousal and upright posture. Circulation 1994; 90: 121-126.
[18] Wennerblom B, Lurje L, Tygesen H, Vahisalo R and Hjalmarson Å. Patients with uncomplicated coronary artery disease have reduced heart rate variability mainly affecting vagal tone. Heart 2000; 83: 290-294.
[19] Kotecha D, New G, Flather M, Eccleston D, Pepper J and Krum H. Five-minute heart rate variability can predict obstructive angiographic coronary disease. Heart 2012; 98: 395-401.
[20] Simula S, Vanninen E, Lehto S, Hedman A, Pajunen P, Syvänne M and Hartikainen J. Heart rate variability associates with asymptomatic coronary atherosclerosis. Clin Autono Res 2014; 24: 31-37.
[21] Feng J, Wang A, Gao C, Zhang J, Chen Z, Hou L, Luo C, Jiang Y and Pan J. Altered heart rate variability depend on the characteristics of coronary lesions in stable angina pectoris. Anatol J Cardiol 2015; 15: 496.
[22] Li HR, Lu TM, Cheng HM, Lu DY, Chiou CW, Chuang SY, Yang AC, Sung SH, Yu WC and Chen CH. Additive value of heart rate variability in predicting obstructive coronary artery disease beyond Framingham risk. Circulation 2016; 80: 494-501.