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Original Article

Which is responsible for cardiac autonomic dysfunction in non-diabetic patients with metabolic syndrome: Prediabetes or the syndrome itself?

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ABSTRACT

Aims: Cardiac autonomic dysfunction (CAD) is associated with both prediabetes and metabolic syndrome (MS). Heart rate variability (HRV) and heart rate turbulence (HRT) are reliable 24-h Holter-ECG findings of cardiac autonomic function. This study aimed to investigate the relation between MS and its components and CAD using HRV and HRT.

Materials and methods: The study included 80 non-diabetic patients with MS and 70 control subjects. All study population and the patients with MS were further analyzed for each diagnostic component of MS to investigate which criteria impaired HRV and HRT.

Results: HRV and HRT parameters were disturbed in patients in the MS group. While impairment in HRV and HRT was significantly related to the presence of the fasting plasma glucose (FPG) criterion, there were no differences between groups in terms of the other 4 MS criteria. Moreover, FPG level was significantly correlated with SDNN ($r = -0.352$, $p < 0.001$), SDNN index ($r = -0.423$, $p < 0.001$), SDANN ($r = -0.301$, $p < 0.001$), RMSSD ($r = -0.237$, $p < 0.001$), pNN50 ($r = -0.237$, $p < 0.001$), turbulence onset (TO) ($r = 0.365$, $p < 0.001$) and turbulence slope (TS) ($r = -0.365$, $p < 0.001$). Among the MS diagnostic criteria, only FPG level was an independent determinant of all HRV and HRT parameters.

Conclusions: This study confirms the relation between MS and CAD. Increased FPG alone appears to be responsible for the mentioned findings among the 5 diagnostic criteria. Accordingly, CAD may be the result of prediabetes, not MS in patients with MS.

1. Introduction

CAD is a frequent chronic complication of diabetes which carries risk of potentially life-threatening events including silent myocardial ischemia and infarction, arrhythmias, sudden death, perioperative cardiovascular instability, orthostatic hypotension and cardiomyopathy [1,2]. CAD is caused by impairment of the autonomic nerve fibers regulating heart rate, myocardial contractility, cardiac electrophysiology, and blood vessel constriction and dilatation [2].

MS is a combination of disorders, comprising central obesity, impaired fasting glucose (IFG), atherogenic dyslipidemia and high blood pressure (BP) [3,4]. It is associated with a twofold increase in cardiovascular mortality and a threefold increase in the risk of myocardial infarction or stroke. In addition, the risk of developing type 2 diabetes mellitus is five times higher [5]. Abdominal obesity and insulin resistance play a key role in the development of MS and prothrombotic and proinflammatory states are also involved [3]. Prediabetes, used to describe individuals with IFG, a component of MS, and/or impaired glucose tolerance, is a continuum between normoglycemia and diabetes mellitus [6]. As in MS, prediabetes also indicates increased risk for cardiovascular diseases and the future development of type 2 diabetes mellitus [6]. Similarly, CAD has been reported to be associated with both MS and prediabetes in previous studies [7–10].

The Holter-ECG parameters of HRV and HRT are useful in the assessment of cardiac autonomic function [11,12]. The most commonly used methods for the diagnosis of CAD are based on HRV (the physiological variation in the time interval between

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heartbeats) examination [11]. HRT is a reliable indicator of baroreceptor sensitivity following an episode of isolated premature ventricular beats (PVBs) and can be used for the evaluation of CAD [12]. A decrease in HRV is known to be the first finding of cardiac autonomic neuropathy [13]. Similarly, disturbed HRT has been found in patients with cardiac autonomic neuropathy [14].

In this study we aimed to investigate the relation between MS and its components and CAD using both HRV and HRT.

2. Subjects, materials and methods

This prospective study examined 240 subjects with sinus rhythm. Exclusion criteria were as follows: non-sinus rhythm, known diabetes mellitus, the use of any antidiabetic medication, coronary artery disease defined as a stenosis of more than 50% in at least 1 of the epicardial coronary arteries in a past coronary angiography, acute coronary syndrome or a previous myocardial infarction, typical stable angina pectoris, cardiomyopathies, heart failure (left ventricular (LV) ejection fraction of <50%), severe valvular disease, hyperthyroidism-hypothyroidism, ventricular tachycardia on Holter-ECG, and use of medicine, including beta blockers, non-dihydropyridine calcium channel blockers or antiarrhythmic drugs that may effect HRV and HRT indices.

The study population underwent a 24-h Holter-ECG examination to obtain HRV and HRT parameters and were evaluated for the presence of MS as stated in the revised Adult Treatment Panel III of National Cholesterol Education Program (NCEP ATP III) [4]. The MS group included 102 patients and the control group 138 age-gender matched subjects without MS. Of these, 22 patients in the MS group and 68 subjects in the control group were excluded, as HRV and HRT parameters could not be appropriately obtained from the Holter recordings due to the absence of PVBs. The remaining 80 patients with MS and 70 controls were enrolled in the study. The revised NCEP ATP III defines MS as the presence of at least 3 of the following 5 factors: elevated FPG (≥100 mg/dL) or drug treatment for elevated glucose, elevated BP (systolic BP ≥130 or diastolic BP ≥85 mmHg) or antihypertensive drug treatment of previously diagnosed hypertension, raised triglycerides (≥150 mg/dl) or on drug treatment for elevated triglycerides, reduced HDL cholesterol (<40 mg/dL in men, <50 mg/dL in women) or on drug treatment for reduced HDL cholesterol, and elevated waist circumference (≥102 cm in men and ≥88 cm in women). Subjects in the control group had 0–2 of the diagnostic components for MS, most commonly elevated BP criterion (Table 1). The number of MS components in the control group was as follows: 0 component 8.6%, $n = 6$; 1 component 37.1%, $n = 26$; 2 components 54.3%, $n = 38$. The number of MS components in the MS group was as follows: 3 components 60%, $n = 48$; 4 components 33.8%, $n = 27$; 5 components 6.3%, $n = 5$. All subjects and patients with MS were further analyzed for each diagnostic component of MS to investigate which criteria impaired HRV and HRT. As CAD is an entity of overt diabetes, only non-diabetic patients were evaluated.

Holter-ECG recordings were acquired using three-channel digital recorders (Cardioscan Premier version 12, DM Systems Co., Ltd. Beijing, China). Recordings lasting more than 20 h and of sufficient quality for evaluation were analyzed. A physician totally blind to the study assessed the Holter-ECG records. Before analysis, data were manually reviewed to check all complexes marked as true PVBs. HRV parameters were as follows: the standard deviation of the normal-to-normal (NN) interval (SDNN), the standard deviation of the average NN interval (SDANN) calculated over 5-min periods, the mean of the 5-min standard deviation of the NN interval (SDNN index) calculated over 24 h, the square root of the mean squared differences of successive NN intervals (RMSSD), and the division of the number of interval differences of successive NN intervals of more than 50 ms by the total number of NN intervals (pNN50). The mean R-R interval was also calculated. All measurements were performed according to the standards determined by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [11].

Table 1
Baseline characteristics, echocardiographic and laboratory findings.

Variables	MS group ($n = 80$)	Control group ($n = 70$)	p-Value
Age, years	63 (49.3/74)	57 (48/70)	0.333
Gender, female/male, numbers (%)	55/25 (68.8/31.2)	42/28 (60/40)	0.263
Current smoking, numbers (%)	15 (18.8)	17 (24.3)	0.409
Hypertension, numbers (%)	33 (41.3)	21 (30)	0.152
Height, cm	160 (155/169.5)	162 (155.8/174)	0.369
Weight, kg	80 (73.3/88)	75 (65.8/82)	0.001
Body mass index,[a] kg/m^2	30.8 ± 4.7	27.7 ± 5.2	<0.001
Waist circumference,[a] cm	96.8 ± 8.4	88.1 ± 12.3	<0.001
FPG, mg/dL	101.5 (90.25/111)	91 (85/97.3)	<0.001
Total cholesterol,[a] mg/dL	203.1 ± 43.4	198.2 ± 45.2	0.498
HDL cholesterol, mg/dL	40.5 (36/47)	48 (41.8/57)	<0.001
LDL cholesterol, mg/dL	114.5 (94/147)	120 (99.8/153.3)	0.778
Triglycerides, mg/dL	168 (131/212)	110.5 (85.8/137)	<0.001
Systolic BP, mmHg	135 (130/150)	120 (110/130)	<0.001
Diastolic BP, mmHg	80 (70/90)	75 (70/80)	0.001
Mean heart rate,[a] beats/min	76 ± 11.4	74.3 ± 9.8	0.324
LV diastolic diameter, mm	46 (41/48)	46 (41/49)	0.813
LV systolic diameter, mm	29 (26.3/33)	29 (27/32)	0.649
IVS thickness, mm	12 (11/13)	11 (9/12.3)	0.020
PW thickness, mm	11 (10/12)	10 (9/11.3)	0.010
LV mass,[a] g	186.8 ± 44.1	175.1 ± 60.1	0.182
LV mass index,[a] g/m^2	98 ± 24.4	95.7 ± 33.3	0.630
Ejection fraction, %	65 (60/66.8)	65.5 (60.8/68)	0.089
Left atrial diameter, mm	37 (32/38)	36 (33/40)	0.455
MS components			
Elevated waist circumference, n (%)	57 (71.3)	19 (27.1)	<0.001
Elevated triglycerides, n (%)	55 (68.8)	11 (15.7)	<0.001
Reduced HDL-cholesterol, n (%)	60 (75)	28 (40)	<0.001
Elevated BP, n (%)	61 (76.3)	32 (45.7)	<0.001
Elevated FPG, n (%)	45 (56.3)	12 (17.1)	<0.001

Data presented as median (25/75% interquartile range).
[a] Data presented as mean ± standard deviation.

HRT defines fluctuations in the sinus rhythm cycle length following isolated PVBs. After an initial acceleration, the sinus rate decelerates after a PVB. There are two components of HRT: TO and TS. A transient vagal inhibition triggers the mentioned initial acceleration in the heart rate as a reaction to the missed baroreflex afferent input due to hemodynamically ineffective ventricular contraction. The successive deceleration in heart rate is caused by a sympathetically mediated overshoot of BP through vagal recruitment [15]. After manual review of the 24-h Holter recordings, TO and TS were calculated as reported in the previously published method [12]. A TO value below 0% shows early sinus acceleration and is considered normal while a TS value over 2.5 ms/R-R interval indicates normal expected late deceleration [12]. HRT values are usually classified into three categories: HRT category (HRTc) 0 indicating normal TO and TS, HRTc 1 indicating an abnormal TO or TS, and HRTc 2 indicating abnormal TO and TS [12].

The study was approved by the local ethics committee and was performed in accordance with the Helsinki declaration. All subjects gave informed consent prior to enrollment.