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Heart Rate Variability is Associated with Glycemic Status After Controlling for Components of the Metabolic Syndrome ☆

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ABSTRACT

Objective: To evaluate the relationship between heart rate variability (HRV) and glycemic status after controlling for metabolic syndrome (MetS) in a healthy working cohort.
Background: A growing body of literature suggests that reduced HRV, a physiological marker of autonomic nervous system activity, is associated with various pathological conditions including glycemic disorders and cardiovascular diseases. The extent to which this association is confounded by other more traditional markers of cardiovascular risk, such as MetS, is unclear.
Methods: We recruited 2441 study participants (age 17-65) employed at three sites of an airplane manufacturing plant in southern Germany. All subjects underwent medical examination, blood sampling, and 24-hour ambulatory heart rate recording while on their normal work routine. Indices of HRV were determined from readings made throughout the 24-hour examination period, those during either the day or night only as well as a night to day ratio. Pearson correlations and multivariate-adjusted partial correlation coefficients (PCCs) were calculated.
Results: Pearson correlations suggested inverse associations between HRV measurements and glycemic status (e.g. High frequency $r = -0.07$, $p<0.001$; SDNN $r = -0.09$, $p<0.001$). After multivariate adjustment of all other components of MetS (triglyceride, blood pressure, waist circumference, high density lipoproteins), medical and demographic variables, these associations persisted (e.g. High frequency PCC = -0.05, $p<0.001$; SDNN PCC = -0.06, $p<0.001$).
Conclusions: We confirm a negative correlation between HRV and glycemic status that appeared to be almost linear in a large cohort of healthy workers. Importantly, we showed that this association was independent of potential confounders, especially all of the MetS components and inflammation.

1. Introduction

The prevalence of abnormal glycemic status (fasting plasma glucose (FPG) ≥5.6 mmol/l) has dramatically increased in the past decades. Abnormal glycemic status is a predisposition to several chronic diseases including type 2 diabetes, sleep apnea, and cardiovascular diseases [1–3] and has been associated with obesity, hypertension and other components of the metabolic syndrome (MetS) [4,5]. The MetS is a cluster of symptoms including abdominal obesity, elevated blood pressures (BP), glucose and triglyceride (TRI) levels, and decreased high density lipoprotein (HDL) levels that has been associated with increased risk for mortality and morbidity [6]. Therefore an enhanced understanding of the common pathophysiologic pathway(s) of the MetS and abnormal glycemic status might help to improve prevention strategies for these chronic diseases as well as help explain the common clustering of dysregulated conditions as subsumed in the MetS [6].

Like the metabolic syndrome, measures of decreased vagally-mediated heart rate variability (HRV) have been associated with significant morbidity and mortality from a wide range of disorders including diabetes and cardiovascular disease [5]. Numerous studies have reported an association between low vagally-mediated HRV and abnormal glycemic status [reviewed in 5,7]. In addition, low vagally-mediated HRV has been shown to be associated with various components of the MetS [1,8]. However, to date, the independent association between HRV and glycemic status has not been examined after controlling for the associations among HRV and the various MetS components. Thus, the observation that HRV and glycemic status are related may be due to the association of HRV with components of the MetS and therefore there may exist no independent association of HRV with glycemic status. The primary aim of the present study was to rectify this situation by examining the relationship between HRV and fasting plasma glucose (FPG) and HbA_{1C} levels as indicators for glycemic status after controlling for the other MetS components.

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Table 1
Univariate analyses by glucose group (mmol/l).

	Supernormal	Normal	iFG	DM	P
	< 4.5	4.5 - <5.6	5.6 – <7	≥7	
Participants (N)	551	1683	183	24	2441
Glucose (mmol/l)	4.3 (0.2)	4.9 (0.3)	6 (0.3)	9 (2.4)	<0.001
HbA_{1C} (%)	5.5 (0.3)	5.6 (0.3)	5.9 (0.5)	7.6 (1.5)	<0.001
Age (years)	37.1 (11.4)	42.3 (10.7)	50.4 (9.2)	52.8 (7.8)	<0.001
Female (%)	37.7%	20.0%	14.2%	20.8%	<0.001
Current Smoker (%)	12.5%	14.4%	12.6%	12.5%	0.661
Alcohol intake*	1.7 (0.9)	1.9 (1)	2.2 (1.1)	1.9 (1.1)	<0.001
History of high lipids (%)	8.2%	13.7%	25.1%	37.5%	<0.001
History of high BP (%)	9.1%	14.9%	32.2%	41.7%	<0.001
History of high glucose (%)	0.5%	1.3%	12.0%	62.5%	<0.001
History of CVD (%)	1.1%	2.1%	8.2%	10%	<0.001
Hematocrit (%)	42.8 (3.5)	43.5 (3.1)	44 (3.1)	43.9 (3.1)	<0.001
Waist Circumference (cm)	84.6 (10.8)	90.4 (11.5)	99.9 (11.9)	106 (15.8)	<0.001
High density lipoproteins (mg/dl)	61.5 (15.1)	57.9 (13.7)	53.2 (12.2)	52.3 (13.2)	<0.001
Triglycerides (mg/dl)	116 (61.0)	135 (89.9)	178 (118)	222 (52.3)	<0.001
Systolic BP (mmHg)	133 (12.8)	137 (14.0)	144 (13.2)	149 (16.6)	<0.001
Diastolic BP (mmHg)	75.7 (10.5)	80 (10.9)	85 (9.8)	86.4 (11)	<0.001
Number of MetS components (0-5)	1.1 (0.9)	1.5 (1.1)	3.3 (1)	3.5 (1)	<0.001
HF (ms^2)‡†	5.5 (0.8)	5.2 (0.8)	4.8 (0.9)	4.3 (0.9)	<0.001
LF (ms^2)‡†	6.6 (0.5)	6.5 (0.6)	6.1 (0.6)	5.8 (0.7)	<0.001
RMSSD (ms)‡†	3.4 (0.4)	3.3 (0.4)	3.1 (0.4)	2.9 (0.4)	<0.001
SDNN (ms)‡	64.4 (13.1)	61.8 (14.4)	55.3 (14.4)	46.4 (13.3)	<0.001
Heart Rate (BPM)	74 (9.11)	74.6 (8.99)	76 (9.94)	76.6 (8.39)	<0.001

Values are given in means (sd). ‡24 h average. †Log transformation for analysis.
*Alcohol = No alcohol, 1-2 times/month, 1-2 times/week, 3-5 days/week, 6-7 days/week.
Difference determined by ANOVA for continuous variables or Chi-square test for categorical variables.

In addition, there are significant circadian variations in a number of physiological systems and disruption of the normal variations have been associated with increased end organ damage, morbidity, and mortality [9–11]. Of particular relevance for the current investigation, vagally-mediated HRV is known to increase at night and blunted night-time increases in HRV have been found in various conditions associated with poor health including acute stress, work stress, alcoholism, and older age [12–15]. However, the extent to which night-time and diurnal variation in HRV correlate with glycemic status is currently unclear.

Therefore a secondary aim of the present study was to examine the relationship between night-time and diurnal variation in HRV and glycemic status in a large sample of working adults.

2. Material and Methods

2.1. Study sample

This report is based on cross-sectional data from an industrial cohort in southern Germany. The data were collected as part of a voluntary health risk assessment that was offered to all employees during working hours. The health risk assessment and data collection were conducted by an agent independent from the employer (HealthVision Ltd, Berlingen, Switzerland).

Table 2a
Pearson's Correlations between measures of fasting plasma glucose and HbA_{1C} with HRV.

	Glucose (mmol/l)	HbA_{1C} (%)
Participants (N)	3005	3003
HF (ms^2) ‡†	-0.271***	-0.214**
LF (ms^2) ‡†	-0.273***	-0.235**
RMSSD (ms) ‡†	-0.278***	-0.226**
SDNN (ms)‡	-0.222***	-0.171***
N/D HF (ms^2)†	-0.066***	-0.034
N/D LF (ms^2)†	-0.163***	-0.141***
N/D RMSSD (ms)†	-0.045*	-0.019
N/D SDNN (ms)	-0.094***	-0.097***

‡24 h average. †Log transformation for analysis. N/D = Night to Day- ratio.
* $p<0.05$; ** $p<0.01$; *** $p<0.001$.

Recruitment took place at three different factory plants (A B C). A total of 6080 (A = 1614; B = 1178; C = 3288) participants were invited to take part in the "Work Health Check" Study. This sample spanned the entire work force between 17 and 65 years. All participants were Caucasians.

In total 54.8% (A = 58.7%; B = 51.3%; C = 54.1%) participants filled out an online questionnaire. After completing the questionnaire, participants were able to schedule a medical examination including a 24-hour recording of heart rate (HR). Of these, 2441 subjects (73.3%) had complete data allowing us to perform full multivariate linear regression analysis. Participants providing incomplete data did not differ significantly from members of the analytic sample, except that more women provided incomplete data ($p = 0.007$).

Because of the epidemiological nature of our study, we did not exclude subjects based on their medical history and medication use but controlled for medical history using binary indicators. All data were collected between September 2009 and May 2010. The secondary analysis of this data was approved by the Ethical Committee of the Mannheim Medical Faculty, Heidelberg University. All participants gave written informed consent.

2.2. Data collection

All participants were enrolled and examined between 10 am and 5 pm on a typical work day (Monday – Friday). Upon arrival a medical examination was performed. All participants had in general no shiftwork. Blood pressure (BP) using the oscillometric technique was recorded twice using the CRITIKON Dinamap Portable Adult/Pediatric and Neonatal Vital Signs Monitor (Model 8100). Measurements were taken from the dominant arm in the seated position after a 5 min rest period. A study physician repeated the reading using sphygmomanometry if one or more BP values exceeded 135mmHg (systolic) or 90mmHg (diastolic). The arithmetic mean of all two to three measurements was calculated. Weight, height as well as waist and hip circumferences were measured by usual means by trained personnel.

Heart rate was recorded as beat-to-beat intervals using a t6 Suunto Memory Belt (SuuntoVantaa, Finnland), sampling at a rate of 1000 Hz. The Suunto Memory Belt has been shown to be a reliable measure of ECG compared to a 5 lead ECG [16]. Beat-to-beat intervals were determined as the interval between two successive R-spikes. After attaching the ambulatory HR recorder, participants commenced their routine work duties followed by after work leisure and sleep activities. Participants were asked to return the HR recorder after minimum 22-hours of wearing or in case of any difficulties. The next morning, between 7 am and 9 am, a fasting blood sample was collected from all individuals. Samples were transported to a commercial laboratory (Synlab, Augsburg, Germany) within 2 hours of sample collection and analyzed within 24-hours. Blood lipids and plasma glucose were determined using routine laboratory analyzers (HDL = OSR6187; TRI = OSR60118; GLUC = OSR6121, Olympus). HbA_{1C} was measured using the assay "Tina-quant, Hemoglobin A1c Gen.2", Roche Diagnostics [17]. Four glucose groups are defined according to the definition of the American Diabetes Association (ADA) by FPG level as followed: Supernormal (<4.5 mmol/l), Normal (4.5 – <5.6 mmol/l) impaired fasting glucose (iFG 5.6 – <7 mmol/l) Diabetes Mellitus (DM ≥7 mmol/l).