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ORIGINAL ARTICLE

Cardiac autonomic modulation in response to a glucose stimulus

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Abstract

This paper focuses on the effect of a sudden increase of plasma glucose concentration in the cardiac autonomic modulation using time-domain and frequency-domain heart rate variability (HRV) measures. Plasma glucose and insulin levels, measured each 30 min during an oral glucose tolerance test, and $\overline{RR}$ (mean of the RR interval), SDNN (standard deviation of normal-to-normal heartbeats), rMSSD (root-mean-square of successive differences between normal heartbeats), TP (total spectral power), LF and HF (power of the low- and high-frequency bands), LF norm and HF norm (LF and HF in normalized units), and LF/HF ratio of the HRV signal, obtained from 5-min-long ECG recordings during each phase of the test, were analyzed for subjects with the metabolic syndrome, marathon runners, and a control group. Results show that, after the glucose load, subjects with the metabolic syndrome experienced an increased sympathetic and decreased parasympathetic tone, which suggests an imbalance in cardiac autonomic modulation as a consequence of hyperglycemia and hyperinsulinemia. The significance of this study lies in the use of the ECG to assess the effects of a sudden increase in plasma glucose concentration on the cardiac autonomic modulation in subjects with different cardiovascular and metabolic conditions.

Keywords Heart rate variability · Time-domain analysis · Frequency-domain analysis · Electrocardiogram

1 Introduction

Diseases related to the cardiovascular system are the leading cause of deaths worldwide; yearly, more people die from cardiovascular causes than from any other cause. Approximately 17.5 million people died in 2012 from cardiovascular diseases and, of those deaths, approximately 6.7 millions were due to heart attacks and strokes. By 2030, it is expected that around 23.6 million people will die from cardiovascular causes, and these diseases will continue to be the main reason of death worldwide [25]. Obesity, a serious public health issue in constant increase, associated with poor diet and a sedentary lifestyle, increases the risk of cardiovascular diseases. According to the WHO, in 2014, 13% of adults were obese, that is, some 600 million people [24], and by 2030, it is expected that 51% of the population will suffer from obesity [4]. Obesity is one of the medical factors of the metabolic syndrome; the others are hypertension, hyperglycemia, and dyslipidemia. The metabolic syndrome increases the risk

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of developing type 2 diabetes, cardiovascular diseases, and the autonomic nervous system (ANS) disorders such as diabetic neuropathy [5]. Changes in lifestyle, including healthy eating and physical activities, are fundamentals to prevent and treat the metabolic syndrome [16].

The electrocardiogram (ECG) is a simple noninvasive exploration tool for the cardiac electrical activity. The ECG signal carries fundamental information to assess the ANS and to diagnose cardiovascular diseases. The cardiac autonomic modulation, a consequence of the interaction between the sympathetic and parasympathetic divisions of the ANS, can be assessed from the ECG signal by analyzing the heart rate variability (HRV). The HRV, a phenomenon about the slight variation of the cardiac cycle length from beat to beat, is derived from the series of RR intervals, after the time alignment of the R wave and the exclusion of non-normal RR intervals (abnormal RR intervals produced by false or missed detection of the beat detector or by ectopic beats). The analysis of the HRV generally involves parameters in time and frequency domain. For instance, three typical time-domain parameters are the average of RR ($\overline{RR}$), the standard deviation of normal-to-normal heartbeats (SDNN) that, depending on the length of the ECG recording, can reflect long-term variability, and the root-mean-square of successive differences between normal heartbeats (rMSSD) that reflects short-term variability and high-frequency variations in heart rhythm. On the other hand, the power on certain predefined frequency bands, estimated using spectral techniques, can reflect the oscillatory components responsible for cardiac autonomic modulation. For instance, for short-term ECG recording ($\leq$5 min), there are three well-identified frequency bands of the HRV: very low frequency (VLF, $\leq$0.04 Hz), low frequency (LF, 0.04–0.15 Hz) and high frequency (HF, 0.15–0.4 Hz) [18, 22].

It has been shown that different stimuli can elicit different HRV responses: relaxant baroque music reduces global heart rate variability [17], other music features such as tempo and complexity reduce SDNN and the LF/HF ratio affecting the balance between sympathetic and parasympathetic system [10], venipuncture pain reduces the LF and HF components of HRV in very low birth weight infants [13], and alcohol reduces SDNN and HF [23]. The relationship between plasma glucose concentration and HRV has been already studied by Perticone et al. [14] who showed that, during the oral glucose tolerance test (OGTT), an increase in plasma glucose and insulin concentrations alters the sympathetic drive in subjects with different glucose tolerance status. Moreover, lower sympathetic and higher parasympathetic responses of the cardiac autonomic modulation have been associated with a rise of plasma glucose concentration in healthy young adults [11], prolonged hypoglycemia (low plasma glucose concentration) reduces the cardiac vagal outflow in patient with type 1 diabetes and healthy subjects [7], and plasma glucose concentration increased is correlated with lower sympathetic and higher parasympathetic responses in subjects with the metabolic syndrome [19].

These findings motivate us to investigate the cardiac autonomic modulation using HRV measures in response to a sudden increase in plasma glucose concentration (glucose stimulus) in age-matched subjects with the metabolic syndrome, professional marathon runners, and subjects without the metabolic syndrome and not involved in sports activities (control group). Around 10-min multilead ECG recordings were performed to all participants at the beginning of each phase of the OGTT, i.e., at fasting (0 min) and at 30, 60, 90, and 120 min after the glucose stimulus (75 grams of glucose load). Nine HRV measurements obtained using time- and frequency-domain techniques were explored and compared using statistical hypothesis tests, and associations between HRV parameters and glucose, insulin, triglycerides, waist circumference, high-density lipoprotein (HDL) cholesterol, and blood pressure were also analyzed. Although the relationships between cardiac autonomic modulation and plasma glucose concentration have been already pointed out, the response of the cardiac autonomic modulation to a sudden increase in plasma glucose concentration in both subjects predisposed to cardiovascular diseases (people with the metabolic syndrome) and subjects with cardiac enlargement (marathon runners) using different heart rate variability measures during a 2-h OGTT can be regarded as the main contribution of this work.

2 Materials and methods

2.1 Subjects

This study had the participation of 40 male subjects: 15 diagnosed with the metabolic syndrome according to the National Cholesterol Education Program's Adult Treatment Panel III criteria [3, 6], 15 marathon runners (180–240 km weekly training), and 10 subjects without the metabolic syndrome and not involved in sport activities (control group). These subjects underwent an OGTT to observe their glucose tolerance and insulin sensitivity. This test consisted of taking five blood samples; the first sample was taken in fasting, early in the morning, to measure glucose, insulin, triglycerides and HDL cholesterol. Systolic and diastolic blood pressures were also determined at this instant. Then, the subject ingested 75 g of liquid glucose and waited 30 min for the next blood sample, in which glucose and insulin were again measured. Glucose and insulin were measured again from three more blood

samples, taken at intervals of 30 min. These five samples were named: 0 min, 30 min, 60 min, 90 min, and 120 min, where 0 min corresponds to the sample taken in fasting condition. Immediately after each blood sample was taken, 12-lead ECG recordings were acquired for at least 10 min. ECG signals were recorded at 1000 Hz of sampling frequency, with 16 bits of resolution [8]. All procedures performed in the study were in accordance with the ethical standards of the University Hospital of Caracas and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All subjects agreed to the study by signing an informed consent.

To reduce the impact of confounding variables and to keep the data as homogeneous as possible, we have only retained those subjects in the metabolic syndrome group who shared four of the following metabolic syndrome factors: abdominal obesity (waist circumference >102 cm), high fasting blood glucose (≥ 100 mg/dL), elevated triglycerides (≥ 150 mg/dL), and high blood pressure ($\geq 130/35$ mmHg). Only 11 out of 15 fulfilled these criteria and were kept for the experiments. On the other hand, subjects from the marathon runner and control groups that exhibited at least one metabolic syndrome factor were excluded from the study. In the end, the dataset was reduced to 30 subjects: 11 with the metabolic syndrome, 14 marathon runners, and 5 control subjects.

2.2 Heart rate variability analysis

The Kubios software was used to assess HRV and estimate the time- and frequency-domain measures [20, 21]. Given the variable duration of the ECG recordings, HRV was assessed from 5-min ECG excerpts taken from minutes 3 to 8 for each subject in each phase of the OGTT.

An RR interval time series was derived from the QRS complexes using an algorithm that optimally combines the QRS detection performed on 12 different ECG leads [9]. The RR interval time series was formed from the differences of two consecutive QRS complexes. RR intervals differing from the previous one by more than 30% were identified as artifacts and were corrected using Kubios' custom filter.

Figure 1 shows examples of a 5-min-long RR interval time series for a subject with the metabolic syndrome, a marathon runner, and a control subject, during each phase of the OGTT. We can observe a larger RR interval and a

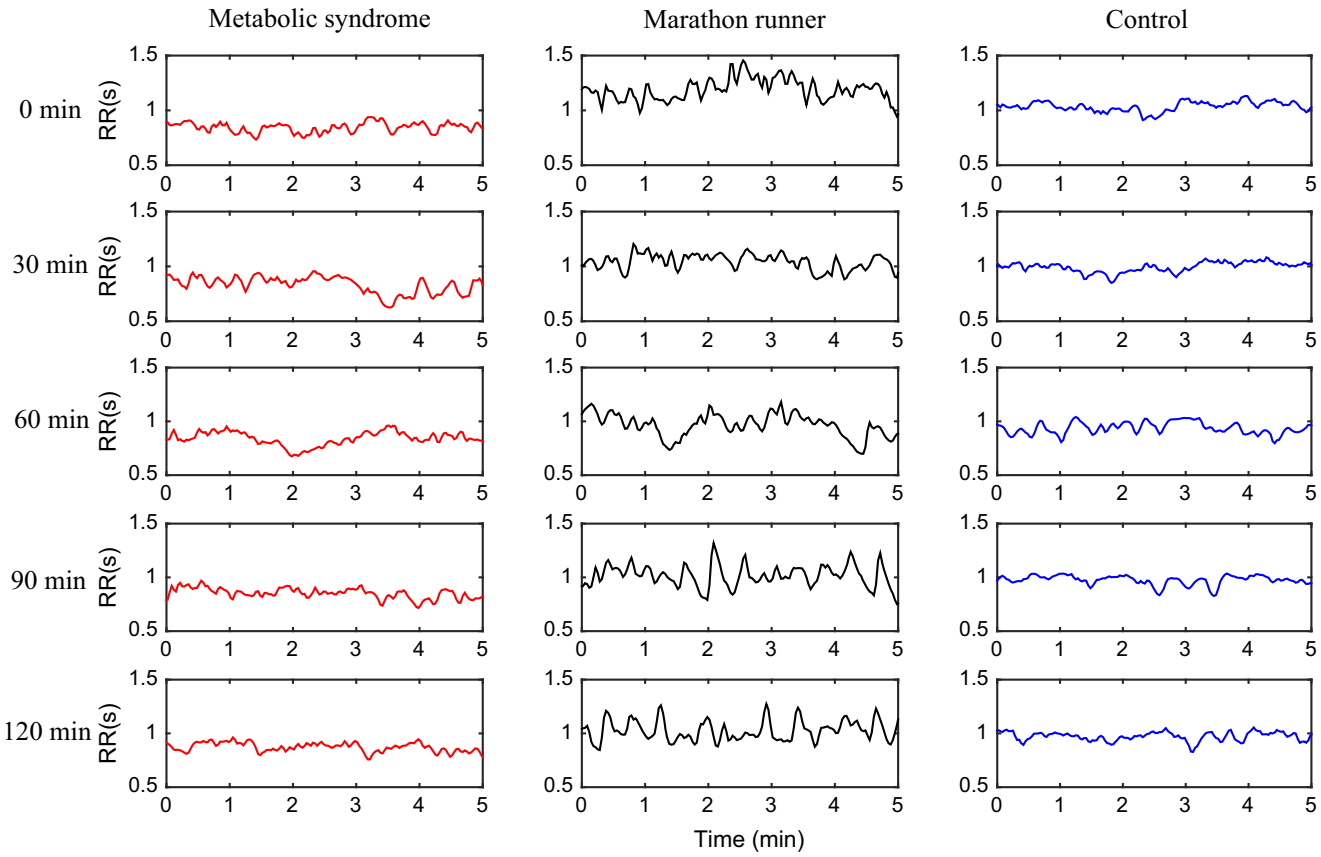

Fig. 1 RR interval time series for a subject with the metabolic syndrome subject (left), a marathon runner (middle), and a control subject (right), during each phase of the OGTT (0, 30, 60, 90, and 120 min, from top to bottom)

greater variability for the marathon runner compared with the other two subjects, in each phase of the OGTT.

2.2.1 Time-domain measures

Three time-dependent HRV measures were explored: (i) $\overline{RR}$, (ii) SDNN $= \sqrt{\frac{1}{N-1}\sum_{n=1}^{N}(RR_n - \overline{RR})^2}$, and (iii) rMSSD $= \sqrt{\frac{1}{N-1}\sum_{n=1}^{N}(RR_{n+1} - RR_n)^2}$, where RR_n denotes the value of the nth RR interval and N is the total number RR intervals.

2.2.2 Frequency-domain measures

For the frequency analysis of HRV, the RR interval time series was evenly sampled at 4 Hz, then the power spectrum density (PSD) was estimated using Welch's periodogram, using a window of 256 ms and overlapping of 50%. Six frequency-dependent HRV measures were estimated: (i) TP, total spectral power, (ii) LF, absolute power of LF band, (iii) HF, absolute power of HF band, (iv) LF norm, power of LF band in normalized units, (v) HF norm, power of HF band in normalized units, and (vi) LF/HF, ratio between LF and HF band powers. Figure 2 shows examples of the PSD of HRV for a subject with the metabolic syndrome, a marathon runner, and a control subject, during each phase of the OGTT. We can observe lower spectral powers in the LF and HF bands for the subject with the metabolic syndrome compared with the other two subjects, in each phase of the OGTT.

The spectral powers in LF and HF are related to the autonomic balance: sympathetic and parasympathetic branches of the ANS modulate the LF component, whereas the parasympathetic activity modulates the HF component. The LF component is correlated with the baroreflex and the HF component represents primarily, respiratory variations. The sympathovagal balance is associated with the LF/HF ratio [22].

2.3 Statistical analysis

Two nonparametric statistical tests were used in this work, namely, the Kruskal-Wallis test to find significant differences in the variables of interest between the study groups (three independent samples) and Friedman's test to find significant differences in the variables of interest between the phases of the OGTT (five dependent samples). In addition Dunn's test and the Wilcoxon signed-rank test were used as post-hoc tests for the independent and the dependent samples, respectively. Associations between clinical features (non-HRV measures) and HRV measures were assessed using Spearman's rank correlation coefficient. A p value less than or equal to 5% was considered to be statistically significant.

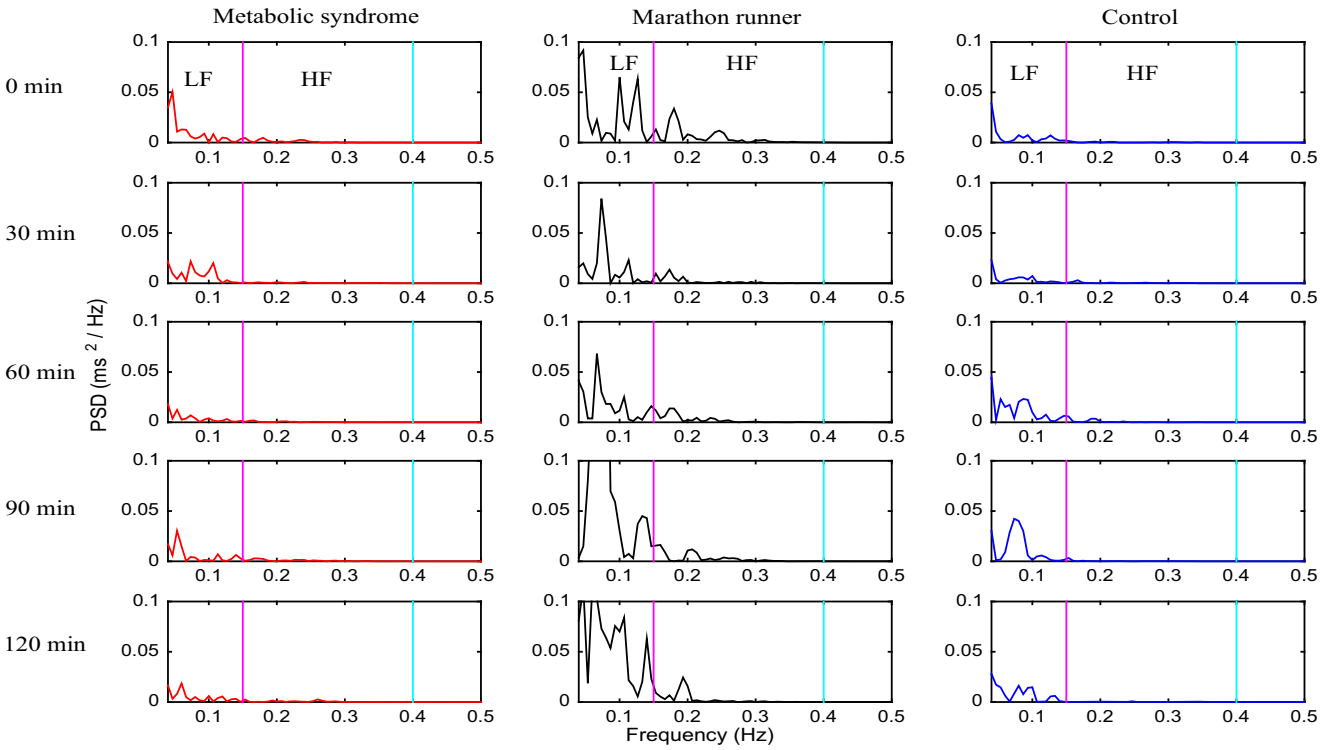

Fig. 2 PSD of HRV for a subject with the metabolic syndrome subject (left), a marathon runner (middle), and a control subject (right), during each OGTT phase (0, 30, 60, 90, and 120 min, from top to bottom)

3 Results

Clinical and metabolic characteristics of the study groups are shown in Table 1. On the one hand, considering the statically significant differences between the phases of the OGTT, compared with fasting plasma glucose concentration, subjects with the metabolic syndrome presented statistically significant higher glucose values at 30, 60, and 90 min, marathon runners presented statistically significant higher glucose values at 30 min, and control subjects presented statistically significant higher glucose values at 30 and 60 min, whereas compared with fasting plasma insulin concentration, subjects with the metabolic syndrome presented statistically significant higher insulin values at 30, 60, 90, and 120 min, marathon runners presented statistically significant higher insulin values at 30, 60, and 90 min, and control subjects presented statistically significant higher insulin values at 30, 60, and 90 min. On the other hand, considering the statically significant differences between groups, compared with control subjects, subjects with the metabolic syndrome presented significantly higher waist circumference, diastolic blood pressure, triglycerides, and fasting insulin level, whereas compared with marathon runners, subjects with the metabolic syndrome presented significantly higher waist circumference, systolic and diastolic blood pressures, triglycerides, plasma glucose, and insulin levels along the OGTT. No significant differences were found between marathoners and control subjects.

Significant correlations between HRV parameters and blood pressure, triglycerides, HDL cholesterol, waist circumference, and plasma glucose and insulin levels during the OGTT are presented in Table 2. From this table, we can observe that triglycerides, waist circumference, and systolic blood pressure were the metabolic syndrome factors most correlated with the time-domain HRV parameters shown, whereas HDL cholesterol and triglycerides were the ones most correlated with the frequency-domain HRV parameters shown. Moreover, $\overline{RR}$, the most simple HRV measure, besides being correlated with triglycerides, waist circumference, and systolic blood pressure, was correlated with plasma glucose and insulin levels in each phase of the OGTT.

Table 3 and Fig. 3 show time-domain and frequency-domain HRV measures during the OGTT for each group. On the one hand, considering the statically significant differences in the HRV parameters between the phases of the OGTT, we have found that subjects with the metabolic syndrome presented statistically significant differences between fasting and other phases of the OGTT in the following HRV parameters: higher SDNN at 30 min ($p = 0.015$), 60 min ($p = 0.0019$), 90 min ($p = 0.016$), and 120 min ($p = 0.03$); higher LF at 60 min ($p = 0.004$), 90 min ($p = 0.025$), and 120 min ($p = 0.016$); higher LF norm at 120 min ($p = 0.006$), higher LF/HF at 120 min ($p < 0.007$), and lower HF norm at 120 min ($p = 0.001$). No statistically significant differences were observed between the fasting state and other phases of

Table 1 Median (IQR) of the characteristics of each group

Attribute	Metabolic syndrome	Marathon runners	Control
Age (year)	33 (7.5)	35 (15)	29 (9)
Waist circumference (cm)[a,b]	108.8 (17.9)	72.9 (9.6)	87.5 (16.6)
Systolic blood pressure (mmHg)[a,b]	137 (6.5)	110 (8)	116 (7.5)
Diastolic blood pressure (mmHg)[a,b]	88 (17.8)	71 (16)	76 (17)
Triglycerides (mg/dL)[a,b]	195 (135)	57 (25)	72 (33.5)
HDL cholesterol (mg/dL)	41 (10.5)	47 (8)	47 (10)
Glucose level (mg/dL), 0 min[a]	109 (8.5)	85.5 (9)	95 (4)
Glucose level (mg/dL), 30 min[a]	161 (31.8)	111(39)	159 (23.8)
Glucose level (mg/dL), 60 min[a]	165 (42.5)	87.5 (24)	137 (10.5)
Glucose level (mg/dL), 90 min[a]	146 (37.5)	83.5 (30)	106 (22.8)
Glucose level (mg/dL), 120 min[a]	136 (23)	69.5 (30)	106 (34.8)
Insulin level (μIU/mL), 0 min[a]	9 (5.5)	2 (0.9)	2 (2.3)
Insulin level (μIU/mL), 30 min[a]	56 (81.8)	28.4 (12.1)	42 (77.5)
Insulin level (μIU/mL), 60 min[a]	69 (62.5)	23.9 (8.7)	28 (51.8)
Insulin level (μIU/mL), 90 min[a]	74 (75.3)	20.5 (15.9)	29 (43)
Insulin level (μIU/mL), 120 min[a]	89 (54.8)	16 (13.5)	32 (21.8)

[a]Significant difference between subjects with the metabolic syndrome and marathon runners

[b]Significant difference between subjects with the metabolic syndrome and control subjects

Table 2 Univariate correlates of the HRV parameters to blood pressure, triglycerides, HDL cholesterol, waist circumference, and plasma glucose (Glu) and insulin (Ins) levels during the OGTT. Variables were correlated by using Spearman's rank correlation. Only significant correlations are shown

	Blood pressure		Trigly.	HDL	Waist	0 min		30 min		60 min		90 min		120 min	
Parameter	Syst	Diast				Glu	Ins	Glu	Ins	Glu	Ins	Glu	Ins	Glu	Ins
$\overline{RR}$, 0 min	−0.57	–	−0.57	–	−0.54	−0.62	−0.54	–	–	–	–	–	–	–	–
$\overline{RR}$, 30 min	−0.61	–	−0.62	–	−0.63	–	–	−0.59	−0.47	–	–	–	–	–	–
$\overline{RR}$, 60 min	−0.53	–	−0.54	–	−0.61	–	–	–	–	−0.55	−0.35	–	–	–	–
$\overline{RR}$, 90 min	−0.56	–	−0.53	–	−0.61	–	–	–	–	–	–	−0.54	−0.63	–	–
$\overline{RR}$, 120 min	−0.67		−0.61	–	−0.66	–	–	–	–	−0.62	–	−0.66	–	−0.66	−0.62
SDNN, 0 min	–	–	−0.53		–	−0.31	–	–	–	–	–	–		–	–
SDNN, 120 min	–	–	−0.45	–	–	–	–	–	–	–	–	–	–	−0.35	−0.39
rMSSD, 0 min	–	–	−0.47	–	–	–	–	–	–	−0.59	–	−0.59	–	–	–
rMSSD, 120 min	−0.47	−0.44	−0.5	–	−0.48	–	–	–	–	–	–	–	–	−0.5	−0.49
LF, 0 min	–	–	−0.46	–		–	−0.39	–	–	–	–	–	–	–	–
LF norm, 0 min	–	–	–	0.38	–	–	–	–	–	–	–	–	–	–	–
LF norm, 120 min	–	–	–	–	−0.40	–	–	–	–	–	–	–	–	–	–
HF norm, 0 min	–	–	–	−0.37	–	–	–	–	–	–	–	–	–	–	–
HF norm, 120 min	–	–	–	–	−0.38	–	–	–	–	–	–	–	–	–	–
LF/HF, 0 min	–	–	–	0.37	–	–	–	–	–	–	–	–	–	–	–
LF/HF, 120 min	–	–	–	–	−0.40	–	–	–	–	–	–	–	–	–	–
TP, 0 min	–	–	−0.44	–	−0.38	–	−0.34	–	–	–	–	–	–	–	–

the OGTT neither for marathon runners nor for control. On the other hand, considering the statically significant differences in the HRV parameters between groups, we have found that, compared with marathon runners, subjects with the metabolic syndrome presented lower fasting $\overline{RR}$ ($p = 0.0018$), lower fasting SDNN ($p = 0.03$), lower fasting rMSSD ($p = 0.01$), lower fasting LF ($p = 0.0025$), lower fasting TP ($p = 0.008$), lower rMSSD at 30 min ($p = 0.03$), and lower rMSSD at 120 min ($p = 0.005$). Compared with control subjects, subjects with the metabolic syndrome presented lower fasting LF norm ($p = 0.004$), higher fasting HF norm ($p < 0.0041$), and lower fasting TP ($p < 0.01$). Marathon runners showed statically significantly lower fasting LF norm ($p < 0.01$), lower fasting LF/HF ($p < 0.01$), and higher fasting HF norm ($p = 0.014$) than control subjects.

4 Discussion

Marathon runners handled better the rapid increases of plasma glucose than the other two groups (see Table 1). This improvement in the glucose uptake by the skeletal muscle can be explained by a greater GLUT4 expression [15] and an enhanced insulin sensitivity as a consequence of physical exercise [2]. Indeed, physical exercise increases the insulin action on the skeletal muscle in obese people, insulin-resistant subjects, and mice [1]. Moreover, the importance of physical exercise in the treatment of the metabolic syndrome can be highlighted by the fact that marathon runners showed higher fasting HRV parameters (see Table 3), both in time and frequency domains, than subjects with the metabolic syndrome ($\overline{RR}$, SDNN, LF, and TP). We have also found that subjects with the metabolic syndrome showed lower fasting LF norm, LF/HF, and TP than healthy ones. Similarly, Ma et al. showed that subjects with the metabolic syndrome presented lower fasting HRV parameters (SDNN, PNN20, VLF, LF, and HF) than healthy ones, in 4-h ECG recordings [12].

The associations between non-HRV and HRV measures along the OGTT (see Table 2), particularly $\overline{RR}$ and plasma glucose and insulin concentrations in each phase of the OGTT, provided relevant information about the modulation of the ANS in response to a blood glucose increase and glucose homeostasis. In this sense, the information derived from the ECG, an inexpensive and noninvasive screening tool, could be used, beyond the assessment of cardiac function, as a window of the metabolic status, avoiding thus taking blood samples.

The increase in plasma glucose and insulin concentrations along the OGTT in subjects with the metabolic syndrome was accompanied with an increase in SDNN (30, 60, 90 and 120 min), LF (60, 90 and 120 min), LF norm

Table 3 Median (IQR) of the HRV parameters during the OGTT

Parameter	Metabolic syndrome	Marathon runners	Control
$\overline{RR}$ (ms), 0 min[a]	851.3 (161.3)	1136.5 (270.8)	1014.1 (176.3)
$\overline{RR}$ (ms), 30 min[a]	891.5 (100.5)	1094.5 (143.7)	959.8 (190.4)
$\overline{RR}$ (ms), 60 min[a]	952.8 (121)	1238.6 (252.5)	987.6 (180.6)
$\overline{RR}$ (ms), 90 min[a]	868.3 (160.7)	1205.4 (266.3)	917 (166.2)
$\overline{RR}$ (ms), 120 min[a]	893.9 (77.2)	1109.8 (198.9)	978.5 (106.7)
SDNN (ms), 0'min[a]	38.4 (10.5)	66.7 (26.3)	53.8 (30.6)
SDNN (ms), 30 min	46.2 (14.4)	64.2 (26.4)	42.1 (16.6)
SDNN (ms), 60 min	52 (29.6)	59.4 (32)	48.1 (23.9)
SDNN (ms), 90 min	46.3 (20.9)	55.2 (24.4)	50.6 (20.8)
SDNN (ms), 120 min	42.1 (18.4)	62.8 (32.7)	52.9 (23.7)
rMSSD (ms), 0 min	33.2 (19.9)	55.5 (35.4)	42.2 (39.5)
rMSSD (ms), 30 min[a]	38.3 (17.6)	60.9 (19.1)	36 (15)
rMSSD (ms), 60 min	48.3 (30.9)	62 (35.3)	41 (37.6)
rMSSD (ms), 90 min	39.3 (21.7)	53 (31.1)	36.8 (22.4)
rMSSD (ms), 120 min[a]	32.8 (17.7)	55.8 (36.1)	39.5 (27.9)
LF (ms^2), 0 min *	701.7 (617.6)	1305.4 (1625.5)	3252.7 (2961.8)
LF (ms^2), 30 min	1145.9 (690.5)	1684.7 (3412)	2293.8 (5097)
LF (ms^2), 60 min	1699.6 (1497.4)	1405.7 (1533.5)	2430.2 (1723.2)
LF (ms^2), 90 min	1771.7 (1110.3)	1750.6 (2492.2)	2058.7 (2859.7)
LF (ms^2), 120 min	1387 (1328)	1557.1 (2555.3)	2296.6 (2097.9)
HF (ms^2), 0 min	445.5 (501.4)	721 (692.6)	613.9 (512.6)
HF (ms^2), 30 min	563.3 (544.4)	701.7 (1004.7)	721.7 (428.9)
HF (ms^2), 60 min	551.5 (1154.6)	843.9 (946.9)	913.1 (1081.8)
HF (ms^2), 90 min	485.9 (667.7)	703.6 (763)	506.5 (778.8)
HF (ms^2), 120 min	409 (247.9)	680.2 (687.8)	507 (1082.6)
LF norm (n.u.), 0 min[b,c]	62.5 (19.1)	63.9 (14.2)	86.8 (2.9)
LF norm (n.u.), 30 min	60.3 (23.7)	74.5 (23.8)	83.8 (15.8)
LF norm (n.u.), 60 min	71.2 (11.2)	67 (31.9)	66.9 (15.3)
LF norm (n.u.), 90 min	70.8 (15.7)	69 (16.9)	80.2 (25.2)
LF norm (n.u.), 120 min	79.2 (12.5)	69.8 (9.6)	69.7 (18.1)
HF norm (n.u.), 0 min[b,c]	37.4 (19.1)	36.1 (14.2)	13.2 (2.9)
HF norm (n.u.), 30 min	39.6 (23.6)	25.5 (23.8)	16.2 (15.7)
HF norm (n.u.), 60 min	28.7 (11.2)	33 (31.9)	33.1 (15.4)
HF norm (n.u.), 90 min	29.1 (15.8)	30.8 (17)	19.7 (25.2)
HF norm (n.u.), 120 min	20.7 (12.5)	30.1 (9.4)	30.3 (18.1)
LF/HF, 0 min[b,c]	1.7 (1.3)	1.8 (1.2)	6.6 (2.1)
LF/HF, 30 min	1.5 (2.8)	2.9 (3.6)	5.2 (6.7)
LF/HF, 60 min	2.5 (1.3)	2 (3.6)	2 (3.7)
LF/HF, 90 min	2.4 (2.6)	2.2 (2.1)	4.1 (8.1)
LF/HF, 120 min	3.8 (2.7)	2.3 (1)	2.3 (3.4)
TP (ms^2), 0 min[a,b]	1397.8 (1002.7)	2964.3 (2883.1)	3991 (4099.2)
TP (ms^2), 30 min	1955.1 (1061)	2712 (4018.6)	3480.1 (5819.8)
TP (ms^2), 60 min	2882.9 (3298.7)	3348.6 (2558.3)	4056.4 (3032)
TP (ms^2), 90 min	2257 (1719.3)	2751.1 (4058.5)	2609.2 (3945.6)
TP (ms^2), 120 min	1995.5 (1544.4)	2431.3 (2360.5)	1468.6 (3766.6)

[a]Significant difference between subjects with the metabolic syndrome and marathon runners

[b]Significant difference between subjects with the metabolic syndrome and control subjects

[c]Significant difference between marathon runners and control subjects

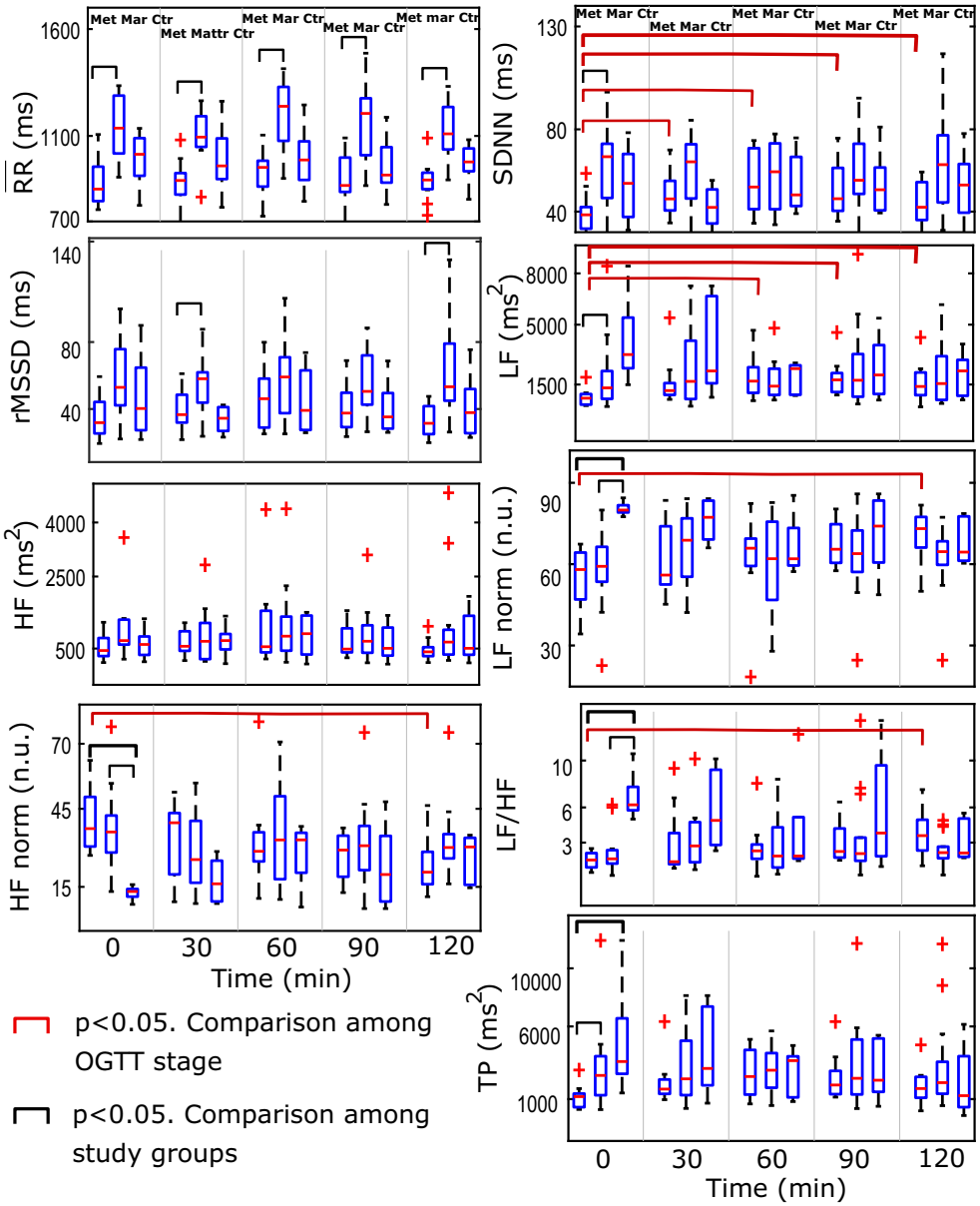

Fig. 3 Box plots of HRV parameters during the OGTT. Met stands for metabolic syndrome, Mar for Marathoners and Ctr for control

(120 min) and LF/HF (120 min), and a reduction in HF norm (120 min) (see Table 3). Both branches of the ANS were thus affected by the sudden increase of plasma glucose concentration, i.e., higher sympathetic (SDNN, LF, LF, norm and LF/HF) but lower parasympathetic (HF norm), suggesting that hyperglycemia and hyperinsulinemia may alter the modulation of the ANS in this population. These findings are in agreement with to those reported in the literature. For instance, Straznicky et al. found a blunted sympathetic nervous system response to a glucose load in subjects with the metabolic syndrome and insulin resistance that is related to central adiposity and the insulin response [19], while Lutfi and Elhakeem related a blood glucose concentration increased with higher parasympathetic but lower sympathetic cardiac autonomic modulation in healthy young adults [11].

5 Conclusion

This study has shown that time-domain and frequency-domain measures of HRV are affected after ingestion of 75 g of glucose, i.e., the glucose stimulus, in subjects with the metabolic syndrome: increased SDNN (30, 60, 90 and 120 min), LF (60, 90 and 120 min), LF norm (120 min) and LF/HF (120 min), and reduced HF norm (120 min). In contrast, marathon runners and healthy subjects do not experience a modification of HRV measures along the OGTT. The innovation of this work lies on the use of the HRV, a simple noninvasive tool, to unveil the effects of a sudden increase in plasma glucose concentration on the cardiac autonomic modulation of subjects with different cardiovascular and metabolic conditions.

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