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ORIGINAL ARTICLE

Cardiac autonomic activity, endothelial function, and physical fitness in type 2 diabetic patients

Atividade autonômica cardíaca, função endotelial e aptidão física em pacientes diabéticos do tipo 2

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KEYWORDS

Heart rate
Physical fitness
Type 2 Diabetes Mellitus
Vascular endothelium

ABSTRACT

Objective: To investigate the association between cardiac autonomic activity, endothelial function, and physical fitness in patients with type 2 diabetes mellitus (T2D).
Methods: A total of 27 T2D patients with a mean age of 57 ± 9 years and a mean disease duration of 7.4 ± 5 years were investigated. Physical fitness was assessed by the Shuttle Walking Test (SWT), cardiac autonomic modulation by heart rate variability (HRV), and endothelial function by flow-mediated dilation (FMD) of the brachial artery by ultrasound imaging.
Results: The main finding of this study was that some HRV indices (SDNN, RMSSD, and HF) correlated significantly with endothelial function in individuals with T2D, with R values ranging from 0.51 to 0.57 ($p < 0.05$) for all associations. In addition, an association was found between the distance walked on the SWT and the baseline brachial artery diameter ($R = 0.59$, $p = 0.01$).
Conclusion: Our data demonstrate that some HRV indices are associated with FMD, indicating an interaction between these two systems. Furthermore, our findings suggest a correlation between physical fitness and endothelial function in individuals with T2D.

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This study was conducted at Nove de Julho University.

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PALAVRAS-CHAVE

Aptidão física
Diabetes Mellitus tipo 2
Endotélio vascular
Frequência cardíaca

RESUMO

Objetivo: Investigar a associação entre atividade autonômica cardíaca, função endotelial e aptidão física em pacientes com *diabetes mellitus* tipo 2 (DT2).
Métodos: Foram estudados 27 pacientes com DT2, com média de idade de 57 ± 9 anos e tempo médio de doença de 7,4 ± 5 anos. A avaliação da aptidão física foi realizada pelo *Shuttle Walking Test* (SWT), a modulação autonômica cardíaca pela variabilidade da frequência cardíaca (VFC) e a função endotelial foi avaliada pela dilatação mediada por fluxo (DMF) da artéria braquial por meio de imagem ultrassonográfica.
Resultados: O principal achado deste estudo foi que alguns índices de VFC (SDNN, RMSSD e HF) correlacionaram-se significativamente com a função endotelial nos indivíduos com DT2, com valores de R entre 0,51 e 0,57 (p < 0,05), para todas as relações. Além disso, foi encontrada associação entre a distância percorrida no SWT e o diâmetro basal da artéria braquial (R = 0,59; p = 0,01).
Conclusão: Nossos dados demonstram que alguns índices de VFC estão associados à DMF, indicando interação entre esses dois sistemas. Além disso, nossos achados sugerem uma correlação entre aptidão física e função endotelial nos indivíduos com DT2.

INTRODUCTION

Diabetes is a complex disease affecting millions of people worldwide[1,2]. According to the World Health Organization (WHO), about 16 million Brazilians are affected by diabetes. The incidence of the disease has grown 61.8% in the last decade, and Brazil ranks 4th among countries with the highest number of diabetes cases[3].

Type 2 diabetes mellitus (T2D) is a metabolic disease resulting from defects in pancreatic β-cell function and insulin resistance, which causes various cardiovascular and nervous system complications[1,2,4]. Additionally, the resulting damage to autonomic nerves distributed in the heart and blood vessels in patients with T2D may cause cardiovascular autonomic neuropathy, increasing the risk of death[5,6].

Heart rate variability (HRV) reflects the variation in time between each heartbeat, indicating the capacity of cardiac autonomic control to respond to multiple physiological stimuli, such as metabolic and mechanical changes[7]. Any negative alteration in the interaction between the central and peripheral nervous systems (afferent or efferent pathways) decreases the HRV, impairing cardiac autonomic control and increasing the risk of cardiac death[8,9]. T2D may be associated with reduced baroreflex sensitivity and an abnormal chronotropic response, altering heart rate regulation[10].

The endothelium is a key regulator of vascular homeostasis, and its dysfunction is considered an early marker of atherosclerosis and an independent predictor of cardiovascular events. This endothelial dysfunction may be present in patients with T2D. Prolonged hyperglycemia in T2D may cause a series of pathological changes in vascular endothelial cells, increasing the production of reactive oxygen species and inflammatory cytokines that cause mitochondrial dysfunction and oxidative damage[11,12].

Examination of flow-mediated dilation (FMD) of the brachial artery by ultrasound imaging is a noninvasive measure of endothelial function. This technique is based on the principle that increased blood flow due to reactive hyperemia (vasodilator response) could increase shear stress-induced nitric oxide production[13,14].

The literature shows that physical activity can be used as an effective non-pharmacological strategy to increase HRV[15]and improve endothelial function in populations with cardiovascular risk factors[13]. However, studies investigating physical fitness, HRV, and endothelial function in patients with T2D are scarce. To date, no study associating these variables has been found. Thus, this study investigated the association between HRV, endothelial function, and physical fitness in patients with T2D.

METHODS

Study design and population

A cross-sectional study with patients with T2D was conducted in the Cardiopulmonary Rehabilitation Laboratory of Nove de Julho University. It was developed according to the standards for human research established by Resolution 466/2012 of the National Health Council. The research was approved by the Ethics Committee on Human Research of the university (CAAE 77531417.5.0000.5511, decision nr. 2.314.292). Written consent was obtained from subjects after explaining the study's objectives, methods, risks, and potential benefits in detail.

In-person communication was performed by the researchers conducting the study and explanatory leaflets with objectives, methods, and benefits were held at the National Association for Diabetes Care headquarters in São Paulo, SP. The subjects, mostly participants of this association, were recruited from March 2019 to August 2019. Inclusion criteria were age ≥ 40 years, diagnosis of T2D confirmed by a physician (fasting blood glucose ≥ 126 mg/dL and glycosylated hemoglobin (HbA1c) ≥ 6.5% or continuous use of oral hypoglycemic agents or insulin), and sufficient cognitive level to understand the procedures and follow the study instructions. Exclusion criteria were prior factors or illnesses that would limit performance in any study assessment: (1) spinal musculoskeletal disorders or lower limbs with impaired independent gait; (2) exacerbated respiratory disease causing impaired breathing, shortness of breath, and intense fatigue; (3) signs and symptoms of acute or decompensated cardiovascular disease such as chest pain, heart palpitations, pallor, dizziness, and uncontrolled blood pressure (BP); and (4) severe peripheral neuropathy with loss of sensation, weakness, and muscle atrophy in lower limbs leading to impaired gait.

Procedures

The study variables were collected on two consecutive days of evaluation. On the patient's first visit to the laboratory, an interview was conducted to collect information about gender, age, laboratory tests (HbA1c, cholesterol, and triglycerides), comorbidities (systemic arterial hypertension, dyslipidemia, former smoker), used medications (oral hypoglycemic agents, insulins, antihypertensives, statins, and fibrates) and anthropometric measurements. Regarding comorbidities, systemic arterial hypertension was considered when systolic arterial pressure was > 140 mmHg and diastolic arterial pressure > 90 mmHg or chronic use of antihypertensive(s). Dyslipidemia was defined as total cholesterol > 200 mg/dL, low-density lipoprotein (LDL) > 130 mg/dL, or chronic use of statins.

On the same day, after the interview, physical fitness was assessed by the Shuttle Walking Test (SWT). On the second visit, cardiac autonomic modulation was assessed by HRV and endothelial function by FMD.

Anthropometric measurements

Height and weight were measured using conventional methods (light clothing and no shoes) with a stadiometer and an electronic scale, respectively, and the body mass index (BMI in kg/m^2) was calculated by dividing weight by height squared. Body composition (lean and fat body mass) was assessed by the bioimpedance method (Biodynamics® Model 450, TBW).

Assessment of physical fitness

The SWT is a simple, valid, reliable, and safe walking test. It is helpful in clinical practice to assess physical fitness in some health conditions. In this study, the SWT was performed according to the original description[16]. A 10 m corridor was used, with two cones placed 0.5 m from each extremity, demarcating a distance of 9 m (Figure 1). The patient should walk back and forth along this predetermined path according to the rhythm imposed by the sound stimuli. The single beep signals the patient to maintain their walking speed, and the triple beep indicates the start of a new test level; the patient must walk faster. The complete test consists of 12 levels, each lasting 1 min. Heart rate (HR) and pulse oxygen saturation were monitored during the test using a portable oximeter (Ohmeda-Biox 3700®). Additionally, BP and perceived exertion variables (modified Borg scale) were recorded before and after the test. The SWT was interrupted by the examiner when the patient did not reach the cone at the time of the sound stimulus (the patient could not keep up with the pace of the test) or when the patient reported some discomfort (dizziness, nausea, significant dyspnea, extreme fatigue, or chest pain).

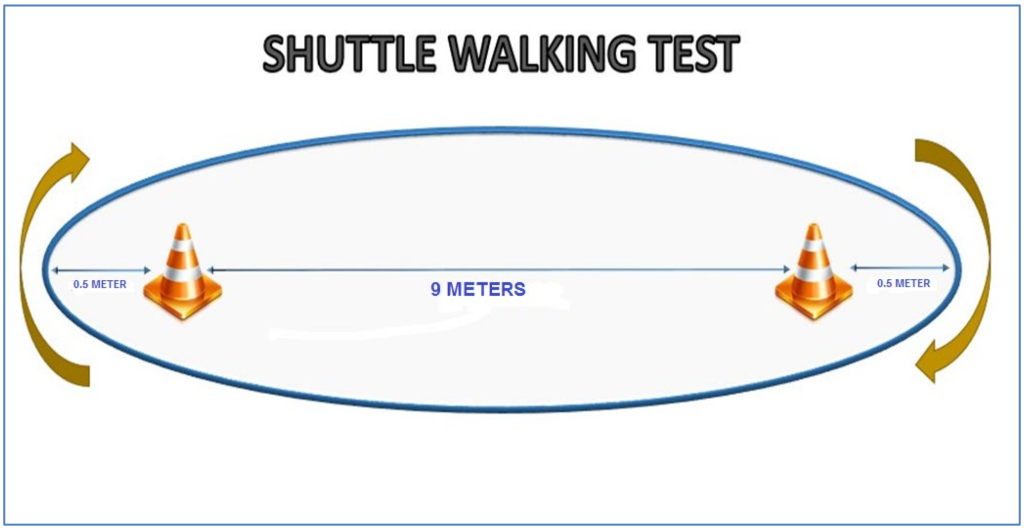

Figure 1 — Cones positioning for the *Shuttle Walking Test* (SWT).

Assessment of cardiac autonomic control

First, each volunteer received the following guidelines for the day before and the day of HRV collection: avoid stimulant drinks (tea, coffee, alcohol), do not practice physical activity, eat light meals, and have a good night's sleep (at least 8 h).The collection was performed in an acclimatized laboratory, with temperatures between 22°C and 24°C, humidity between 50% and 60%, and the same day period (morning or afternoon).

RR intervals (iRR) were recorded continuously by a telemetry system using a Polar S810i cardio-frequency meter (Polar Electro Oy, Kempele, Finland). These data were then used to quantify HRV. Each subject rested for 10 min before the start of data collection to ensure HR stabilization. HR was then recorded continuously for 10 min with the patient in the supine position and another 10 min with the patient standing.

The HR signals were transferred to a microcomputer, and the iRR series was reviewed by visual inspection. Only segments with more than 90% pure sinus beats were included in the final analysis. At the end of the examination, the iRR series were extracted in text format using the Kubios HRV Standard for Windows software (Kubios Oy, Kuopio, Finland, version 3.1.0) to obtain the variables related to the time and frequency domain of HRV (Figure 2). For time domain analysis, the standard deviation of normal RR intervals (SDNN) and the square root of the mean of successive RR interval differences (RMSSD), which represent the overall variability and parasympathetic nervous activity, respectively, were calculated. For frequency domain analysis, the low-frequency component (LF), high-frequency component (HF), and the ratio between low and high-frequency components (LF/HF) were calculated. LF results from the joint action of the vagal and sympathetic components of the heart, with the predominance of the sympathetic, while HF indicates parasympathetic activity in the heart. The LF/HF ratio reflects the absolute and relative changes between the sympathetic and parasympathetic components of the autonomic nervous system, characterizing the sympathetic-vagal balance over the heart[6,17].

Assessment of endothelial function

To assess endothelial function, participants were requested to abstain from vasoactive medications, physical activity, nitrate-rich foods, and caffeine for 24 h and alcohol for 48 h before the test to minimize the effect of these confounding factors. Before the assessment, the participant rested for at least 15 to 20 min. Assessment of the brachial artery was performed using the individual in the dorsal decubitus position, with the dominant arm extended laterally (90°) and stabilized by a foam support.

Changes in the brachial artery diameter were measured by vascular ultrasonography with color Doppler (Philips Medical Systems, ViCare Medical, Denmark) (Figure 3) before and after reactive hyperemia caused by inflating a pressure cuff. A protocol described in previous studies was used[18,19]. It is an effective, simple, and noninvasive method that allows measurement of the vascular response. Thus, the baseline brachial artery diameter (mm), the peak diameter (mm), and the percentage of flow-mediated dilation (FMD%) were measured. Analysis of endothelial function data was performed using the Cardiovascular Suite software (Quipu Group, version 3.4, USA).

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences software (SPSS, Microsoft Inc., Chicago, Il, USA), version 20.0. The Shapiro-Wilk test was used to assess data normality. The descriptive analysis of qualitative variables was based on the distribution of absolute and relative (%) frequencies. Quantitative variables were presented as median and interquartile range (IQR 25%-75%) or mean ± standard deviation when appropriate. Spearman's correlation was used to quantify the association between variables. The significance level used for the tests was 5%.

RESULTS

A total of 30 individuals were initially recruited in a non-probabilistic process. Of these, three were excluded (one had a lower limb musculoskeletal disorder with impaired independent gait preventing the patient from performing the SWT, and two did not show up on the second day). The final sample comprised 27 individuals, the majority overweight and female. Demographic characteristics are described in Table 1.

For physical fitness assessment, the distance walked by patients with T2D in the SWT was 420 m (IQR 330 m - 477.5 m). Variables related to HRV and the assessment of endothelial function are described in Tables 2 and 3, respectively.

The correlations between endothelial function, cardiac autonomic activity, and physical fitness are described in Table 4.

Table 1 — Studied population characteristics (N = 27). Data presented as absolute value (%) or mean ± standard deviation.

Variables	Values
Female gender; n (%)	20 (74)
Age (years)	57 ± 9
Min - max	46 - 69
Disease duration (years)	7.4 ± 5
Laboratory tests	
Glycosylated hemoglobin (%)	7.6 ± 1.9
Total cholesterol (mg/dL)	179 ± 42.5
Triglycerides (mg/dL)	182 ± 78
Bioimpedance	
Body mass index (kg/m^2)	28.8 ± 2.6
Lean body mass (%)	65.4 ± 3.3
Fat body mass (%)	34.5 ± 3.3
Comorbidities	
Systemic arterial hypertension	22 (81.5)
Dyslipidemia	12 (44.5)
Former smoker	2 (7.4)
Medications	
Oral hypoglycemic agents	27 (100)
Insulins	14 (52)
Antihypertensives	22 (81.5)
Statins and/or fibrates	2 (7.4)

DISCUSSION

The main finding of this study was that some HRV indices correlated with endothelial function in patients

Table 2 — Heart rate variability variables (HRV).

Variables	Values
Time domain	
SDNN (ms)	13.95 (12.02 - 17.90)
RR average (ms)	862 (798 - 903)
HR average (bpm)	69.50 (66.50 - 75.00)
RMSSD (ms)	15.60 (10.12 - 21.55)
Stress index	24.25 (20.45 - 27.20)
Frequency domain	
LF (nu)	46.61 (34.65 - 69.64)
HF (nu)	53.11 (30.34 - 65.29)
LF/HF	2.142 (1.314 - 3.907)

SDNN: standard deviation of normal RR intervals; HR: heart rate; RMSSD: square root of the mean of successive RR interval differences; LF: low frequency component; HF: high frequency component; LF/HF: ratio between low and high frequency components. Data presented as median (interquartile range).

Table 3 — Endothelial function variables.

Variables	Values
Baseline diameter (mm)	2.96 (2.54 - 3.53)
Peak diameter (mm)	3.46 (2.93 - 4.21)
FMD (%)	10.18 (6.48 - 15.80)

FMD: flow-mediated dilation. Data presented as median (interquartile range).

with T2D. This may have important clinical implications since reduced HRV in patients with diabetes is considered a hallmark of cardiac autonomic neuropathy, which represents a severe complication associated with an approximately twofold increase in mortality, sudden death, and silent myocardial ischemia[5,20].

A significant reduction of HRV in patients with T2D compared with controls was previously reported in large population studies. They suggested that severe damage to the large, myelinated nerve fibers and generalized neurological degeneration, which usually affects the small nerve fibers of the autonomic nervous system, were responsible for the profound parasympathetic neuropathy in patients with T2D[5,21-23].

Clinical studies have few reports on the interaction between endothelial function and the autonomic nervous system. Lellamo et al.[24] suggested that increased peripheral sympathetic nervous system activity and decreased parasympathetic nervous system activity were associated with impaired endothelial function in healthy first-degree relatives of patients with diabetes.

In various disease states, reduced cardiac vagal activity is accompanied by impaired endothelial function. Evidence from animal studies indicates the interaction between the two systems, but these data are limited in human studies. The interaction may occur centrally due to the influence of endothelial mediators, primarily nitric oxide, on autonomic nervous system function. Nitric oxide synthase, in its endothelial and neuronal isoforms, is distributed in the regions of the central nervous system responsible for autonomic regulation. Recent studies have suggested that the endothelium is an important mediator of autonomic nervous system signaling imbalance[25-27].

Our findings agree with those of Pinter et al.[26], who found a significant positive correlation between HRV indices (RMSSD, PNN50, and HF) and FMD in a recent study with young, healthy male volunteers. They suggested that endothelial mediators, especially nitric oxide released locally from the capillary endothelium, could enhance the effects of vagal inputs during the respiratory cycle. Vagal discharge increases during expiration and decreases during inspiration, producing respiratory sinus arrhythmia. As a result, the main short-term component of HRV, related to respiration, is influenced by endothelial dysfunction[21,26].

Considering the reciprocal relationship between vagal and sympathetic activities, it can be assumed that individuals with low cardiac vagal activity have high sympathetic activity, leading to a reduced FMD. Sympathetic stimulation is known to increase oxidative stress and reduce endothelial nitric oxide production. Furthermore, sympathetic dominance in the autonomic nervous system can lead to increased arterial stiffness, increasing pulsatility, damaging the endothelium, and reducing the FMD[26].

Additionally, our results showed an association between the distance walked on the SWT and the baseline brachial artery diameter. These findings suggest a correlation between physical fitness and endothelial function in patients with T2D. Our data agree with studies showing that physical fitness is associated with lower heart rate, greater cardiac vagal activity, and improved endothelial function [26,28]. In this context, the regular practice of physical activity has been reported as a factor for increasing vagal tone due to the physiological adaptations resulting from increased cardiac work since there is a reduction in the sensitivity of beta receptors[17].

The main limitations of this study are the small sample size and its cross-sectional nature. However, the strength of our research lies in showing that it is imperative to screen for autonomic neuropathy and endothelial dysfunction as early as possible in patients with T2D to prevent or delay its serious cardiac consequences.

CONCLUSION

Studies associating physical fitness, HRV, and endothelial function in patients with T2D are limited in the literature. Our results showed a correlation between some HRV indices and endothelial function, as well as between physical fitness and endothelial function in individuals with T2D. However, further research associating these variables is still necessary. Further investigation of the interaction between cardiovascular autonomic modulation and endothelial function may help clarify the complex mechanisms involved in the development and progression of cardiovascular disease in patients with T2D.

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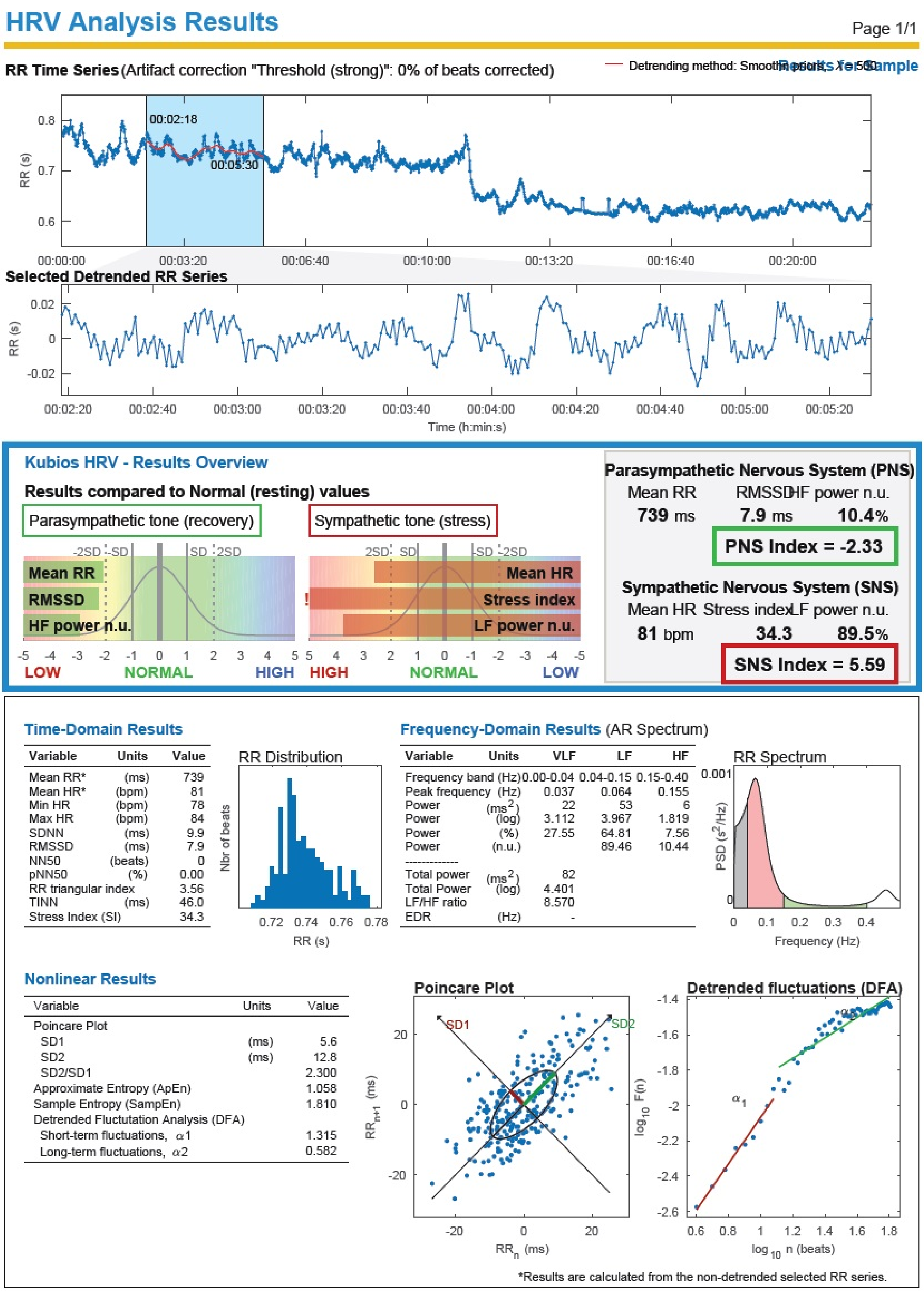

Figure 2 — Analysis of heart rate variability (HRV) results performed by the Kubios HRV Standard software.

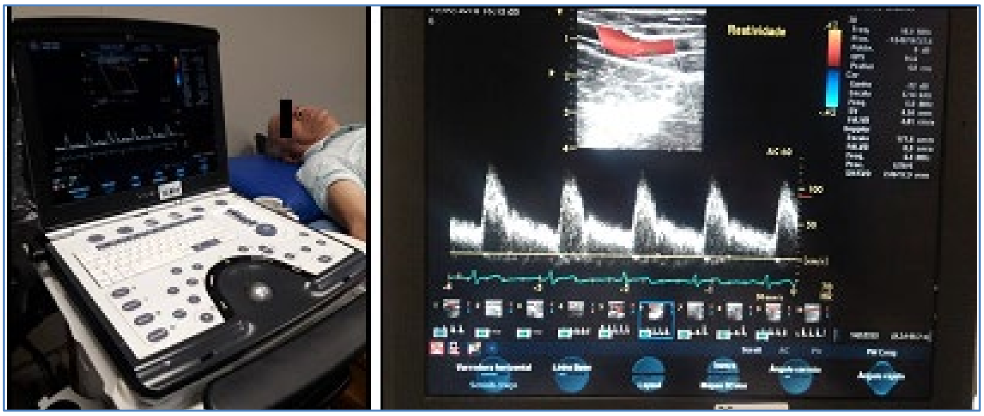

Figure 3 — Doppler vascular ultrasound image of the brachial artery.

Table 4 — Correlations between edothelial function, cardiac autonomic activity and physical fitness.

Variables	Correlation coefficient	P value
FMD (%) x SDNN (ms)	0.51	0.03*
FMD (%) x RMSSD (ms)	0.55	0.02*
FMD (%) x LF (nu)	0.18	0.47
FMD (%) x HF (nu)	0.57	0.01*
FMD (%) x Distance walked on the SWT (m)	0.03	0.91
Distance walked on the SWT (m) x baseline diameter (mm)	0.59	0.01*
Distance walked on the SWT (m) x SDNN (ms)	0.17	0.38
Distance walked on the SWT (m) x RMSSD (ms)	0.20	0.92
Distance walked on the SWT (m) x LF (nu)	0.23	0.24
Distance walked on the SWT (m) x HF (nu)	0.15	0.43

FMD: flow-mediated dilation; SDNN: standard deviation of normal RR intervals; RMSSD: square root of the mean of successive RR interval differences; LF: low frequency component; HF: high frequency component; SWT: *Shuttle Walking Test*.

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Conception and design: CP, LMMS
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Writing of the manuscript: CP
Critical revision of the article: LMMS
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