CorSalud 2019 Jan-Mar;11(1):1-10

Cuban Society of Cardiology

Original Article

Cardiovascular autonomic response during the Cuban dynamic weight-bearing test

Michel Torres-Leyva[1], Std; Ramón Carrazana-Escalona[1], Std; Laura E. Ormigó-Polo[1], Std; Beatriz T. Ricardo-Ferro[2], BS; Erislandis López-Galán[1], MD; Laritza Ortiz-Alcolea[1] , MD; and Miguel E. Sánchez-Hechavarría[3]✉, MD

[1] Universidad de Ciencias Médicas de Santiago de Cuba. Santiago de Cuba, Cuba.
[2] Centro de Biofísica Médica, Universidad de Oriente. Santiago de Cuba, Cuba.
[3] Department of Basic Medical Sciences and Morphology, Faculty of Medicine, Universidad Católica de la Santísima Concepción. Concepción, Chile.

Este artículo también está disponible en español

ARTICLE INFORMATION

Received: September 16, 2018
Accepted: October 18, 2018

Conflictos de intereses
Los autores declaran que no existen conflictos de intereses

Abreviaturas
BP: blood pressure
CWT-Morlet: continuous wavelet transform, Morlet type function
HBP: high blood pressure
HF: high frequency
HRV: heart rate variability
LF: low frequency
WBT: dynamic weight-bearing test

✉ *ME Sánchez-Hechavarría*
Alonso de Ribera 2850.
Concepción, Chile. CP 4090541. E-mail addresses:
misanchez@ucsc.cl;
miguel.sanchez881119@gmail.com

ABSTRACT

Introduction: The dynamic weight-bearing test (WBT) is a Cuban isometric exercise, similar to the hand grip test, which is very useful to induce hemodynamic modifications to identify cardiovascular hyperreactivity in at-risk populations. However, changes in the cardiovascular autonomic response during weight-bearing test are poorly understood.

Objectives: To determine the cardiovascular autonomic response during the Cuban dynamic WBT.

Method: Quasi-experimental crossover trial with 16 healthy subjects; blood pressure and heart rate variability were assessed, 5 minutes before (rest) and during the WBT (2 minutes for maneuver and 3 minutes for recovery), through the frequency (Fourier) and time-frequency (Wavelet) analysis of high-frequency (HF: 0.15-0.4 Hz) and low-frequency (LF: 0.04-0.15 Hz) bands, as well as temporal and non-linear analysis (Shannon entropy) of the RR interval series.

Results: Although temporal indicators (SDNN, RMSSD, pNN50) showed no significant differences ($p>0.05$) nor the frequencies (LF, HF, LF/HF); we found an increase ($p<0.05$) in blood pressure and a significant decrease ($p<0.05$) in complexity (entropy) in the WBT with respect to rest, associated with an HF peak and LF/HF ratio at nearly 2 minutes reflected with the time-frequency methods.

Conclusions: There was a dynamic increase in the cardiovascular sympathetic response during the WBT associated with a decrease in the complexity of this physiological process, which is not evident with the traditional linear methods of heart rate variability.

Keywords: Dynamic weight-bearing test, Autonomic response, Heart rate variability, Cardiovascular system

Respuesta autonómica cardiovascular durante la prueba isométrica cubana del peso sostenido

RESUMEN

Introducción: La prueba del peso sostenido (PPS) es un ejercicio isométrico cubano, similar a la de handgrip, de mucha utilidad para inducir modificaciones hemodinámicas que permiten identificar la hiperreactividad cardiovascular en poblaciones de riesgo. Sin embargo, los cambios en la respuesta autonómica cardiovascular durante la PPS no se encuentran totalmente dilucidados.

Objetivo: *Determinar la respuesta autonómica cardiovascular durante la prueba isométrica cubana del peso sostenido.*

Método: *Estudio cuasi-experimental (crossover) con 16 sujetos sanos, donde se evaluaron la presión arterial y la variabilidad de la frecuencia cardíaca, 5 minutos antes (reposo) y durante la PPS (2 minutos de maniobra y 3 minutos de recuperación), a través del análisis frecuencial (Fourier) y en tiempo-frecuencia (wavelet) de las bandas de altas (HF: 0,15-0,4 Hz) y bajas frecuencias (LF: 0,04-0,15 Hz), así como el análisis temporal y no-lineal (entropía de Shannon) de la serie de intervalos RR.*

Resultados: *Aunque no existieron diferencias significativas (p>0,05) en los indicadores temporales (SDNN, RMSSD, pNN50), ni en los frecuenciales (LF, HF, LF/HF), se encontraron incrementos (p<0,05) de la presión arterial y una disminución significativa (p<0,05) de la complejidad (entropía) en la PPS con respecto al reposo, asociados con un pico en la LF y la relación LF/HF alrededor de los 2 minutos reflejados con los métodos en tiempo-frecuencia.*

Conclusiones: *Existió un incremento dinámico en la respuesta simpática cardiovascular durante la PPS que se asocian a una disminución de la complejidad de este proceso fisiológico, lo que no es evidente con los métodos lineales tradicionales de la variabilidad de la frecuencia cardíaca.*

Palabras clave: *Prueba del peso sostenido, Respuesta autonómica, Variabilidad de la frecuencia cardíaca, Sistema cardiovascular*

INTRODUCTION

High blood pressure (HBP) is one of the diseases that most afflicts the world population. According to the World Health Organization, one in five adults suffers from HBP and nearly 9.4 million deaths occur every year due to secondary complications attributable to HBP[1,2]. Therefore, it is urgent to take immediate action to control such disease. Every effort aimed at increasing the etiopathogenic knowledge of the pathophysiological mechanisms underlying HBP are a foundation where prevention, diagnosis and treatment actions for HBP would rest.

Early stages of hypertension (and some instances of pre-hypertensive states, particularly in individuals with a family history of hypertension) are characterized by a hyperkinetic circulatory state, which is mediated by an increase in adrenergic activity and a reduction of the parasympathetic function[3]. Different methods have been used to evaluate the autonomic imbalance for many years[4,5]; but it is not until the last four decades, with the development of computerized methods for heart rate variability assessment (HRV), that an accelerated advance in this area is evident.

Heart rate variability is the fluctuation in the time intervals between consecutive heartbeats.

At present HRV is typically assessed using time-domain, frequency-domain, and non-linear indices[6-8]. The former quantifies the sequence of RR intervals as a set of unordered intervals or as paired intervals and uses different techniques to express data variance[6-11]. The spectral analysis consists of decomposing the tachogram (record of heart rate in time) which looks like a complex wave, to obtain the spectral components, components of high frequency (HF), related to the parasympathetic tone and the components of low frequency (LF), related to the modulation of the sympathetic and parasympathetic nervous systems. Although still a controversy, the ratio between these components (LF/HF) has been proposed as an indicator of sympatho-vagal balance[8].

Time-frequency methods are derived from frequency methods that allow analyzing changes in present time in the spectral analysis of HRV. Continuous Wavelet Transform, Morlet type function (CWT-Morlet), is one of the most frequently used time-frequency methods to assess HRV as it provides adequate resolution when describing changes in the frequency spectrum occurring throughout time[12]. Generally, HRV indicators are related to physiological adaptations to changes in the internal and external environment and the presence of diseases.

Cardiovascular and sympathetic hyperreactivity clarifies part of the etiopathogenesis of hypertension and other cardiovascular diseases[13]. There is a number of techniques to induce cardiovascular reactivity. Physical loads have shown to be more sensitive and specific than the rest[14,15]. The isometric stress test is one of the most widespread among them and has shown a high predictive value and sensitivity in HBP diagnosis[16-18]. In our setting we use the dynamic weight-bearing test (WBT), a variant for the isometric stress test. This test has great practical value for carrying out massive research on HBP[19,20]. It consists of holding a 500 grams weight in the left hand with the arm extended right-angled to the body for 2 minutes. Blood pressure (BP) is taken in the opposite arm before exercise and during its last 10 seconds[21]. WBT has shown that cardiovascular hyperreactive subjects have a higher risk of hypertension than normorreactive subjects. Cardiovascular hyperreactivity is a critical predictor of hypertension[22].

Though such tests are widely used in medical practice in both national and international settings, all the studies conducted with the WBT are based on the hemodynamic response from the BP so it is necessary to know the way dynamics behave in the time of cardiac autonomic regulation during WBT in normal normotensive and normorreactive subjects by measuring HRV. Therefore, the objective of this research was to determine the cardiovascular autonomic response during the Cuban isometric WBT.

METHOD

A non-observational, quasi-experimental (crossover) trial was conducted with 16 healthy normotensive and normal weight participants, (aged 25.8±7.5 years), who served as their own control: 5 minutes resting and another 5 during the Dynamic weight-bearing test. This research was approved by the Medical Ethics Committee from the Universidad de Ciencias Médicas de Santiago de Cuba and subsequently performed in the Basic Sciences Laboratory of the institution.

Exclusion criteria

Subjects suffering from nervous system disorders (stroke, neuromuscular disorders), generalized skin conditions, implanted electronic devices (pacemakers or implantable cardioverter defibrillator), having any upper or lower limbs amputated, suffering from HBP, women who were pregnant or menstruating, subjects with any type of arrhythmia after ECGs records were visually inspected in the 10-15 adaptation lapse, as well as noncooperative subjects who did not give their informed consent.

Physiological records

At the beginning of the ECG recording session in the morning (08:30-12:00 am), the participants sat in a comfortable chair, in a dimly lit room with controlled temperature between 24 and 27 degrees Celsius. They were allowed to rest for 10-15 minutes to adapt to local conditions.

After skin was cleaned with alcohol wipe, electrodes were attached in the DII lead, extended to the limbs and recording was performed for 5 minutes (at rest); BP was subsequently taken with certified sphygmomanometer and stethoscope. The 5 WBT state included 2 minutes holding the 500 grams weight and 3 minutes for recovery.

The Powerlab® electrocardiography signal, with a bandpass filter 0.5-30 Hz, was digitized at a sampling rate of 1000 samples/second (1 kHz), in the 2012 LabChart® software package, both Australian-made, AD Instruments company.

ECG signal processing, R waves discrimination and RR intervals calculation

All recordings were visually examined. We used the Sabarimalai-Manikandan method for R-peak detection in ECG signal and calculation of the RR intervals[23]. All subsequent HRV analysis was carried out based on the set of RR intervals previously obtained.

Pre-processing of RR intervals

The HRVAS program (heart rate variability analysis software [https://sourceforge.net/projects/hrvas)][24], Copyright 2015 by John T. Ramshur was used for preliminary processing of the RR interval series[24]. A 20% percentage filter from the previous interval was used to detect ectopic beats, which were replaced from the polytomic cubic interpolation. The Wavelet Packet Detrending was used to remove low frequency trends over the baseline.

Analysis of heart rate variability

In the traditional analysis of HRV, as recommended by the International Consensus of Experts on HRVD of 1996[9], the HRV32 Version 2.0.3.2 program for Windows was used, from the Facultad de Biología de la

Universidad de la Habana[25], using the following indicators:

- SDNN, standard deviation of NN intervals, known as Total Variability[8,9].
- RMSSD, the square root of the mean squared differences of successive NN intervals. This parameter reports short-term variations of the RR intervals and is used to observe the influence of the parasympathetic nervous system on the cardiovascular system. It is directly associated with short-term variability[8,9].
- pNN50, proportion derived by dividing NN50 by the total number of NN intervals. A high pNN50 value gives us valuable information about spontaneous high variations in heart rate[8,9].
- Low frequencies (LF) (n.u.): normalized energy in the spectrum of 0.04 to 0.15 Hz in which time series of consecutive RR intervals is decomposed: $LFn.u. = \frac{LF}{(LF+HF)}$. It is the most controversial area in its interpretation since it may be attributed to influences of the sympathetic and parasympathetic nervous systems[8,9].
- High frequencies (HF) (n.u.): normalized energy in the 0.15 to 0.4 Hz spectrum in which the time series of consecutive RR intervals is decomposed: $HFn.u. = \frac{HF}{(LF+HF)}$. HF is clearly related to the activity of the parasympathetic nervous system and is influenced by the respiratory rate[8,9].
- LF/HF relation: LF/HF ratio. Although controversial, it has been proposed as an indicator of sympathetic-vagal balance[8,9].
- Shannon entropy: Shannon formula is applied in the theory of information field (Shannon, 1948) and is used to calculate the amount of information contained in the sequence of RR interval: $Entropia\ de\ Shannon = -\sum_{j=1}^{nc}\left[prob(bin_j) * log_2\left(prob\left(bin_j\right)\right)\right]$ Where, prob (binj) is the statistical or appearance probability of the j-th interval class, that is, nj/n[25].

Calculation of HRV indicators in time-frequency

RR intervals were re-sampled with a 2 Hz interpolation (0.5 seconds) for the time-frequency analysis.

Table. Effects of the Dynamic weight-bearing test on the hemodynamic parameters.

Variables	Rest		WBT		p
	χ	SD	χ	SD	
Heart rate (beats / minute)	64,93	10,83	67,81	12,34	0,190
Systolic blood pressure (mmHg)	106,87	10,78	112,75 ¥	13,10	**0,017***
Diastolic blood pressure (mmHg)	74,12	8,53	80,12 ¥	8,04	**0,047***
Mean arterial pressure (mmHg)	85,04	8,59	91,00 ¥	9,22	**0,026***
Pulse pressure (mmHg)	32,75	7,75	32,62 ¥	8,31	0,950
SDNN	122,13	67,72	107,28	65,82	0,125
RMSSD	71,31	39,32	65,96	30,25	0,339
pNN50	37,06	21,89	31,98	21,26	0,126
Low frequencies (LF, un)	52,02	16,14	53,93	13,75	0,642
High frequencies (HF, un)	47,96	16,14	46,06	13,75	0,642
LF/HF ratio	1,20	0,84	1,42	0,99	0,339
Shannon entropy	-6,93	0,68	-7,15	0,54	**0,017***

¥ Evaluated at 2 minutes during the Dynamic weight-bearing test.

***** Variables with significant variations after the test is applied.

pNN50, proportion derived by dividing NN50 by the total number of NN intervals; RMSSD, the square root of the mean squared differences of successive NN intervals; SDNN, standard deviation of NN intervals; un, standardized units.

The CWT-Morlet was used for the HRV time-frequency analysis. This technique uses short windows to the HF and long for the LF, and can be satisfactorily applied to the processing of non-stationary signals, indicating which frequencies are present in a moment of time, showing good temporal resolution to the HF and good spectral resolution to the LF. Theoretically, the CWT-Morlet function is calculated for infinitesimally small translations and scale factors. For a signal x(t) and the wavelet function $\Psi_{ab}(t)$, the continuous wavelet transform coefficient is given by: $W(\tau,\alpha)=\frac{1}{\sqrt{\alpha}}\int_{-\infty}^{\infty}x(t)\Psi^{*}\left(\frac{t-\tau}{\alpha}\right)dt$, where $\Psi^{*}(t)$ is the complex conjugate of the mother wave, α is the dilatation parameter and τ is the location parameter. The CWT-Morlet function was used as a Gaussian, which is balanced in time and frequency defined as: $\Psi_0(t)=\pi^{-1/4}e^{i\omega_0 t}e^{\frac{-1}{2}t^2}$, where ω is a dimensionless frequency, which defines the cycles number of the CWT-Morlet function; with $\omega=6$ a good quality in the temporal and frequency resolution was provided. The bivariate function $W(\tau,\alpha)$ shows the similarity of x(t) to a wave scaled by α at a given time τ.

To obtain the time-frequency values, instantaneous power methods were used, where the square module of the wavelet coefficient was integrated in the whole frequency band analyzed [f1 f2]. The instantaneous power of a frequency band [f1 f2] is given by:

$$P_{CWT}(t)=\frac{1}{C\Psi}\int_{\alpha_1}^{\alpha_2}|W(t,\alpha)|^2\frac{d\alpha}{\alpha^2}=\frac{1}{C\Psi f\Psi}\int_{f_1}^{f_2}|W(t,f_\Psi/f)|^2\,df$$

Traditional HRV frequency bands were used as recommended by the International Expert Consensus on heart rate variability (HRV) in 1996[9], which were for low frequencies of [*LF*: 0.04-0.15 Hz]; high frequencies of [HF: 0.15-0.4 Hz]. The CWT-Morlet was exported in a "file.txt", a matrix of results for each subject for 5 minutes records (300 s), from the interpolation of 2 Hz (0.5 seconds); leaving 600 values in the HRV frequency bands (LF, HF). Frequency bands were normalized (n.u.) for better statistical management, as recommended[9].

Statistical data processing methods

With the use of the SPSS 22.0 System, mean values ($\bar{\chi}$) are exposed as well as standard deviation of the variables to which a nonparametric statistical analysis was performed with the signed Wilcoxon rank test for the samples related to a significance level of $p<0.05$.

Authors have elaborated the dynamic graphs in time (graphs 1 and 2) in the applied version of the Matlab 2013b program. It was used from the average of the matrices of the normalized values in all frequency bands of the HRV calculated from the CWT-Morlet during the Dynamic weight-bearing test (300 s) and interpolated at 2 Hz (0.5 s).

RESULTS

Table shows that within the hemodynamic parameters studied only significant differences were found in the mean, systolic and diastolic BP, though heart rate had a tendency to increase.

Figure 1 shows the significant reduction in Shannon entropy during weight bearing when testing normotensive patients.

Figure 2 shows an increase in the sympathetic component of the cardiac autonomic response near minute 2, while there is a simultaneous decrease in the parasympathetic component.

Figure 3 shows an increase in the sympathetic component of the cardiac autonomic response, predominating its activity on the parasympathetic component around minute 2, which then decreases.

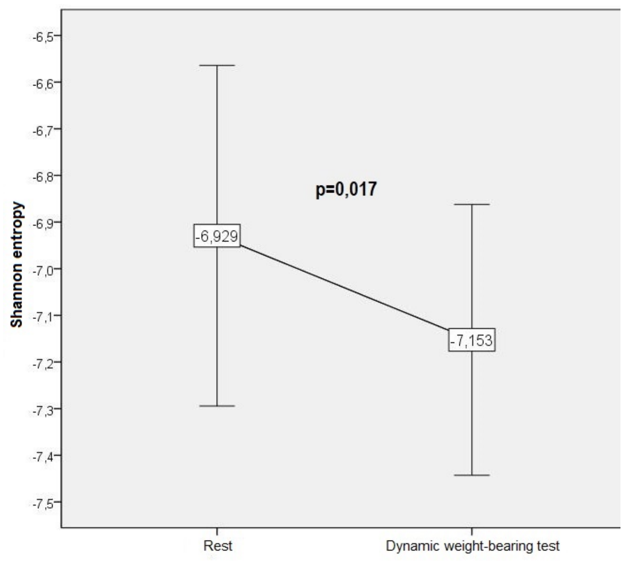

Figure 1. Dynamic weight-bearing test effect on the Shannon entropy parameter of non-linear heart rate variability in healthy subjects.

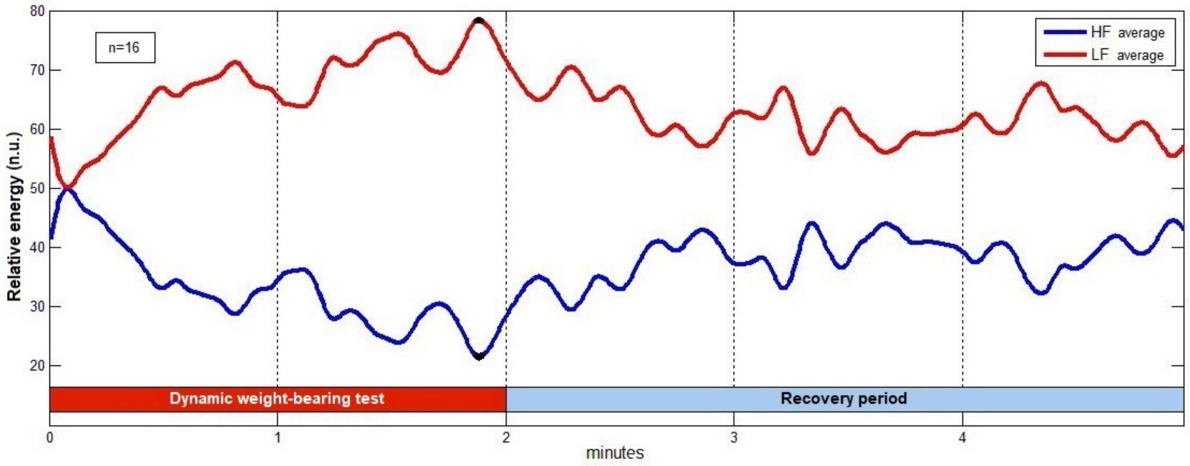

Figure 2. Dynamic weight-bearing test effect on dynamic parameters (LF and HF) over time of heart rate variability.

DISCUSSION

The presence of significant variations in systolic, diastolic and mean arterial pressures shown in **table** coincides with the reference literature[26-28]. In previous studies in which the isometric stress test was used. As already mentioned, there were variations in the values of these variables due to the effect of this stressful stimulus[28]. We cannot fail to point out that although the heart rate did not show significant changes, it did increase. To understand this behavior, it is necessary to say that the heart rate is measured during 5 minutes, once the WBT has started, but this only lasts 2 minutes so the remaining three respond to a recovery period. All this implies that although there are variations with respect to the heart rate, this will not have significant variations when averaging it in the 5 minutes corresponding to the WBT and the recovery period, since the second stage will distort the real average of the first, so it would be advisable to average out WBT and recovery periods separately.

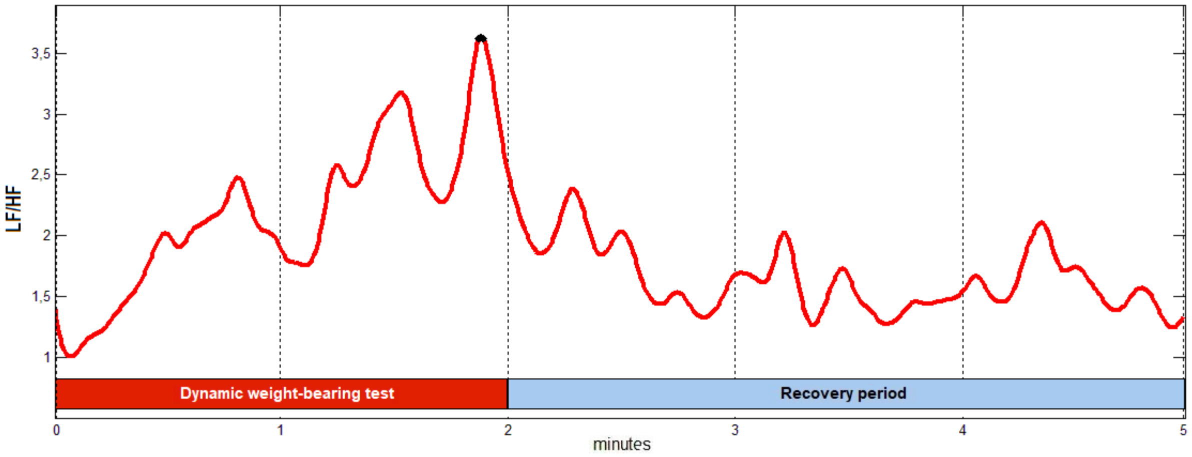

Figure 3. Dynamic weight-bearing test effect on dynamic parameters over time of the heart rate variability in the LF/HF ratio.

Goulopoulou *et al*[29], suggest that changes in heart rate occur during static exercises, among which is the WBT. In these cases, the suggested neural mechanisms are two: one that activates the central neuronal circuits that control the cardiovascular system and the somatomotor, and will produce changes in the sympathetic and parasympathetic efferent activity, which will cause changes in the cardiovascular responses. The other mechanism states that changes in autonomic efferent activity are a reflex cause of the stimulation of type III muscle fibers, which produce an inhibitory stimulus at the level of the solitary nucleus that produces a decrease in vagal influx and an increase in heart rate (early mechanoreflex muscle response to isometric exercise)[30,31].

It is important to note that Lellamo *et al*[32] also reported that static exercise produces stimulation of sympathetic activity, creating elevations of systolic, diastolic and heart rate. This reaffirms that sympathetic mechanoreflex muscle excitation contributes to the regulation of heart rate during static exercise and coincides with the results obtained by Bunsawat and Baynard[33] in the control group composed of healthy subjects in whom there was also elevation of systolic, diastolic and average BP values during the isometric exercise.

Chaos intrinsically takes advantage of the wealth related to its structure, which is why there are benefits for these systems from the adoption of chaotic regimes with a wide range of possible behaviors[34]. Thus, some works show that entropy is reduced with aging, just as pathological systems show lower entropies than healthy ones[35,36], which from the perspective of complexity theory can be interpreted as loss of adaptability of the heart rate regulating systems. It has also been shown that entropy is an alternative non-linear measure of the sympathetic-vagal balance, which decreases in tests that imply an increase in sympathetic response (Tilt table test and mental stress)[36,37], while there is an increase in entropy in vagally prevalent salutogenic conditions, such as the regular practice of physical exercises[38], hypnosis[39] and meditation[40]. This is consistent with our findings because **figure 1** shows that there is a Shannon entropy decrease in the WBT with respect to the resting state in normotensive subjects, since this test causes an increase in the sympathetic tone and the pressor substances, which cause the system to becomes more rigid tending towards a point of maximum activationse.

Figure 2 shows how in the application of time-frequency methods an increase in baroreflex sympathetic activity (LF) is observed simultaneously with a depression in the activity of the parasympathetic nervous system (HF). This is manifested in the 2 minutes in which the WBT is performed, which is subsequently normalized during the recovery period[32]. On the other hand, the same figure shows a sympathetic predominance in the sympathetic vagal balance (LF/HF) coincidentally in the first two minutes, during the WBT, reaching its maximum value at minute 2.

These results coincide with those of Tiinanen *et al*[41] that in a study conducted in 11 healthy men, using the exercise of the isometric stress test, they found that in the last two minutes of the test the greatest sympathetic response was reached, translated by the elevation of the systolic BP, LF, as well as in the decrease of the HF parameter. But the highest values recorded in these parameters were observed at the last minute, so we consider that it is precisely in this last minute of registration in the isometric exercises that sympathetic activity can be observed more intensely on the cardiovascular system.

With this study, by applying time-frequency methods of HRV, the dynamic changes in time present during WBT in the autonomic nervous system were evidenced, which makes it possible to characterize the normal pattern of response during WBT in normotensive and normorreactive subjects.

CONCLUSIONS

The dynamics of the cardiac autonomic response during the Dynamic weight-bearing test is characterized by an increase in the cardiovascular sympathetic response, which becomes evident at the end of the second minute, accompanied by elevations in blood pressure, followed by an immediate recovery with parasympathetic activation. The cardiovascular autonomic response during Cuban isometric exercise is associated with a decrease in entropy and therefore the complexity of the physiological process, which is not evident with traditional linear methods of heart rate variability.

REFERENCES

1. Organización Mundial de la Salud. Preguntas y

respuestas sobre la hipertensión [Internet]. Ginebra: OMS; 2015 [citado 31 Ago 2018]. Disponible en: https://www.who.int/features/qa/82/es/

2. Organización Mundial de la Salud. Información general sobre la hipertensión en el mundo. Una enfermedad que mata en silencio, una crisis de salud pública mundial [Internet]. Ginebra: OMS; 2013 [citado 31 Ago 2018]. Disponible en: http://apps.who.int/iris/bitstream/10665/87679/1/WHO_DCO_WHD_2013.2_spa.pdf?ua=1
3. Grassi G. Neuroadrenergic abnormalities in hypertension and hypertension-related cardiovascular disease. Hipertens Riesgo Vasc. 2013;30(2):70-4.
4. Mathias CJ. Autonomic diseases: clinical features and laboratory evaluation. J Neurol Neurosurg Psychiatry. 2003;74(Supl 3):31-41.
5. Medina Durango E. Pruebas de función autonómica. En: Cabrales Neira MF, Vanegas Cadavid DI, eds. Manual de métodos diagnósticos en electrofisiología cardiovascular. 1ra ed. Bogotá: Sociedad Colombiana de Cardiología y Cirugía Cardiovascular; 2006. p. 131-40.
6. Germán-Salló Z, Germán-Salló M. Non-linear methods in HRV analysis. Procedia Technology. 2016;22:645-51.
7. Mirescu SC, Ciocoiu AL, David L, Tarba C. Heart rate variability: a practical review for the beginner. Studia Universitatis Babeş-Bolyai. Biologia. 2017; 62(1):87-100.
8. Rodas G, PedretCarballido C, Ramos J, Capdevila L. Variabilidad de la frecuencia cardíaca: concepto, medidas y relación con aspectos clínicos (I). Arch Med Deporte. 2008;25(123):41-7.
9. Anónimo. 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 Electrophysiology. Circulation. 1996;93(5):1043-65.
10. Restrepo Jaramillo CA. Variabilidad de la frecuencia cardíaca: cambio de vocación para una prueba. En: Cabrales Neira MF, Vanegas Cadavid DI, eds. Manual de métodos diagnósticos en electrofisiología cardiovascular. 1ra ed. Bogotá: Sociedad Colombiana de Cardiología y Cirugía Cardiovascular; 2006. p. 93-7.
11. Billman GE, Huikuri HV, Sacha J, Trimmel K. An introduction to heart rate variability: methodological considerations and clinical applications. Front Physiol [Internet]. 2015 [citado 10 Sep 2018];6:55. Disponible en: https://www.frontiersin.org/articles/10.3389/fphys.2015.00055/full
12. Bravi A, Longtin A, Seely AJ. Review and classification of variability analysis techniques with clinical applications. Biomed Eng OnLine [Internet]. 2011 [citado 10 Sep 2018];10:90. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3224455/pdf/1475-925X-10-90.pdf
13. Mancia G. Björn Folkow Award Lecture. The sympathetic nervous system in hypertension. J Hypertens. 1997;15(12):1553-65.
14. Esler MD, Thompson JM, Kaye DM, Turner AG, Jennings GL, Cox HS, *et al.* Effects of aging on the responsiveness of the human cardiac sympathetic nerves to stressors. Circulation. 1995;91(2):351-8.
15. Matthews EL, Greaney JL, Wenner MM. Rapid onset pressor response to exercise in young women with a family history of hypertension. Exp Physiol. 2017;102(9):1092-9.
16. O'Driscoll JM, Taylor KA, Wiles JD, Coleman DA, Sharma R. Acute cardiac functional and mechanical responses to isometric exercise in prehypertensive males. Physiol Rep [Internet]. 2017 [citado 11 Sep 2018];5(7):e13236. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5392522/pdf/PHY2-5-e13236.pdf
17. Watanabe K, Ichinose M, Tahara R, Nishiyasu T. Individual differences in cardiac and vascular components of the pressor response to isometric handgrip exercise in humans. Am J Physiol Heart Circ Physiol. 2014;306(2):251-60.
18. Garg R, Malhotra V, Dhar U, Tripathi Y. The isometric handgrip exercise as a test for unmasking hypertension in the offsprings of hypertensive parents. J Clin Diagn Res. 2013;7(6):996-9.
19. Ballesteros Hernández M, Guirado Blanco O, Alfonso Rodríguez J, Marrero Martínez JA, Fernández Caraballo D, Heredia Ruiz D. Concentraciones de oligoelementos y reactividad vascular en mujeres en edades fértiles y posmenopáusicas. Medicentro [Internet]. 2017 [citado 12 Sep 2018]; 21(4):316-22. Disponible en: http://www.medicentro.sld.cu/index.php/medicentro/article/view/2369/2082
20. León Regal ML, Benet Rodríguez M, Mass Sosa LA, Willians Serrano S, González Otero LH, León Valdés A. La hiperreactividad cardiovascular como factor predictivo de la hipertensión arterial en la mujer. Medisur [Internet]. 2016 [citado 12 Sep 2019];14(3):269-79. Disponible en: http://medisur.sld.cu/index.php/medisur/article/

view/3095/2052

21. Sánchez Hechavarría ME, Rodríguez Gutiérrez LC, Rodríguez Nuviola J, Ortiz Alcolea L, Sarmiento González R. Relación entre la práctica de actividad física extraescolar y la hiperreactividad cardiovascular en adolescentes. Rev Cub Med Dep & Cul Fís [Internet]. 2016 [citado 13 Sep 2018];11(1). Disponible en: https://www.researchgate.net/publication/304953793_Relationship_between_the_practice_of_out_of_school_physical_activity_and_the_cardiovascular_hyperreactivity_in_adolescents
22. Benet Rodríguez M, Morejón Giraldoni A. Hiperreactividad cardiovascular: un marcador de riesgo poco conocido en la predicción de la hipertensión arterial. En: Consejo Nacional de Sociedades Científicas del Ministerio de Salud Pública de Cuba. Premio Anual de la salud 2012. 37 ed. La Habana: Ecimed; 2013. p-88-96.
23. Sabarimalai Manikandan M, Soman KP. A novel method for detecting R-peaks in electrocardiogram (ECG) signal. Biomed Signal Process Control. 2012;7(2):118-28.
24. Ramshur JT. Design, evaluation, and application of heart rate variability analysis software (HRVAS) [Tesis]. Memphis: The University of Memphis [Internet]; 2010 [citado 13 Sep 2018]. Disponible en: https://doi.org/10.13140/RG.2.2.33667.81444
25. Machado García A, Estévez Báez M, González Gómez H. Optimización de los métodos para estudiar la variabilidad de la frecuencia cardiaca y su aplicación a grupos de sujetos sanos y enfermos [Tesis]. Ciudad de La Habana: Universidad de La Habana [Internet]; 2008 [citado 13 Sep 2018]. Disponible en: http://tesis.sld.cu/index.php?P=DownloadFile&Id=555
26. Lydakis C, Momen A, Blaha C, Herr M, Leuenberger UA, Sinoway LI. Changes of elastic properties of central arteries during acute static exercise and lower body negative pressure. Eur J Appl Physiol. 2008;102(6):633-41.
27. Jones RI, Lahiri A, Cashman PM, Dore C, Raftery EB. Left ventricular function during isometric hand grip and cold stress in normal subjects. Heart. 1986;55(3):246-52.
28. Benet Rodríguez M, Apollinaire Pinnini JJ, Torres Ros J, Peraza Pons S. Reactividad cardiovascular y factores de riesgos cardiovasculares en individuos normotensos menores de 40 años. Rev Esp Salud Pública. 2003;77(1):143-50.
29. Goulopoulou S, Fernhall B, Kanaley JA. Developmental changes in hemodynamic responses and cardiovagal modulation during isometric handgrip exercise. Int J Pediatr [Internet]. 2010 [citado 14 Sep 2018];2010:153780. Disponible en: https://www.hindawi.com/journals/ijpedi/2010/153780/
30. Gladwell VF, Fletcher J, Patel N, Elvidge LJ, Lloyd D, Chowdhary S, *et al*. The influence of small fibre muscle mechanoreceptors on the cardiac vagus in humans. J Physiol. 2005;567(2):713-21.
31. Drew RC. Baroreflex and neurovascular responses to skeletal muscle mechanoreflex activation in humans: an exercise in integrative physiology. Am J Physiol Regul Integr Comp Physiol. 2017; 313(6):654-9.
32. Iellamo F, Pizzinelli P, Massaro M, Raimondi G, Peruzzi G, Legramante JM. Muscle metaboreflex contribution to sinus node regulation during static exercise: insights from spectral analysis of heart rate variability. Circulation. 1999;100(1):27-32.
33. Bunsawat K, Baynard T. Cardiac autonomic modulation and blood pressure responses to isometric handgrip and submaximal cycling exercise in individuals with down syndrome. Clin Auton Res. 2016;26(4):253-60.
34. Naranjo Orellana J, De La Cruz Torres B. La entropía y la irreversibilidad temporal multiescala en el análisis de sistemas complejos en fisiología humana. Rev Andal Med Deporte. 2010;3(1):29-32.
35. Costa M, Goldberger AL, Peng CK. Multiscale entropy analysis: a new measure of complexity loss in heart failure. J Electrocardiol. 2003;36(Supl 1):39-40.
36. Goldberger AL, Peng CK, Lipsitz LA. What is physiologic complexity and how does it change with aging and disease? Neurobiol Aging. 2002; 23(1):23-6.
37. Baumert M, Czippelova B, Ganesan A, Schmidt M, Zaunseder S, Javorka, M. Entropy analysis of RR and QT interval variability during orthostatic and mental stress in healthy subjects. Entropy. 2014; 16(12):6384-93.
38. Millar PJ, Levy AS, McGowan CL, McCartney N, MacDonald MJ. Isometric handgrip training lowers blood pressure and increases heart rate complexity in medicated hypertensive patients. Scand J Med Sci Sports. 2013;23(5):620-6.
39. de la Paz EM, Salvador E, Sanchez-Hechavarria ME, Cutiño I, Carrazana-Escalona R, de la Paz R. Activity of the autonomic nervous system cardi-

vascular in different states of hypnotic depth. Int J Psychophysiol 2016;108:170 [Resumen].

40. Kindelán-Cira EH, Syed E, Sánchez-Hechavarría ME, Hernández-Cáceres JL. El análisis de la variabilidad de frecuencia cardíaca como una herramienta para evaluar los efectos de la meditación chi sobre la regulación cardiovascular. Rev Cuba Inform Méd [Internet]. 2017 [citado 15 Sep 2018];9(1):30-43. Disponible en: http://www.revinformatica.sld.cu/index.php/rcim/article/view/214/pdf_58
41. Tiinanen S, Kiviniemi A, Tulppo M, Seppanen T. Time-frequency representation of cardiovascular signals during handgrip exercise. 2009 Annual International Conference of the IEEE Engineering in Medicine and Biology Society. Minneapolis (USA); 2009.