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Dynamics of cardiac autonomic regulation during isometric sustained weight test in hypertensive patients

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Authorship contribution

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2. Data curation: RCE, MTL, LOA

3. Formal analysis: RCE, GABM

4. Acquisition of funds: FAAT, ICC

5. Research: MTL, LOA

6. Methodology: RCE, GABM, FAAT

7. Project administration: ICC,

8. Resources: ICC, FAAT

9. Software: RCE

10. Supervision: ICC

11. Display: ELG, NASM

13. Drafting - original draft: NASM, ELG,

14. Drafting - revision and editing: MESH, MTL, LOA, RCE, ELG, FAAT, GABM, NASM, ICC

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Abstract:

Background: The Sustained Weight Test (SWT) is an isometric exercise test that has great practical value for carrying out massive studies on hypertension, however, is insufficient knowledge of the dynamics of cardiac autonomic regulation during this test. The aim of this study was to determine variations in the dynamics of cardiac autonomic regulation and in hemodynamic response during SWT in hypertensive subjects.

Methods: A quasi-experimental study was conducted on 15 hypertensive patients of both sexes, paired with 30 normotensive individuals, measuring arterial blood pressure, entropy sample and the Heart Rate Variability (HRV) in time-frequency with the Continuous Wavelet Transform Morlet-type (CWT morlet) through the electrocardiographic signal of the polygraph AD Instruments in the functional states of Rest and SWT.

Results: A significant increase in heart rate and blood pressure was found, as well as a decrease in sample entropy in the functional states of normotensive and hypertensive patients. In hypertensive patients, an early response pattern increased with multiple fluctuations during SWT in the time-frequency analysis of HRV with the CWT morlet.

Conclusions: SWT produces an increase in blood pressure, which is more frequent and evident in hypertensive subjects. Cardiac autonomic regulation during SWT increases the sympathetic and decreases the parasympathetic components, manifesting itself in hypertensive patients with a pattern of imbalance in the regulation of both sympathetic and parasympathetic response.

KEY WORDS: Hypertension; Sustained Weight Test; Heart Rate Variability, Continuous Wavelet Transform Morlet-type.

Abbreviation definition List

SWT: Sustained Weight Test

HRV: Heart Rate Variability

SampEn : Sample Entropy

CWT morlet: Morlet-type Wavelet Continuous Transform

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HF: high frequencies

LF: Low frequencies

HT: Hypertension

Introduction

Currently, most evidence supports the autonomic nervous system's (ANS) central role in the etiology of hypertension (HT), sympathetic hyperactivity together with parasympathetic hypoactivity. They are central factors not only in the genesis of HT, but also in the maintenance of it; there is data that associates the sympathetic nervous system's role in the regulation of cardiovascular homeostasis directly with promoting sympathetic hyperactivity, cardiac and vascular functional and structural alterations.[1, 2]

One of the tools that makes it possible to evaluate the autonomic changes associated with hypertension is the Heart Rate Variability (HRV), which is no more than the measurement of the variation of a normal cardiac cycle to the next normal heartbeat.[3] There are different methods to analyze HRV, which allow obtaining multiple and varied parameters. Currently, the most commonly used methods are those based on time domain, frequency domain, time-frequency methods and non-linear methods.[3-5] In general, the HRV indicators are correlated with physiological adaptations to changes in the internal and external environment, the presence of diseases, and in short-term registries express cardiac autonomic regulation.[5]

Cardiovascular and sympathetic hyperactivity clarifies part of the etiopathogenesis of arterial hypertension and other cardiovascular diseases.[2] Currently, it is well known that increased sympathetic tone may already be present in early stages of hypertension, and that these subjects have elevated coronary risk.[6] The Sustained Weight Test (SWT) is an isometric exercise test that has great practical value for carrying out massive studies on hypertension and, in addition, guarantees adequate sensitivity, specificity and feasibility for the diagnosis of this disease and cardiovascular hyperreactivity[7]. This test has been applied to evaluate physiological imbalances in obese adolescents with emotional eating[8] and autonomic dysfunction in diabetic patients[9]. At the primary level of health care, studies carried out with

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SWT are based on the hemodynamic response with Insufficient knowledge of the dynamics of cardiac autonomic regulation during this test in hypertensive patients.[8-13] Therefore, the objective of this study was to determine the variations in the dynamics of cardiac autonomic regulation in the hemodynamic response during SWT in hypertensive subjects.

Methods

A non-observational, quasi-experimental (crossover) study was conducted with 15 subjects (9 women) with hypertension and 30 healthy, normotensive subjects (16 women) who served as a control group. Subjects were evaluated for 5 minutes in the resting state and 5 minutes in the state of the Sustained Weight Test in the Laboratory of Basic Sciences of the University of Medical Sciences of Santiago de Cuba. This evaluation was approved by this center's ethics committee.

Exit criteria: Subjects with the following characteristic were excluded: generalized disorders of the nervous system (cerebrovascular accident, neuromuscular disorders); generalized skin conditions; implanted electronic devices (pacemakers or automatic defibrillators), amputated upper or lower limbs; pregnancy or with menstruation. In addition, those patients who presented some type of arrhythmia in the visual inspection of the electrocardiographic record in the period of 10 to 15 minutes of acclimatization to the premises, as well as the subjects who did not wish to be part of the investigation without giving their informed consent, were excluded.

Physiological Records: At the beginning of the electrocardiogram session in the morning (8: 30-12: 00 p.m.), the subjects were seated in a comfortable chair, located in a room with controlled temperature between 24 and 27 degrees Celsius and dim light. In these conditions, they were allowed to rest for 10 to 15 minutes until they achieved a better adaptation to the conditions of the premises. The surface electrodes of the electrocardiogram were placed after cleaning the skin with alcohol and were placed in the DII lead extended to limbs, and a recording was made for 5 minutes (Rest State), after which the blood pressure was taken with a certified Sphygmomanometer and stethoscope. The Sustained Weight Testing State of 5 minutes included 2 minutes holding a 500 gram weight and 3 minutes of recovery. The Powerlab ® electrocardiography signal with a bandpass filter (0.5-30 Hz) was digitized at a sampling

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rate of 1000 samples / second (1 kHz) in the 2012 LabChart ® software package; both were produced by the Australian AD Instruments company.

Processing of the electrocardiographic signal and discrimination of R waves and calculation of RR intervals: Further processing of the digitized records included their visual inspection, the discrimination of the R peaks from the digitized signal and the calculation of the RR intervals, and were performed using the Sabarimalai-Manikandan method.[14] The obtained set of RR intervals was stored and constitutes the series of data from which all the subsequent analysis of the HRV was carried out.

Pre-processing of RR intervals

The pre-processing of the RR interval series was carried out using the HRVAS program, (https://sourceforge.net/projects/hrvas) Copyright (C) 2015 by John T. Ramshur,[15] using a percentage filter with a value of 20% of the previous interval to detect ectopic beats. The replacement of the ectopic intervals was made from the cubic polytomic interpolation. Wavelet Packet Detrending was used to remove the tendency of very low frequencies on the baseline.

Analysis of Cardiac Frequency Variability

Sample Entropy (SampEn): The SampEn was introduced (Richmann and Moorman 2002) to correct certain errors that were produced in the previous methods.[16] The SampEn is the negative of the natural logarithm of the conditional probability that two similar patterns of m points remain similar if we increase the number of points to m + 1. SampEn measures the degree of regularity of a time series, hence a regular value corresponds to a small value of SampEn and a complex series corresponds to a higher value.[17]

Calculation of HRV indicators in time-frequency

The RR intervals were re-sampled with a 2 Hz interpolation (0.5 seconds) for the time-frequency analysis. The Continuous Wavelet Transform Morlet-type (CWT morlet) was used for the time-frequency analysis of the HRV. CWT Morlet uses short windows at high frequencies and long windows for low frequencies, and can be applied satisfactorily to the processing of non-stationary signals, indicating which frequencies are present in a moment of time, showing good temporal resolution at high frequencies and good spectral resolution at low frequencies. Theoretically, CWT-morlet is calculated for infinitesimally small translations and for scale factors. For a signal x (t) and the wavelet function Ψ_{ab} (t), the Wavelet's Continuous 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 Ψ * (t) is the complex conjugate of the mother wavelet, α is the parameter of dilation and τ is the location parameter. Morlet type wavelet function was used as a Gaussian, which is balanced in time and frequency defined as:

$$\Psi_0(t)=\pi^{\frac{-1}{4}}e^{i\omega_0 t}e^{\frac{-1}{2}t^2}$$

Where ω is a dimensionless frequency that defines the number of cycles of the Morlet type wavelet function, with ω = 6 indicating a good quality in the temporal and frequency resolution was provided. The bivariate function W (τ, α) shows the similarity of x (t) to a wavelet 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 throughout the analyzed frequency band [f1 f2]. The instantaneous power of a frequency band [f1 f2] is given by:

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

The traditional frequency bands of HRV were used as recommended by the International Expert Consensus on Heart Rate Variability of 1996, which were for the low frequencies of [LF: 0.04-0.15 Hz] ; high frequencies of [HF: 0.15-0.4 Hz].[5] The CWT-morlet was exported in a "file.txt", a matrix of results was given for each subject for records of 5 minutes (300 s), from the interpolation of 2 Hz (0.5 seconds); leaving 600 values in the frequency bands of the HRV (LF, HF). For better statistical management, the frequency bands were normalized (nu) as recommended.[5]

Statistical processing of data

With the use of the SPSS 22.0 System, the mean values (X) and the standard deviation (SD) of the variables were exposed to which a non-parametric statistical analysis was performed with the Wilcoxon signed-rank test for the samples related to a level of significance of P <0.05. the Octave software 2019 version 5.1.0 (https://www.gnu.org/software/octave/download.html) was used for the elaboration of the dynamic graphs in time (Figure 2, 4 and 5), calculated from the average of the matrices of the normalized

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values of the frequency bands of the HRV calculated from the CWTmorlet during the Sustained weight test (300 s) and interpolated at 2 Hz (0.5 s).

Results

Table 1. Distribution of the subjects studied according to age and anthropometric variables.

Variables	Normotensive		Hypertensive		p
	X	**SD**	**X**	**SD**	
Age	39,06	10,75	40,66	8,59	0,894
Weight	70,47	14,14	73,40	15,70	0,265
Size	1,66	0,10	1,65	0,13	0,456
Body Mass Index	25,26	4,10	25,84	4,87	0,503

Level of significance $p < 0.05$; X: mean; SD: standard deviation

Table 1 shows the paired distribution of normotensive and hypertensive subjects according to age and anthropometric variables, without significant differences between them.

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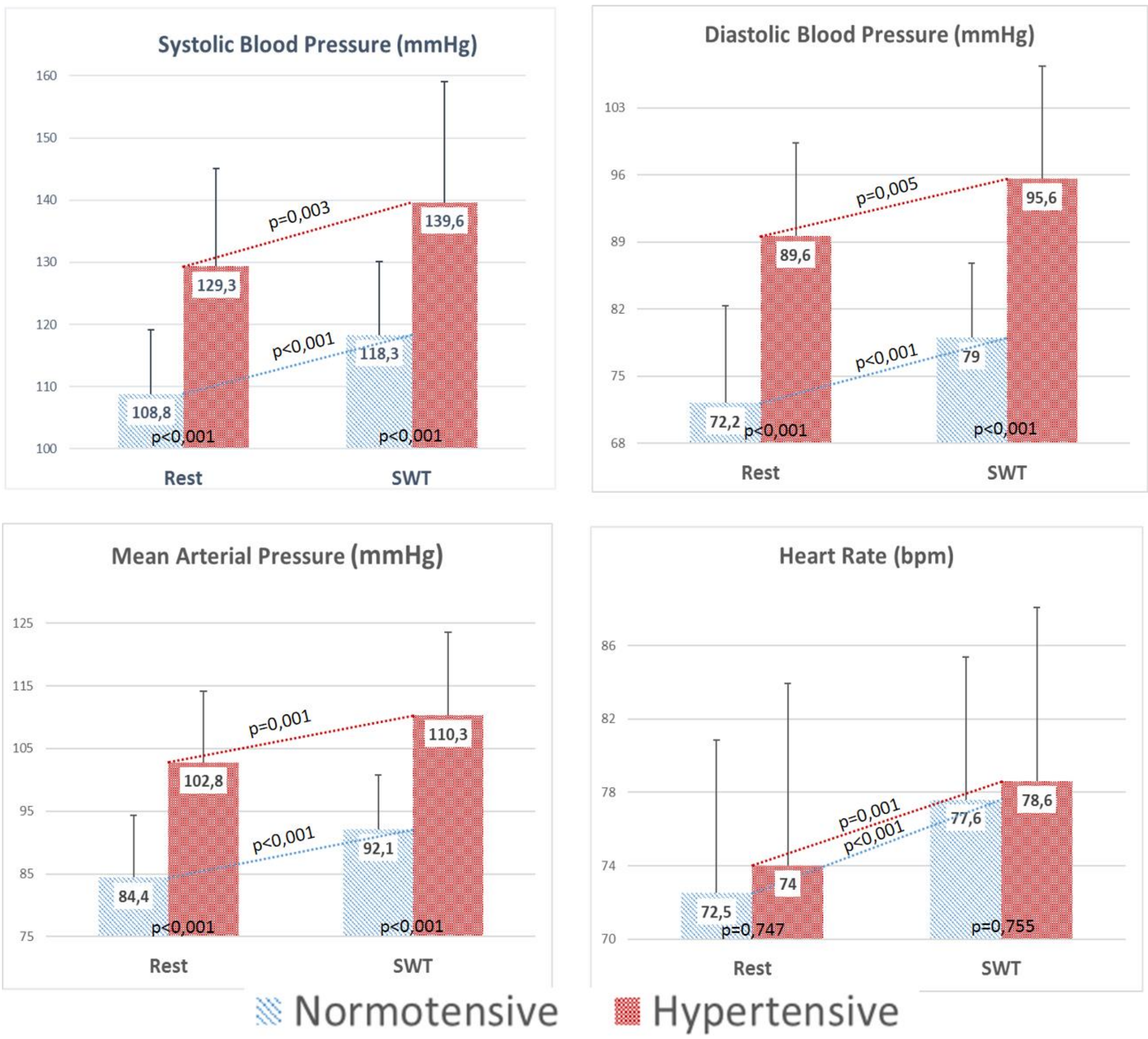

Figure 1: Effects of the Sustained Weight Test on the hemodynamic parameters in normotensive and hypertensive subjects

Figure 1 illustrates the significant differences in systolic, diastolic and mean arterial pressures between normotensive and hypertensive subjects during rest ($p < 0.05$) and during the SWT ($p < 0.05$). When analyzing the differences in heart rate between the study groups, higher but not significant values were observed in the hypertensive patients at rest ($p = 0.747$) or during the SWT ($p = 0.755$). We found a significant increase ($p < 0.05$) in the values of arterial pressures and heart rate when comparing Cuban isometric exercise with rest in both normotensive and hypertensive patients.

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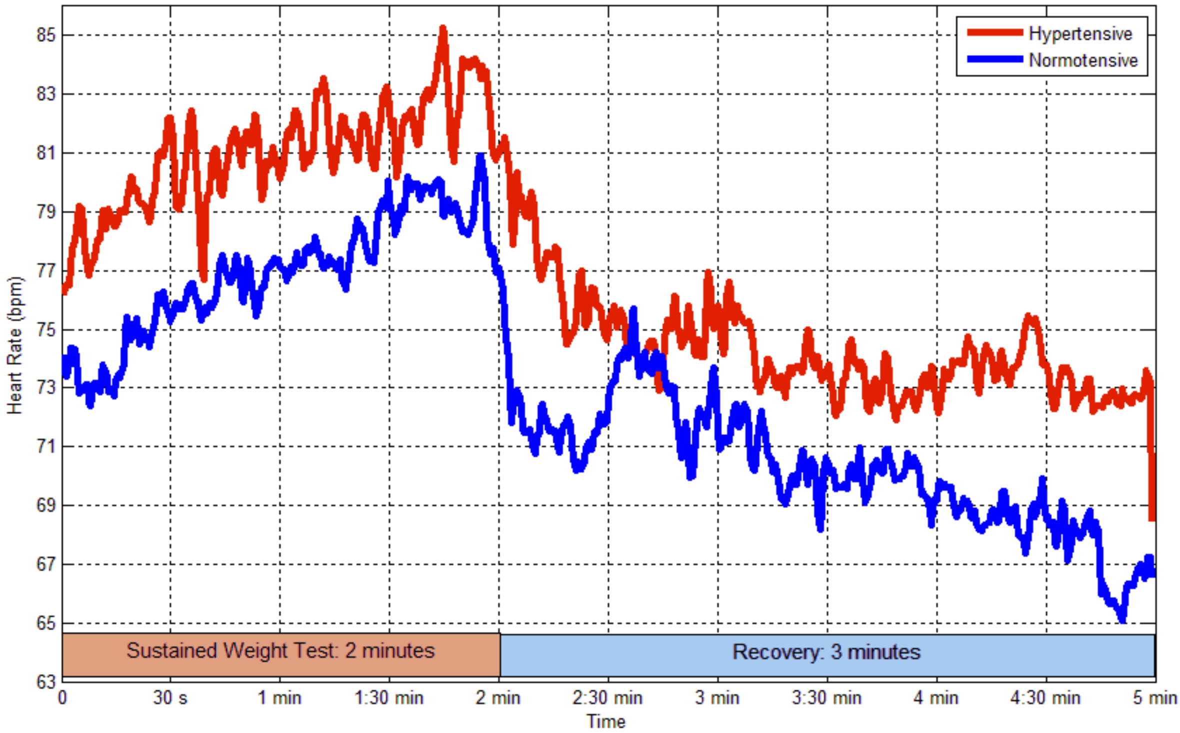

Figure 2: Dynamic changes in heart rate time during the sustained weight test in normotensive and hypertensive subjects

When the dynamic changes are analyzed over time (Figure 2), sustained weight test, as it can be observed that hypertensive subjects present maintained in heart rate increase throughout the SWT and during recovery from normotensives.

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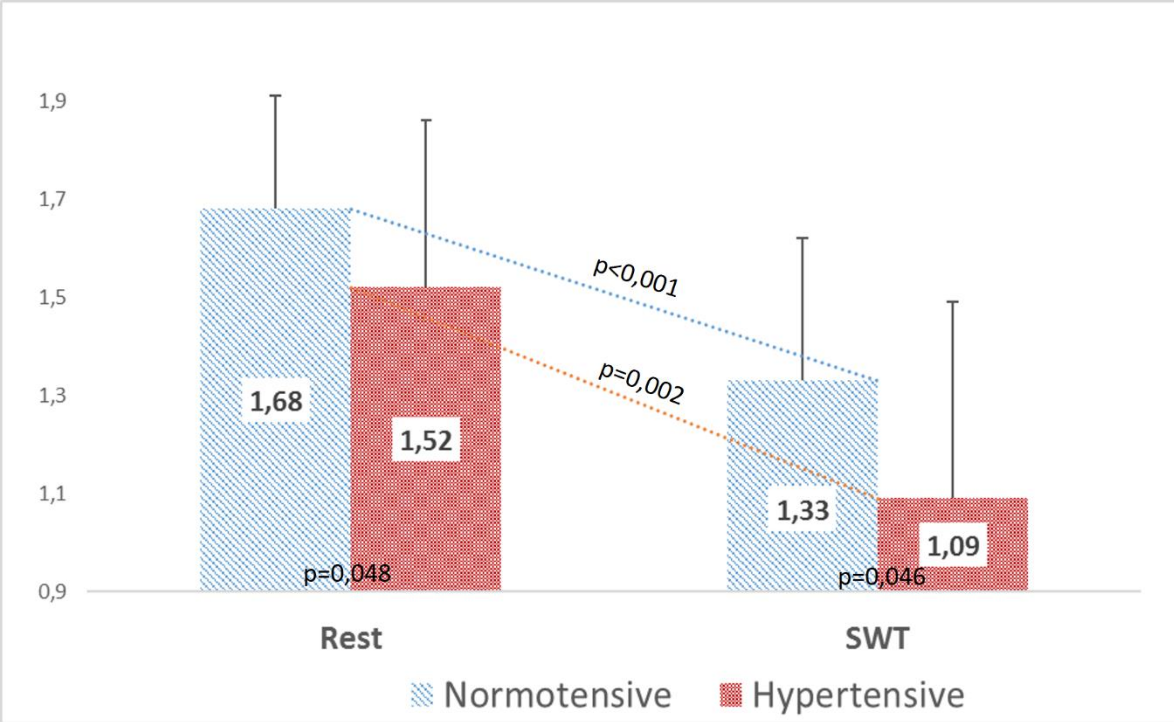

Figure 3: Effect of the Sustained Weight Test (SWT) on the Sample Entropy of the non-linear variability of the heart rate in normotensive and hypertensive patients.

Figure 3 shows a significant decrease in sample entropy in hypertensive subjects compared to normotensive subjects during rest (p = 0.048) and during SWT (p = 0.046), as well as a significant decrease in the values of sample entropy when comparing the Cuban isometric exercise with rest other tests in both the normotensive (p <0.001) and hypertensive (p = 0.002) subjects.

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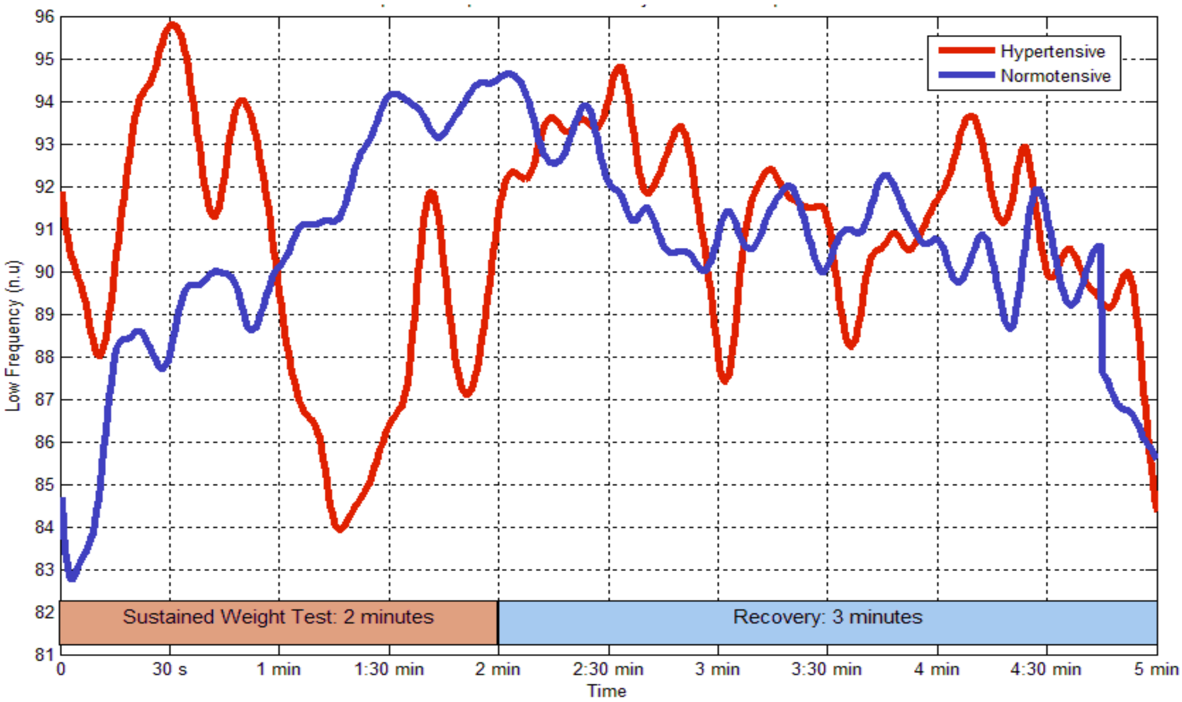

Figure 4: Dynamics over time of the sympathetic component of cardiac autonomic regulation during the Sustained Weight Test in normotensive and hypertensive subjects

Figure 4 shows an increase in time of the sympathetic component of cardiac autonomic regulation during SWT in normotensive subjects, reaching its highest values around 2 minutes of the test, and then falling in recovery. It can be observed that hypertensive subjects present an initial increased response that reaches its maximum at 30 seconds, as well as multiple fluctuations making it possible to characterize the response pattern of early sympathetic hyperreactivity.

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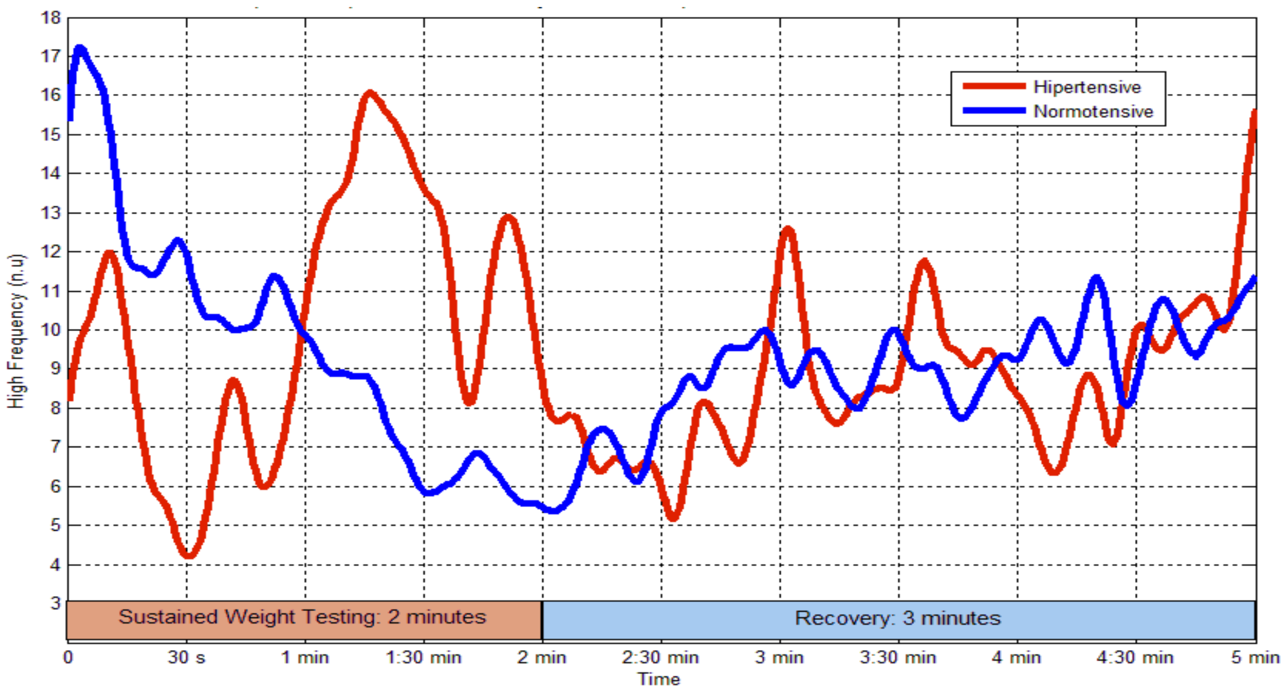

Figure 5. Dynamics over time of the parasympathetic component of cardiac autonomic regulation during the sustained weight test in normotensive and hypertensive subjects.

Figure 5 shows a decrease in time of the parasympathetic component of cardiac autonomic regulation during the test of sustained weight in normotensive subjects, reaching its lowest values around 2 minutes of the test and then slowly increasing during recovery. It ca be seen that in hypertensive subjects there is a minimum response that is reached at 30 seconds, there is an increased response that is reached maximum at 1:15 seconds as well as multiple fluctuations that make it possible to characterize the response pattern as inconstant and atypical.

Discussion

The SWT commenced in the late 1980's in the Cuban province of Villa Clara, and was initiated by Dr. Hiram Paz-Basanta and collaborators.[7] Comparative tests were conducted between the HandGrip and the SWT, obtaining more favorable results with the SWT.[7] By applying the sustained weight test, it has been demonstrated that cardiovascular hyperreactive individuals have a higher risk of hypertension than

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cardiovascular normorreactive individuals, with cardiovascular hyperreactivity constituting a very important predictor of hypertension.[18]

Blood pressure

The hyperreactive response to the Sustained Weight Test is a predictor of early stage hypertension in at risk populations,[10, 11, 12, 18] which strengthens and reaffirms the findings found in this study. These results are consistent with several authors who report that the Sustained Weight Test[10,11,12,13,18,19] and the Handgrip test[20, 21] produce an increase in blood pressure. Both the Handgrip test and the Sustained Weight Test are static isometric exercises, where their responses are mediated by type III and type IV afferent fibers, activated by products of anaerobic metabolism and by activation of central mechanisms that constitute the so-called pressure reflex of exercise.[22] The pressor response to exercise produces an increase in mean arterial pressure, heart rate, cardiac output and an increase in peripheral vascular resistance.[23] These changes are characteristic of the mecanoreflex response to isometric physical exercise that produces activation of type III afferent fibers found inside the muscle, which is integrated with the response of the cerebral cortex to exercise in the subcortical structures of the motor vessel center, producing an increase in HR and BP.[22,23,24] In addition to this, it is important to note that Drew (2017)[24] reports that vasoconstriction of the renal afferent arteriole occurs as part of the pressor response to isometric physical exercise, which in turn produces an activation of the renin-angiotensin-aldosterone mechanism that entails to hydrosaline retention, an increase in vasoconstriction due to the action of angiotensin II, to greater peripheral vascular resistance, to an increase in afterload and to an increase in blood pressure. The exaggerated changes in blood pressure in hypertensive patients compared to normotensive patients during this test are the result of sympathetic over activation in relation to endothelial dysfunction, changes in vascular remodeling with increased vascular resistance as well as afterload and decrease in renal flow due to the vasoconstriction of the afferent arteriole with the release and / or stimulation of pressor substances.[25] In turn, these changes in the flow of the afferent arteriole cause a decrease in renal filtration, which in the long term produces a decrease in the fluid-renal volume, which constitutes the most potent mechanism of blood pressure regulation.[24, 25] Multiple systemic alterations that condition inadequate adaptive responses are found in hypertensive patients,

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and are more evident with the application of isometric type tests such as the Sustained Weight Test. The significant effects of the Sustained Weight Test in normotensive and hypertensive patients, as well as the intergroup differences in each of the physiological states to be evaluated, is consistent with the mecanoreflex cardiovascular response, which is reported in several studies by Cuban authors in the prediction of arterial hypertension.[9,10,11,12,13,18,19,]

Heart Rate

When analyzing the differences between the study groups, the resting heart rate shows higher but not significant values in the hypertensive patients. These results coincide with several studies [10,13 25, 26] performed in hypertensive patients and in pre-hypertensive patients that also report no significant changes in resting heart rate; although the values of heart rate are higher in early stages of this disease (pre-hypertension),[27] other population studies reaffirm the fact that HR increases when hypertensive patients are not treated.[28] In this study, all patients were under a medical treatment regimen, which agrees with these studies. In spite of the above, when analyzing the dynamic changes in time during the Sustained Weight Test, it stands out as in the hypertensive there is a sustained increase in the heart rate throughout the SWT and during the recovery with respect to the normotensive subjects. Studies in healthy humans report how the early mecanoreflex muscle response to isometric exercise, which stimulates type III fibers, constitutes an inhibitory stimulus at the level of the solitary tract nucleus that produces a decrease in vagal influx and an increase in heart rate.[25, 29]All this explains the findings found because the decrease in vagal influx because of the mecanoreflex response to isometric exercise in relation to the increase in blood catecholamines present in hypertension leads to an increase in the chronotropic response of the heart with an increase in heart rate.

Entropy

Chaos intrinsically takes advantage of the wealth related to its structure, which is why there are benefits to these systems from the adoption of chaotic regimes with a wide range of possible behaviors.[17] The concept of entropy is used to quantify the regularity of a time series, so that the more regular a series is, the more predictable and less complex it will be, which corresponds to a less adaptive system.[30, 31] Therefore, in any temporal series that represents an output variable of the system, entropy is a measure

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of its uncertainty,[31] Thus, there are studies that show that entropy is reduced with aging, just as pathological systems show lower entropies than healthy systems,[32, 33] In this study, we find that in hypertensive patients there is a decrease in entropy, which from the perspective of the theory of complexity can be interpreted as a loss of the heart rate's adaptability in regulating systems. Furthermore, this is even more evident when SWT was applied as a stressor: entropy is lower in hypertensive subjects than in normotensive subjects. These results coincide with the efficacy found by Poddar (2014),[34] whose diagnostic model of arterial hypertension uses sample entropy, which is based on the reduction of this parameter present in hypertensive patients during rest. This is because the sample entropy constitutes a non-linear indicator of the sympathetic-vagal balance in the autonomic regulation of the heart,[35] decreasing in diseases where there is an increased sympathetic tone (sal-sensitivity),[36] metabolic syndrome,[37] heart failure[32] and increasing in salutogenic and resting conditions where the parasympathetic predominates.[38, 39] The decrease in entropy found in this study reflects a loss of complexity and an increase in the sympathetic component during the test. This is also consistent with the study carried out by Porta (2007),[35] who used a tilting table with different degrees of inclination, and therefore of sympathetic baroreflex activation, which found that as the sympathetic baroreflex response increases, the sample entropy decreases. However, it seems that the changes in the complex behavior of the regulation depend on the type of exercise. Weippert (2015)[40] reported that dynamic exercise produces an increase in entropy, while static produces a decrease in comparison to rest; also finding higher arterial pressures, peripheral vascular resistance and myocardial oxygen consumption during the static isometric exercise with respect to the isotonic dynamic. All of this is consistent with what has been found in hypertensive patients with cardiovascular hyperreactivity, an increase in sympathetic tone and pressor substances, leading to a decrease in entropy with compared to normotensive subjects, both at rest and during the Sustained Weight Test.

Cardiac autonomic modulation

The contribution of the muscle metabolic reflex to the regulation of the sinus node during static exercise it has been explored by Lellamo (1999)[41] since the end of the 1990s. When seen from the spectral analysis of the heart rate variability, it shows how the low frequency band usually increases;

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meanwhile the dynamic changes in time that occur are evident only with the time-frequency methods of the HRV.[19, 42] This reaffirms the findings in normotensives, and the low frequency band is the result of the mainly sympathetic influence of the regulatory centers on the heart. On the other hand, the results found in hypertensive patients are congruent to those found by Delaney (2010)[43] in his study on hypertensive subjects, where he showed that subjects who were administered the Handgrip test presented an increased response of the sympathetic vascular eference evaluated with microneurography and in the heart rate compared with normotensive subjects. In their studies with animal models of renovascular hypertension, Spranger (2015) [26], Sala-Mercado(2013)[44] and Delaney (2010) [43] found that sympathetic cardiovascular discharges were increased during the mecanoreflex response to isometric exercise. Even in another study where the pressor response in time to physical exercise was evaluated in young people with a family history of hypertension, an early increase in it was found.[45] Thus, the pattern of early and exaggerated response in hypertensive patients in the sympathetic component of cardiac rhythm regulation may be caused by the fact that the stimulation produced in isometric exercise produces an increased adrenal and sympathetic response in hypertension. The diminishing response of the parasympathetic regulation of the heart during the mecanoreflex that is produced by the isometric tests type Handgrip and SWT is a characteristic normal pattern found by multiple authors;[26, 43] which is congruent with the dynamic change in time found in this present study. By characterizing this dynamic response over time in hypertensive subjects who have an exaggerated and early sympathetic response, we see how this produces a compensatory parasympathetic feedback response from the heart rate regulating systems evaluated with time-frequency methods. Although we do not find anything in the literature regarding this dynamic response over time, Makino (1999)[46] reports that in hypertensive patients, the involvement of the ventrolateral portion of the medulla oblongata where some of the regulatory centers are located leads to exaggerated sympathetic responses with an imbalance of the autonomic nervous system. Our findings suggest that there is a decrease in adaptability in hypertensive patients with an imbalance in the heart rate regulating response during SWT.

Conclusions:

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The sustained weight test produces increases in blood pressure and frequency that are more evident in hypertensive subjects. Cardiac autonomic regulation during the sustained weight test produces increases of the sympathetic component and decrease of the parasympathetic, showing a loss of adaptability with a pattern of imbalance in the regulation of both sympathetic and parasympathetic response in hypertensive patients.

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