
Autonomic Modulation of the Heart in Systemic Arterial Hypertension

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Objective – To analyze the heart rate variability in patients with mild to moderate systemic arterial hypertension.

Methods - Thirty-two healthy (group I) and 70 systemic arterial hypertensive (group II) individuals, divided according to age (40 to 59 and 60 to 80 years old, respectively) and with a similar distribution by sex were studied. Thirty-one had left ventricular hypertrophy (LVH), 22 were overweight, and 16 had Type II diabetes mellitus. Smoking, alcohol ingestion, and sedentary habits were the same between groups. Variability in heart rate was analyzed in the time domain, using standard deviations of normal RR intervals (SDNN) and the differences between maximal brady- and tachycardia ($D-BT_{max}$) during sustained inspiration. Analysis of the frequency band of the power spectrum between 0.05 and 0.40 Hz at rest and during controlled respiration was chosen for analysis of the frequency domain.

Results - In both time and frequency domains, variables were lower in group II than in group I. Within groups, statistically significant variables were only found for individuals in the 40 to 59 year old group. The presence of LVH, overweight, or diabetes mellitus did not influence the variability in heart rate to a significant extent.

Conclusion - Variability in heart rate was a valuable instrument for analyzing autonomic modulation of the heart in arterial hypertension. The autonomic system undergoes significant losses in cardio-modulatory capacity, more evident in subjects between 40 and 59 years old. In those over 60 years old, reduced variability in heart rate imposed by aging was not significantly influenced by the presence of systemic arterial hypertension.

Key words: autonomic cardiac modulation, systemic arterial hypertension, heart rate variability

Clinical and experimental studies have demonstrated that the autonomic modulator capacity of the cardiovascular apparatus is altered in diseases directly or indirectly affecting the heart¹⁻⁹. In diseases accompanied by alterations in the vagosympathetic system leading to the development of potentially fatal arrhythmia, both morbidity and mortality are significantly influenced by such functional alterations¹⁰⁻¹⁸.

Interest in the evaluation of autonomic modulation of the heart by analysis of beat-for-beat variability in heart rate in systemic arterial hypertension (SAH) has been variously demonstrated. Results have proven that this variability can identify alterations in the mechanism of autonomic control of SAH, also aiding in the evaluation of the action of drugs that interfere with the regulation of cardiovascular function^{9,19-27}.

The present work represents a study of the autonomic modulation of the heart, using the analysis of the variability in heart rate of selected groups of healthy and primary arterial hypertensive subjects.

Methods

The study protocol was set up in accordance with the principles of the Helsinki Declaration and authorized by the Ethics Commission of the National Institute of Cardiology of Laranjeiras (INCL).

The study was transversally performed in 102 subjects admitted for initial evaluation at the outpatient clinic of the Division of Arterial Hypertension of the Institute-between January 1998 and July 2000. Subjects were between 40 and 80 years old and were divided in two groups paired by age and sex. Group I was composed of 32 healthy individuals; group II was composed of 70 subjects having mild to moderate hypertension defined by a systolic arterial pressure of ≥ 140 mmHg and ≤ 180 mmHg, and a diastolic arterial pressure of ≥ 90 mmHg and ≤ 110 mmHg. Of group II, 72% of the subjects were under no treatment, and 28% made irregular use of thiazide drugs, dihydropyridine calcium channel antagonists, and angiotensin-converting enzyme inhibitors. All were in sinus rhythm (Table I).

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Table I – Demographic values and parameters evaluated

	Group Ia	Group IIa	p*	Group Ib	Group IIb	+
N	20	40	-	12	30	-
Age (years)**	48.7±5.2 [48.0]	48.7±6.2 [48.0]	NS	71.3±5.9 [71.0]	69.3±5.7 [69.0]	NS
Sex (F/M)	6/14	14/26	NS	8/4	20/10	NS
SAP (mmHg)	125.1±10.0	170.2±14.4	<0,05	138.1±10.6	180.2±12.2	<0.05
DAP (mmHg)	83.2±5.1	98.4±10.2	<0,05	80.5±5.4	90.8±9.1	<0.05
LVH (septum and PP>1.1cm)	-	22	-	-	9	-
Glycemia>120 mg/dL	0	7	-	0	9	-
BMI>25kg×m ⁻²	0	18	-	0	4	-
MCF (bpm)	69.2±8.6	72.4±13.5	NS	71.0±11.4	73.0±10.3	NS
DPNN (ms)	39.4±14.4	27.0±12.0	<0,001	24.5±8.0	20.6±5.5	NS
HFLnT (Ln ms ²)	5.2±0.9	3.9±1.3	<0,001	4.1±0.9	3.6±1.1	NS
HF RC LnT (Ln ms ²)	7.3±0.7	5.6±1.3	0,02	5.2±0.4	4.9±0.4	NS
TME LnT (Ln ms ²)	6.4±0.7	5.1±1.0	<0,001	4.8±0.8	4.5±0.9	NS
D-BT _{max} (bpm)	21.6±4.1	16.2±7.6	0,03	15.4±4.3	16.7±6.1	NS

*level of statistical significance; ** age expressed as mean±SD (median); other values expressed as mean±SD; HF- high frequency; TME - total modulatory energy; CR- controlled respiration; D-BT_{max} - difference between maximal brady – and tachycardia during and following sustained inspiration; LnT- logarithmic transformation (refer to text for details); BMI - body mass index.

Twenty group I individuals were between 40 and 59 years old (mean ±SD, 48.7±5.2; median 48 years) (group Ia, 14 males), and 12 were between 60 and 80 years old (71.3±5.9, median 71 years) (group Ib, 8 males). Their clinical histories, results of the physical examination, laboratory and radiological examinations, and electrocardiograms (ECG) at rest were within normal limits.

In group II, 40 subjects were between 40 and 60 years old (48.7±6.2, median 48 years) (group IIa, 26 males), and 30 were between 60 and 80 years old (69.3±5.7, median 69 years) (group IIb, 10 males) (Table I). Thirty-one had left ventricular hypertrophy (LVH) on the echocardiogram at rest, defined by septal and left ventricle posterior wall thickness >1.1 cm according to the routine protocol of analysis of the echocardiography sector of the INCL. Twenty-two were overweight defined by a body mass index ≥25kg/m². Sixteen had noninsulin dependent diabetes mellitus of Type II and maintained glycemic control with diet or oral hypoglycemic therapy or both. Smoking habits, alcohol ingestion, and sedentary lifestyle were not different among the groups.

Criteria for inclusion in the study are presented in Table II.

Clinical evaluation included measurements of heart rate, arterial pressure on both arms, antero-posterior thoracic diameter, body weight and height, and body mass index. Anamnesis was directed at the investigation of clinical complaints and physical examination, and complementary examinations including glycemia, cholesterolemia, assessment of renal and liver function, ECG at rest, and thoracic roentgenogram were within normal limits. The Romhilt-Estes index was used for the electrocardiographic diagnosis of LVH. Electrocardiographic signals were used for the analysis of the variability of heart rate as described below. Medical attention and examinations were performed between 8 AM and 6 PM.

Following a 5 to 10 minutes rest period in the dorsal decubitus position, arterial pressure was measured on both arms of subjects seated in a quiet room at 25^o C. Arterial pressure was measured after 1, 3, and 5 minutes, and averages of the last 2 measurements were recorded. The arm showing the highest arterial pressure values was taken as standard. Mercury column sphygmomanometers calibrated by INMETRO (National Institute of Metrology) were used.

Electrocardiographic signals on an AECG03, (Lynx Technology, São Paulo, Brazil) were recorded for 300 seconds

Table II – Criteria for inclusion and exclusion in study groups

Group I		Group II	
Criteria for inclusion	Criteria for exclusion	Criteria for inclusion	Criteria for exclusion
Age ≥40 and ≤80 years	Non-sinus rhythm	Age ≥40 and ≤80 years	Non-sinus rhythm
DAP<90mmHg	Psychiatric or neurologic disease	90≤DAP≤110mmHg	Psychiatric or neurologic disease
SAP<140mmHg	AMI or ACD***	140≤SAP≤180mmHg	AMI or ACD
	Pregnancy		CTI ≥50% or EF <45%
	Thyroid, renal or hepatic dysfunction		Thyroid, renal or hepatic dysfunction
	CTI ≥50%		Use of b-blocker
	Diabetes mellitus		COPD
			Secondary HAS

*DAP- diastolic arterial pressure; **SAP- systolic arterial pressure; ***ACD- previous arterial coronary disease; AMI- previous acute myocardial infarct; CTI- cardio-thoracic index; EF- left ventricular ejection fraction on echocardiogram at rest; COPD- chronic obstructive pulmonary disease.

and analyzed by the SAECG system as already described^{6,7,28}. Signals were taken between 10 AM and 6 PM from subjects kept in the dorsal decubitus position, breathing with their natural frequency in an isolated room at 25°C at least 2 hours following their meals. In smokers, measurements were taken at least 30 minutes after ending tobacco intake.

Additional ECGs of 60 seconds duration each were recorded from subjects randomly selected from each experimental group, (6 from groups Ia and IIa, 4 from groups IIa and IIb) who kept under respiratory control at a respiratory frequency of 12 incursions/min 0.20 Hz, monitored by the examiner with timing equipment. For a second record, 20 individuals from group I (12 from group Ia and 8 from group Ib) and 35 from group II (15 from group IIa, 20 from group IIb) had their ECGs taken during a sustained inspiration maneuver⁷, composed of 3 phases of respectively, 15, 15, and 30 seconds duration. During the first phase, subjects were instructed to breathe spontaneously; during the second phase, of sustentation, they were required to exert apnea following maximal inspiration without expiratory effort, a procedure differing therefore from the Valsalva maneuver. During this phase, an initial rise of 2 to 3 seconds in average values of heart rate was observed was followed by 8 to 10 seconds of intense bradycardia followed in turn by a progressive increase in heart rate. After a 15-second interval, the subjects were instructed to release their inspired air and to return to spontaneous respiration. At this point (3rd phase), heart rate increased to values above averages observed during the first phase and gradually returned to base levels, a typical response of 5 to 10 seconds duration (Figure 1). Records were taken sequentially from subjects remaining in the dorsal decubitus position between readings.

Two domains were analyzed: in the frequency domain, a series of normal consecutive RR intervals was interpolated and the power spectrum calculated using a previously described technique²⁸. The area under the spectrum in the region between 0.05 Hz and 0.40 Hz corresponding to sympathetic and parasympathetic energy modulation was calculated. The region analyzed is classically decomposed into two frequency bands: one, of low frequency between 0.05 and 0.15 Hz, corresponds to predominantly symphatic

tic influences; the other, of high frequency between 0.15 and 0.40 Hz, corresponds to parasympathetic influences on the variability of heart rate. Due to the marked superpositioning of sympathovagal influences at the frontier region of 0.15 Hz, the entire total energy modulation region was chosen for analysis. During the controlled respiration maneuver, practically all the energy of the spectrum was concentrated in the high frequency region, indicating a predominance of vagal activity. The difference between this energy and that obtained during rest periods was considered to represent the autonomic reserve of modulation of the variability of heart rate (Figure 2).

To analyze the time domain, averaged heart rate or means of the 60/RR (RR=RR interval in seconds) relationships and the standard deviations (SDNN) of all normal consecutive intervals were considered. The differences between values of maximal bradycardia during and of maximal tachycardia immediately following the phase of sustained inspiration were taken as indexes of autonomic activity ($D-BT_{max}$) corresponding to the modulator potential of the autonomic nervous system.

Body mass index was calculated with the formula $BMI = \text{weight (kg)} \times \text{height}^2 \text{ (m}^2\text{)}$.

Continuous variables were represented in terms of averages \pm standard deviation. Due to the strong asymmetry of its probability distribution function, for normalization prior to analysis, the variables of total energy modulation were transformed into natural logarithms (LnT).

A comparison between the variations in groups I and II in the frequency and time domains were made using Student's two-tailed *t* test. Discrete variables were analyzed by the chi-square test using Yates correction or Fisher's exact test, for small samples.

The influence of controlled respiration on the high frequency region of the power spectrum was compared with that of the rest period for each group, using Student's two-tailed paired *t* test. Differences between high frequency LnT values at controlled respiration and at rest were compared with this test using unpaired approach.

Individuals in each age of group II were stratified regarding the presence of LVH, overweight, and diabetes and analyzed; a two-tailed Student's *t* test was used to compare their variables in the frequency and time domains.

For analysis of their diagnostic values, variables in the frequency and time domains, were dichotomized as belonging to groups of subjects aged between 40 and 59 years and above 60 years old, respectively. This was achieved by analyzing the function defined by the products of the distributions of the probability functions of each group (see Appendix). Specificity and sensitivity values were identified at points maximizing this function; their statistical significance was evaluated by the application of the chi-square test to the comparisons of proportions. Data were analyzed using the statistical modulus Stratographics (Statistical Graphics Corporation, USA). Global significance levels were set at 0.05 for all tests.

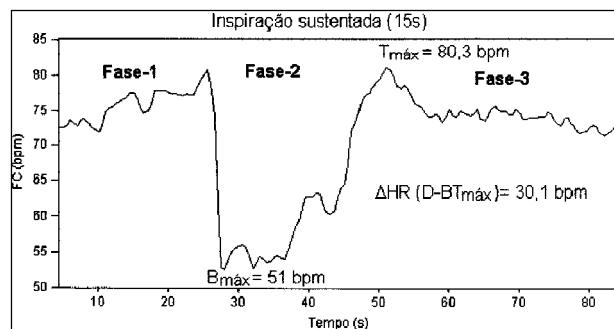


Fig. 1 - Effects of sustained inspiration (SI) on a series of RR intervals in an individual in group I. Note the different phases of the maneuver and the characteristics of Phase 2 that portray the oscillation consequent to sustained inspiration, and the points of analysis and of maximal bradycardia (B_{max}) and tachycardia (T_{max}). Phase 1, pre-SI; phase 2, SI; phase 3, post-SI.

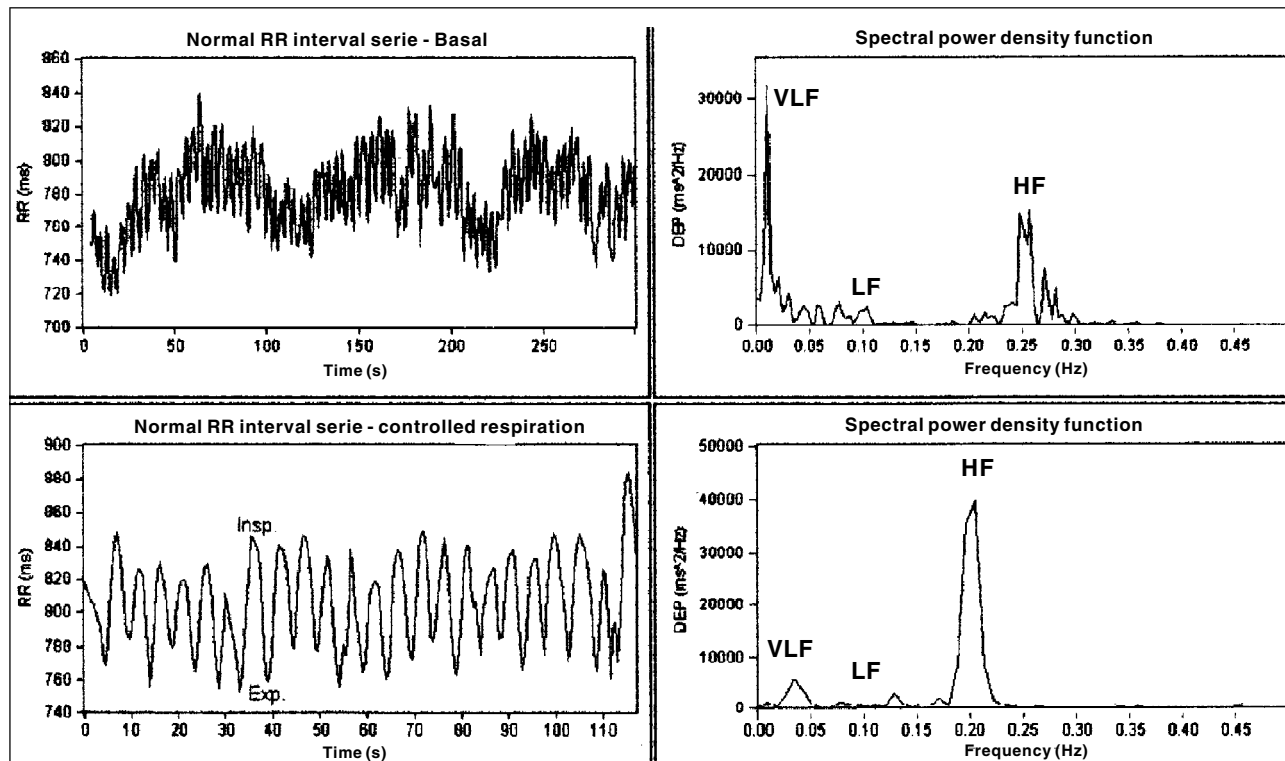


Fig. 2 - Effect of controlled respiration (CR) on the power spectrum of subjects in group I. To the left, a series of normal RR intervals; to the right, the respective power spectrum in a basal record (above) and during the CR maneuver (below). Note that during CR, the energy of the spectrum is concentrated in the high frequency band and its value is significantly increased. VLF, very low frequency (0.01-0.05 Hz); LF, low frequency (0.05-0.15 Hz); HF, high frequency (0.15-0.40 Hz); insp - inspiration; exp - expiration.

Results

Table I presents modulation energy values logarithmically transformed of groups studied in the frequency domain. Values for group IIa were significantly ($p < 0.001$) lower than those for group Ia. Differences between values for groups IIb and group Ib were not significant. LnT rises at high frequency (HF) during controlled respiration (CR) in group IIa were lower than those in group Ia ($p = 0.02$). LnTs in group IIb were not different from those in group Ib ($p > 0.05$).

Values of SDNN and of $D-BT_{max}$ in the time domain of

group IIa were smaller than those in group Ia ($p < 0.001$, and $p = 0.03$, respectively). Records for group IIb were not different from those for group Ib (Table I).

The presence of LVH, overweight, or diabetes did not significantly influence the variability in heart rate in groups IIa and IIb (Tables III and IV). Differences were recorded for HF CR and left ventricular hypertrophy for group IIa.

Table V shows frequency and time domains variables sectioned according to age (for groups I and II). Between 40 and 59 years old, values after sectioning equal 74.1% specificity at high frequency ($p < 0.001$) and 100% specificity at high frequency during controlled

Table III - Comparison between VRR parameters of group IIa patients with and without left ventricle hypertrophy (LVH), type II diabetes mellitus (DM), and overweight (OW)

	LVH	No-LVH	p*	DM	No-DM	p*	OW	No-OW	p*
N	22	18	-	7	33	-	18	22	-
Age (years)	47.8±5.5	49.8±6.7	NS	54.9±5.7	47.4±4.4	0.003	48.2±5.5	48.9±7.2	NS
Sex (F/M)	9/13	5/13	NS	2/5	12/21	NS	7/11	7/15	NS
MCF (bpm)	72.7±14.0	72.1±13.2	NS	73.0±8.0	72.3±14.5	NS	73.1±12.3	71.2±12.1	NS
DPNN (ms)	27.4±11.2	26.5±13.3	NS	26.1±5.8	27.2±13.0	NS	28.1±13.4	27.3±10.6	NS
TME LnT (Ln ms ²)	5.2±1.0	5.0±1.0	NS	5.0±0.4	5.1±1.1	NS	5.2±0.9	5.1±0.9	NS
HF LnT (Ln ms ²)	4.0±1.4	3.9±1.3	NS	3.7±0.8	4.0±1.4	NS	4.1±1.2	3.9±1.2	NS
HF CR LnT (Ln ms ²)	4.1±0.7	6.3±0.7	0.01	5.1±1.3	6.5±0.7	NS	6.0±1.1	4.9±1.8	NS
D-BT _{max} (bpm)	14.9±3.8	17.0±9.5	NS	16.4±8.7	16.0±7.0	NS	15.0±7.6	19.2±7.2	NS

* - Level of statistical significance; values expressed as mean±SD; HF- high frequency; TME LnT- total modulatory energy; CR- controlled respiration; D-BT_{max} - difference between maximal brady-and tachycardia during and following sustained inspiration; LnT- logarithmic transformation (refer to text for details).

Table IV – Comparison between VRR parameters of group IIb patients with and without left ventricle hypertrophy (LVH), type II diabetes mellitus (DM), and overweight (OW)

N	LVH	No-LVH	p	DM	No-DM	p*	OW	Non-OW	p*
	9	21	-	9	21	-	4	26	-
Age (years)	68.9±5.7	70.0±5.5	NS	72.2±5.8	68.5±5.1	NS	72.0±7.0	69.3±5.4	NS
Sex (F/M)	8/1	12/9	NS	6/3	14/7	NS	4/0	16/10	NS
MCF (bpm)	70.6±10.2	73.4±10.4	NS	71.4±11.1	73.1±10.1	NS	71.7±7.8	73.7±9.6	NS
DPNN (ms)	21.0±3.8	20.8±5.9	NS	21.0±4.2	20.8±5.8	NS	20.8±4.8	21.0±5.5	NS
TME LnT (Ln ms ²)	4.5±1.0	4.6±0.8	NS	4.5±1.1	4.5±0.8	NS	5.0±0.8	4.5±0.9	NS
HF LnT (Ln ms ²)	3.4±1.4	3.8±0.9	NS	3.6±1.4	3.7±0.9	NS	4.1±1.1	3.6±1.0	NS
HF CR LnT (Ln ms ²)	4.9±0.4	4.9±0.4	NS	4.6±0.2	5.1±0.6	NS	4.9±0.4	4.9±0.4	NS
D-BT _{max} (bpm)	16.8±6.1	17.0±6.3	NS	18.7±6.2	16.4±6.2	NS	14.9±3.8	14.9±3.8	NS

*- Level of statistical significance; values expressed as mean±SD; HF- high frequency; TME LnT- total modulatory energy; CR- controlled respiration; D-BT_{max}- difference between maximal brady-and tachycardia during and following sustained inspiration; LnT- logarithmic transformation (refer to text for details).

Tabela V – Diagnostic values of variables analyzed

	Value at sectioning	Specificity	Sensitivity
≥ 40 years and < 60 years			
MCF (bpm)	67.2	51.4 % (p<0.001)	33.5 % (p<0.001)
DPNN (ms)	27.8	76.2 % (p<0.001)	61.0 % (p<0.001)
TME LnT (Ln ms ²)	304.9	72.6 % (p<0.001)	80.7 % (p<0.001)
HF LnT (ms ²)	121.5	74.1 % (p<0.001)	67.1 % (p<0.001)
HF CR LnT (ms ²)	497.7	100.0 % (p<0.001)	71.4 % (p<0.001)
D-BT _{max} (bpm)	16.4	91.3 % (p<0.001)	54.3 % (p<0.001)
≥ 60 years and ≤ 80 years			
MCF (bpm)	60.7	60.1 % (p<0.001)	18.3 % (p<0.05)
DPNN (ms)	18.1	65.0 % (p<0.001)	53.8 % (p<0.001)
TME LnT (Ln ms ²)	102.5	48.2 % (p<0.001)	61.6 % (p<0.001)
FH LnT (Ln ms ²)	44.7	54.6 % (p<0.001)	62.3 % (p<0.001)
FH CR LnT (ms ²)	141.2	65.0 % (p<0.001)	75.0 % (p<0.001)
D-BT _{max} (bpm)	15.9	58.7 % (p<0.001)	56.3 % (p<0.001)

respiration (p<0.001). Values of 72.6% specificity (p<0.001) were found for total modulation energy.

Sensitivity was 67.1% at high frequency (p<0.001), 71.4% at high frequency during controlled respiration (p=0.001), and 80.7% for total modulation energy (p<0.001) in the frequency domain.

Variable values at sectioning in the time domain were 76.2% specificity for SDNN (p<0.001) and 91.3% for D-BT_{max} (p<0.001). Sensitivities had values of 61.0% for SDNN (p<0.001) and 54.4% for D-BT_{max} (p<0.001).

Discussion

Initial studies on the behavior of the variability of heart rate in systemic arterial hypertension were performed using techniques that analyzed reflex control of heart rate mediated by baroreceptors. Bristow et al²⁹ and Gribbin et al³⁰ showed that the reduction in heart rate consequent to baroreceptor activation evoked by increased arterial pressure was significantly less conspicuous in hypertensive individuals. Mancini et al³¹ verified that reflex tachycardia caused by a lowered arterial pressure consequent to deactivation of baroreceptors was significantly smaller in hypertensive subjects. These findings demonstrate the close

relation between mechanisms controlling arterial pressure and the variability of heart rate, which are impaired in systemic arterial hypertension.

In the frequency domain, the power spectrum band representing modulation energy of the vagosympathetic system (or total modulation energy) showed significantly lower values in group IIa compared with values in group Ia (Table I). This demonstrates that in hypertensive individuals of this age group variability in heart rate is significantly blunted. On the other hand, in agreement with Aono et al³², we verified that values of total modulation energy were not different between groups Ib and IIb, verifying that in group IIa-autonomic modulation of the heart was impaired by systemic arterial hypertension, but in group IIb, the reduced modulation caused by aging was not worsened by hypertension. This is reinforced by the analysis of the predominantly vagal modulation. Thus, comparing groups I and IIa, both at rest and during controlled respiration, values were larger in group Ia (p<0.05). However, when values at high frequency and high frequency controlled respiration were analyzed under identical conditions, no significant differences between individuals in groups Ib and IIb were found (Table I).

On analyzing differences between high frequency values observed prior to and during controlled respiration within each group, we observed that the increase in vagal modulation energy was less expressive in group IIa, Ib and IIb. This result verifies that in the process of autonomic demodulation of the heart the parasympathetic loop was significantly blunted both by age and by arterial hypertension. It is important to note that in individuals 60 years old and above, the presence of arterial hypertension does not intensify the decrease in modulating energy imposed by aging; this contrasts with effects observed among individuals in group IIa. In the higher age group, increased arterial wall rigidity consequent to aging, which directly decreases pressoreceptor sensitivity, is not aggravated by increased levels of tension. In other conditions, like Parkinson's disease, in which direct lesions of the autonomic nervous system may occur, values of the potency energy spectrum in the aged are significantly smaller than those observed in controls of the same age group⁷. Similarly to that observed in the frequency domain, variables in the time domain also

underwent alterations. On analyzing the DPNN values of group IIa, we verified that they were significantly smaller than those in group Ia ($p=0.001$, Table I). These differences were not significant between groups Ib and IIb. Yet, in the time domain, we observed that $D-BT_{max}$ was significantly smaller in group IIa compared with that in group Ia ($p=0.03$), but it was not different in groups Ib and IIb.

The analysis of the variability in heart rate as a function of the existence of diabetes, LVH, or overweight, we observed that this variability was not aggravated by the presence of these morbid conditions, both in regards to frequency and time (Tables II and IV). This finding differs from some reports in the specialized literature³³⁻³⁵. It appears plausible, therefore, that these conditions do not aggravate alterations determined by systemic hypertension properly.

From the etiopathogenetic viewpoint, autonomic dysfunction determined by aging^{32,36} or due to various diseases^{6,7} is related to 2 basic causes: 1) alterations in pressoreceptor mediated reflexes and 2) intrinsic alteration of the vagosympathetic system.

In healthy individuals, oscillation of intrathoracic pressure evoked by respiratory movement determines increases and decreases in systolic ejection volume³⁷. These variations contribute to a significant extent to modifications in arterial pressure during the respiratory cycle. Variation in intravascular arterial pressure conditioned by respiratory movement is perceived by pressoreceptors that modify, moment by moment, efferent potentials conducted to the vasomotor center by the aortic and carotid depressor nerves. Upon arrival to the center and proper processing, this information travels via vagosympathetic efferent pathways towards the heart and vessels causing respectively, cyclic variation in heart rate (respiratory sinus arrhythmia) and peripheral arterial resistance, counteracting variations in stroke volume and preventing large fluctuations in arterial pressure (Figure 3).

In systemic arterial hypertension, pressoreceptor me-

diated regulatory mechanisms undergo recycling³⁸ and in the same manner as in the aged become less sensitive. Consequently, reflexes show a reduction in gain, that is, a smaller number of action potentials per mm Hg of oscillation of arterial pressure in the depressor nerves occurs. The first reflexes act by displacing the threshold of pressoreceptor action to higher arterial pressure levels. The second stop the processing of small arterial pressure variations, attenuating the reflex-modulating capacity of the vagus nerve on heart rate variability, enhancing that of the sympathetic system on arterial vessels.

From the diagnostic viewpoint, by presenting better indexes of discrimination between groups I and II, total modulating energy (TME) and that relative to autonomic modulation including high frequency control of respiration and $D-BT_{max}$, may constitute an important auxiliary tool for the diagnosis of systemic arterial hypertension. Controlled high frequency respiration allowed the identification of 100% of the individuals in group Ia and 71.4% of those in group IIa; among all variables analyzed, it had the highest diagnostic value for subjects in groups Ib and IIb. Therefore, the presence of alterations in these indexes in patients with high pressure values reinforces a diagnosis of systemic arterial hypertension indicating the existence of an impaired cardiac modulating system.

Thus, we may state that variables that quantify variability in heart rate both in the frequency and time domains, if recorded from patients with systemic arterial hypertension, have significantly lower values compared with the values in healthy subjects. This difference reflects the degree of impairment in baroreflex mediated autonomic cardiac modulation; it can corroborate the diagnosis of systemic arterial hypertension, bringing out the importance of age in the process of autonomic control of the heart.

Appendix

For the calculation of sensitivity and specificity, an empirical formula having the following steps was developed:

a) construct a histogram of distribution of values of variable X, divided into N classes with an amplitude interval for each numbered class (C_i), for groups I and II (see definition under Methods). Intervals C_i are defined by lower $[(Inf)C_i]$ and upper $[(Sup)C_i]$, so that variable X belongs to the interval when $Inf(C_i) \leq X < Sup(C_i)$. Thus, functions $p(X \in C_i)$ and $q(X \in C_i)$, representing the values of the probability of X, associated with each C_i class of the respective histograms of groups I (p) and II (q), become defined.

b) the probability distribution function of variable X is defined by the cumulative sum of the probabilities of all N (C_i) of the histogram of each group. Thus, functions $p(X \leq C_i)$ and $Q(X \leq C_i)$ are functions of the distribution probability of X to represent the probability that values of X < Sup(C_i), respectively to groups I (p) and II (Q). $p(X \leq C_i)$ and $Q(X \leq C_i)$ are equal to 1 for C_N , zero for C_0 , and grow monotonically.

c) Function $M(C_i)$ is defined as $[1-p(X \leq C_i)] Q(X \leq C_i)$. $M(C_i)$ has values equal to zero at the extremes (C_N and C_0) and the maximal value between them (C_{max}). Sensitivity is defined as $Q(X \leq C_{max})$, and specificity as $[1-p(X \leq C_{max})]$.

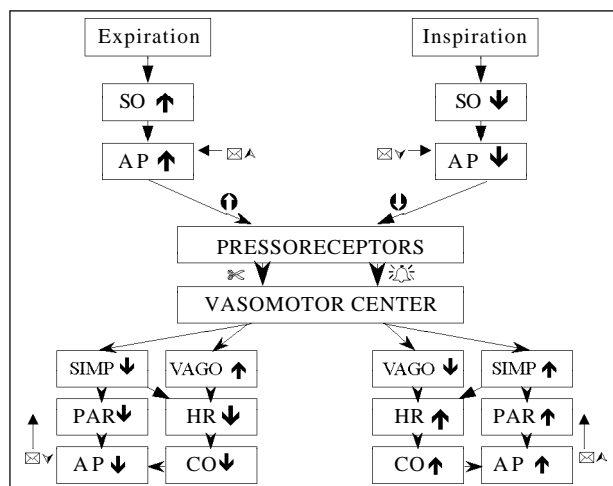


Fig. 3 - Representative scheme of the effect of respiratory phases of inspiration and expiration on the control of heart rate mediated by pressoreceptors. SO, systolic output; AP, arterial pressure; SIMP, sympathetic; PAR, peripheral arterial resistance; CO, cardiac output.

References

1. Kavachi I, Sparrow D, Vokonas PS, et al. Decrease heart rate variability in men with phobic anxiety (data from the normative aging data). *Am J Cardiol* 1995; 75: 882-5.
2. Ajiki K, Murakawa Y, Yanagisawa-Miwa Usui M, et al. Autonomic nervous system activity in idiopathic dilated cardiomyopathy and in hypertrophic cardiomyopathy. *Am J Cardiol* 1993; 71: 1316-20.
3. Ryan SM, Goldberger AL, Ruthazer R, et al. Spectral analysis of heart rate dynamics in elderly person with postprandial hypotension. *Am J Cardiol* 1992; 69: 201-5.
4. Bernardi L, Ricordi L, Lazzari P, et al. Impaired circadian modulation of sympathovagal activity in diabetes: a possible explanation for altered temporal onset of cardiovascular disease. *Circulation* 1992; 86: 1443-52.
5. Saul JP, Arai Y, Berger RD, et al. Assessment of autonomic regulation in chronic congestive heart failure by heart rate spectral analysis. *Am J Cardiol* 1988; 61: 1292-9.
6. Barbosa PR, Barbosa FJ, Morais de Sá CA. Influência da idade, sexo e doença coronária sobre a modulação autonômica do coração. *Arq Bras Cardiol* 1996; 67: 325-9.
7. Barbosa Filho J, Barbosa PRB, Papais-Alvarenga RM, et al. Modulação autonômica cardíaca na doença de Parkinson. *Rev Bras Neurol* 1999; 35: 75-80.
8. Singh M, Juneja R, Bali HK, et al. Autonomic function in restrictive cardiomyopathy and constrictive pericarditis: a comparison. *Am Heart J* 1998; 136: 443-8.
9. Huikuri HV, Ylitalo A, Pikkujämsä SM, et al. Heart rate variability in systemic hypertension. *Am J Cardiol* 1996; 77: 1073-7.
10. Huikuri HV, Linnaluoto MK, Spänänen T, et al. Circadian rhythm of heart rate variability in survivors of cardiac arrest. *Am J Cardiol* 1992; 70: 610-5.
11. Dougherty CM, Burr RL. Comparison of heart rate variability in survivors and nonsurvivors of sudden cardiac arrest. *Am J Cardiol* 1992; 70: 441-8.
12. Hartikainen JE, Malik M, Staunton A, et al. Distinction between arrhythmic and nonarrhythmic death after acute myocardial infarction based on heart rate variability, signal-averaged electrocardiogram, ventricular arrhythmia and left ventricular ejection fraction. *J Am Coll Cardiol* 1996; 28: 296-304.
13. Bigger Jr JT, Fleiss JL, Rolnitzky LM, et al. The ability of several short-time measures of RR variability to predict mortality after myocardial infarction. *Circulation* 1993; 88: 927-34.
14. La Rovere MT, Bigger JT, Marcus FI, et al. Baroreflex sensitivity and heart rate variability after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* 1998; 351: 478-84.
15. Kjellgren O, Ip J, Suth K, et al. The role of parasympathetic modulation of the reentrant arrhythmic substrate in the genesis of sustained ventricular tachycardia. *Pacing Clin Electrophysiol* 1994; 17: 1276-87.
16. Huikuri HV, Mäkilä TH, Airaksinen J, et al. Power-law relationship of heart rate variability as a predictor of mortality in the elderly. *Circulation* 1998; 97: 2031-6.
17. Mäkilä TH, Koistinen J, Jordaens L, et al. Heart rate dynamics before spontaneous onset of ventricular fibrillation in patients with healed myocardial infarcts. *Am J Cardiol* 1999; 83: 880-4.
18. Mäkilä TM, Höber S, Köber L, et al. Fractal analysis of heart rate dynamics as a predictor of mortality in patients with depressed left ventricular function after acute myocardial infarction. *Am J Cardiol* 1999; 83: 836-9.
19. Parati G, Di Rienzo M, Groppelli A, et al. Heart rate and blood pressure variability and their interaction in hypertension. In: Malik M, Camm AJ (eds): *Heart Rate Variability*. Armonk, NY: Futura Publishing Co. Inc., 1995; cap. 35: 467-78.
20. Kosh M, Hausberg M, Barenbrock M, et al. Studies of cardiac sympathovagal balance and large artery distensibility in patients with untreated essential hypertension. *J Hum Hypertens* 1999; 13: 315-9.
21. Guzzetti S, Piccaluga E, Casati R, et al. Sympathetic predominance in essential hypertension: a study employing spectral analysis of heart rate variability. *J Hypertens* 1988; 6: 711-7.
22. Piccirillo G, Munizzi MR, Fimognari, et al. Heart rate variability in hypertensive subjects. *Int J Cardiol* 1996; 53: 291-8.
23. Singh JP, Larson MG, Tsuji H, et al. Reduced heart rate variability and new onset hypertension: insight into pathogenesis of hypertension: the Framingham Heart Study. *Hypertension* 1998; 32: 293-7.
24. Minami J, Kawano Y, Ishimitsu T, et al. Blunted parasympathetic modulation in salt-sensitive patients with essential hypertension evaluation by power-spectral analysis of heart rate variability. *J Hypertens* 1997; 15: 1997.
25. Presciutti B, Duorez D, De Buyzere M, et al. How to study sympatho-vagal balance in arterial hypertension and the effect of antihypertensive drugs. *Actas Cardiol* 1998; 53: 143-52.
26. Ylitalo A, Airaksinen J, Sellin L, et al. Effects of combination antihypertensive therapy on baroreflex sensitivity and heart rate variability in systemic hypertension. *Am J Cardiol* 1999; 83: 885-9.
27. Petretta M, Bonaduce D, Marciano F, et al. Effects of 1 year of lisinopril treatment on cardiac autonomic control in hypertensive patients with left ventricular hypertrophy. *Hypertension* 1996; 27: 330-8.
28. Barbosa PRB. A signal-averaging system for surface ECG signal analysis. *Phys Med Biol* 1994; 39: 412.
29. Bristow JD, Honour AJ, Pickering GW, et al. Diminished baroreflex sensitivity in high blood pressure. *Circulation* 1969; 39: 48-54.
30. Gribbin B, Pickering TG, Sleight P, et al. Effect of age and high blood pressure on baroreflex sensitivity in man. *Circ Res* 1971; 29: 424-31.
31. Mancia G, Ferrari A, Gregori L, et al. Blood pressure variability in man: its relation to age, high blood pressure and baroreflex sensitivity. *Clin Sci* 1980; 59: 401-3.
32. Aono T, Sato T, Nishinaga M, et al. Power spectral analysis of spontaneous blood pressure and heart rate variability in elderly hypertensives. *Hypertens Res* 1996; 19: 9-16.
33. Heikki VH, Ylitalo A, Pikkujämsä SM, et al. Heart rate variability in systemic hypertension. *Am J Cardiol* 1996; 77: 1073-7.
34. Kohara K, Hanara-Nakamura N, Hiwada K. Left ventricular mass index correlates with heart rate variability. *Am J Hypertens* 1995; 8: 183-8.
35. Pikkujämsä SM, Huikuri HV, Airaksinen KE, et al. Heart rate variability and baroreflex sensitivity in hypertensive subjects with and without metabolic features of insulin resistance syndrome. *Am J Hypertens* 1998; 11: 523-31.
36. Barbosa PR, Barbosa Filho J, Morais de Sá CA. Efeito da idade sobre a modulação autonômica do coração. *Rev SOCERJ* 1995; 3: 79-84.
37. Taylor JA, Eckberg D. Fundamental relations between short-term RR interval and arterial pressure oscillation in humans. *Circulation* 1996; 93: 1527-32.
38. Michelini LC. Regulação momento a momento da pressão arterial na normotensão e hipertensão. *Hipertensão* 2000; 3: 90-8.