ORIGINAL ARTICLE

Circadian autonomic disturbances in resistant hypertension with and without white coat phenomenon

Distúrbios autonômicos do ritmo circadiano na hipertensão resistente com e sem o fenômeno do avental branco

Valéria Nasser Figueiredo[1], Luiz Cláudio Martins[1], Leandro Boer-Martins[1,2], Ana Paula Cabral de Faria[1], Carolina de Haro Moraes[1], Heitor Moreno Junior[1]

Received from Laboratório de Farmacologia Cardiovascular, Faculdade de Ciências Médicas da Universidade Estadual de Campinas, Campinas, SP, Brazil.

ABSTRACT

BACKGROUND AND OBJECTIVE: The current definition of resistant hypertension includes both patients whose blood pressure is uncontrolled on three or more medications and those whose blood pressure is controlled when using four or more antihypertensive medications. Ambulatory blood pressure monitoring is an indispensable method to diagnose resistant hypertension and classify it into 2 groups: resistant hypertension without white-coat response and resistant hypertension with white-coat response. The aim of this study was to evaluate the circadian autonomic profile of resistant hypertension with and without white-coat phenomenon. **METHODS**: Forty four resistant hypertension patients were divided into two groups: resistant hypertension with white-coat phenomenon (n=25) and resistant hypertension without white-coat (n=19) phenomenon. All patients underwent office blood pressure measurement, ambulatory blood pressure monitoring, and 24-hour Holter monitoring. **RESULTS**: No differences were observed between the resistant hypertension with white-coat phenomenon and resistant hypertension without white-coat phenomenon groups regarding age, body mass index or gender. The group of resistant hypertension with white-coat phenomenon had greater autonomic imbalance evaluated by heart rate variability parameters in frequency domain compared to resistant hypertension patients without white-coat phenomenon. Moreover, nighttime frequency domain parameters of resistant hypertension group with white-coat phenomenon correlated positively with office resistant hypertension and office pulse pressure ($r=0.57$, $p<0.05$ and $r=0.55$, $p<0.05$, respectively). **CONCLUSION**: The presence of the white-coat response in resistant hypertension patients implies worse autonomic imbalance.
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Keywords: Hypertension; White-coat hypertension; Heart rate; Blood pressure, determination; Autonomic nervous system diseases

RESUMO

JUSTIFICATIVA E OBJETIVO: A definição de hipertensão arterial resistente inclui pacientes cuja pressão arterial permanece acima da meta apesar do uso de 3 classes de anti-hipertensivos bem como aqueles que usam 4 ou mais classes e possuem pressão controlada. A monitorização ambulatorial da pressão arterial é um método indispensável para o diagnóstico da hipertensão arterial resistente, excluindo a pseudorresistência, e classificar o hipertenso resistente em 2 grupos: hipertensão arterial resistente sem e com a presença do fenômeno do avental-branco. O objetivo deste estudo foi avaliar o perfil circadiano autonômico da hipertensão arterial resistente com e sem resposta ao fenômeno do avental-branco. **MÉTODOS**: Quarenta e quatro pacientes com hipertensão arterial resistente foram divididos em dois grupos: hipertensão arterial resistente com presença do fenômeno do avental-branco (n=25) e hipertensão arterial resistente sem presença do fenômeno do avental-branco (n=19). Todos os pacientes foram submetidos à medida da pressão arterial de escritório, monitorização ambulatorial da pressão arterial e eletrocardiografia ambulatorial para análise da variabilidade da frequência cardíaca. **RESULTADOS**: Não foram observadas diferenças entre a hipertensão arterial resistente com e sem a presença do fenômeno do avental-branco em relação à idade, índice de massa corporal ou de gênero. No grupo de hipertensão arterial resistente com a presença do fenômeno do avental-branco observou-se maior desequilíbrio autonômico avaliado por parâmetros da variabilidade da frequência cardíaca no domínio da frequência em comparação aos pacientes sem o fenômeno do avental-branco. Além disso, os parâmetros da variabilidade da frequência cardíaca noturnos no grupo da hipertensão arte-

1. Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Campinas, SP, Brazil.
2. Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.

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Correspondence address:
Valéria Nasser Figueiredo
Laboratório de Farmacologia Cardiovascular
Faculdade de Ciências Médicas da Universidade Estadual de Campinas, Campinas, SP, Brazil.
Zip code: 13083-970 – Campinas, SP, Brazil
Phone.: 55 (19) 35218788 - E-mail: vanasserfig@yahoo.com.br

rial resistente com a presença do fenômeno do avental-branco correlacionaram-se positivamente com a hipertensão arterial resistente e pressão de pulso de consultório (r=0,57, p<0,05 e r=0,55, p<0,05, respectivamente). **CONCLUSÃO**: A presença do fenômeno do avental-branco na hipertensão arterial resistente implica em pior desequilíbrio autonômico.

Descritores: Hipertensão; Hipertensão do jaleco branco; Frequência cardíaca; Determinação da pressão arterial; Doenças do sistema nervoso autônomo

INTRODUCTION

The current definition of resistant hypertension (RH) includes both patients whose blood pressure (BP) is uncontrolled on three or more medications and those whose BP is controlled when using four or more antihypertensive medications[1]. Ambulatory blood pressure monitoring (ABPM) is an indispensable method to diagnose RH and classify it into 2 groups: RH without white-coat (WC) response (office BP≥140/90mmHg and 24-hour BP≥130/80mmHg) and RH with WC response (office BP≥140/90mmHg and 24-hour BP<130/80mmHg)[2-4].

White-coat phenomenon originates from an alerting reaction by the patient while being examined at the doctor's office[3,5] and is frequently associated with an increase in heart rate (HR) by the influence of autonomic nervous system[6].

The autonomic nervous system can be assessed by the heart rate variability (HRV). It assesses the modulation of the autonomic control of heart rate and the balance between its sympathetic and parasympathetic components and can be evaluated by spectral analysis of HRV in time and frequency domains[7]. Variations in HRV are normally observed in association with diurnal rhythms and BP changes[8]. The HRV parameters are different in many studies, although the consensus is that lower values of the indices of vagal as well as high indices of sympathetic functions are associated prospectively with death and disability[9].

In humans, the disturbances of the circadian rhythms of HRV and BP[1] have been intensively studied, mainly due to the increased cardiovascular death reported during the morning hours[10]. The contribution of this study is the inedited evaluation of the circadian autonomic profiles of RH with and without WC.

METHODS

Forty-four RH subjects regularly followed up at the cardiovascular clinical pharmacology out-patients' clinic, and who complied with pharmacological prescription for hypertension (HTN), were recruited to participate in this transversal and observational study. All individuals completed a medical history questionnaire and were submitted to physical examinations, electrocardiography and laboratory tests. Pseudoresistance cases, including lack of blood pressure control secondary to poor medication adherence, as well as secondary forms of hypertension were properly observed and excluded[3-5]. White-coat hypertension was excluded by ABPM[6]. All individuals were regularly followed up during the first 6 months for drug therapy optimization[7]. Regarding obstructive sleep apnea (OSA), only patients classified as "low risk" by Berlin sleep questionnaire were enrolled[8].

After 3 months of the first RH with WC response diagnosis, ABPM was used to confirmatory of the diagnosis[9]. The patients were divided into two groups: RH with WC (n=25) and RH without WC (n=19). All the subjects gave written informed consent and the study was approved by the university ethics committee.

Study design

Non-pharmacologic therapies were optimized, including dietary salt control monitored by measuring urinary sodium excretion (<100mEq/24h). All patients were submitted to office BP (OBP) measurement, ABPM and 24-hour Holter monitoring. After ABPM, patients were classified as RH with WC response if mean 24-hour BP was <130/80mmHg[10].

Measurements

Office blood pressure

The patient's BP was measured by the nurse[11]. Clinical values of BP were obtained three times from each patient, using a digital sphygmomanometer (Omron HEM-907 XL)[12] assessed at our morning medical appointments, strictly scheduled between 8:00 – 10:00 a.m. While BP was measured the participant remained seated with the arm comfortably placed at heart level[7]. The average of two consecutive measurements with a variation lower than 5mmHg was used.

Ambulatory blood pressure monitoring

The appropriate sized cuff was placed around the non-dominant arm. All participants underwent 24-hour ABPM on a usual working day. They were instructed to act and work normally[13]. A Spacelabs 90217 ambulatory blood pressure monitor (Spacelabs Inc, Redmon, WA, USA) was used[2]. Readings were obtained automatically at 20-minute intervals throughout the 24-hour monitoring period. All participants comprising the study had at least 80% of the total measurements validated. Parameters evaluated were mean 24-hour, daytime, and nighttime systolic BP (SBP) and diastolic BP (DBP). The nighttime period was ascertained for each individual patient from registered diaries.

Laboratory assessment

Baseline blood samples for the measurement of glycemia (mg/dL), total cholesterol (mg/dL), LDL cholesterol (mg/dL), triglycerides (mg/dL), creatinine (mg/dL), serum uric acid, serum sodium, serum potassium, plasma aldosterone concentration (PAC) and plasma renin activity (PRA) were collected at 08:00 after overnight fasting. During this time, the volunteers rested in the supine position for 8h, followed by 1h in an upright position in an air-conditioned room (22–24 1C). PRA was

measured by a private laboratory (Mayo Clinic Laboratories, Rochester, Minnesota, USA) using standard techniques. PRA levels were measured by radioimmunoassay.

Heart rate variability

Heart rate variability (HRV) parameters were derived from the recording of 24-hour Holter monitoring and analyzed in frequency domains. The measurements were stratified in two periods of 1 hour each at 3 a.m. (nighttime period) and 3 p.m. (daytime period). A three-channel, 24-hour Holter recording was obtained from each subject using a Cardio light digital 24-hour recorder device and CardioSmart Institutional CS 550 software (Cardio Sistema Comércio e Indústria Ltda, São Paulo, SP, Brazil).

Frequency domain HRV parameters included the following measurements[3]: low frequency (LF) and high frequency (HF) measured in normalized units, which represent the relative value of each power component in proportion to the total power minus the very low frequency (VLF) component. Normalized LF (LF nu) was calculated as LF power in normalized units LF/ (total power-VLF) x 100, and normalized HF (HF nu) as HF power in normalized units HF/ (total power-VLF) x 100. LF nu and HF nu denote the energy in the heart period power spectrum between 0.04 and 0.15 Hz (which is due to the joint action of the vagal and sympathetic components on the heart, with a predominance of the sympathetic) and 0.15 and 0.40 Hz (which corresponds to the respiratory modulation and is an indicator of the performance of the vagus nerve on the heart), respectively. "Daytime" and "nighttime" were established at 3:00 p.m. and 3:00 a.m., respectively, in order to collect HRV data during wake and sleep periods.

Statistical analysis

Data were expressed as mean (μ) and standard deviation (SD) or mean (μ) and standard error of the mean (SEM) for HRV measures. Unpaired groups were compared using Mann-Whitney U test whilst correlation analysis were performed using Spearman´s rank test. Fisher exact test was used to determine whether certain group had significantly different proportion of a particular characteristic. A significance level of the difference between the groups less than 0.05 was accepted as statistically significant. The Statistical Analysis System, version 8.02 (SAS Institute Inc., Cary, NC, USA), was used for all statistical analyses.

Table 1. Baseline characteristics, BP, HR measurements and anti-hypertensive drug distribution in resistant hypertension patients

Characteristics	RH with WC (n=25)	RH without WC (n=19)	*p*-value
Women, %	56	63	0.43
Age, years	56±9	53±10	0.52
BMI, kg/m^2	29±5	31±6	0.39
Office BP			
SBP, mmHg	162±6	170±6	0.04
DBP, mmHg	91±6	96±7	0.08
Average 24-h BP			
SBP, mmHg	121± 9	137± 8	0.003
DBP, mmHg	73±8	87± 7	0.023
Average daytime BP			
SBP, mmHg	124± 6	140± 5	0.006
DBP, mmHg	77± 5	89±7	0.004
Average nighttime BP			
SBP, mmHg	118±7	123±9	0.67
DBP, mmHg	72±7	77±8	0.78
Heart rate			
Daytime (bpm)	85±8	86±14	0.58
Nighttime (bpm)	67±10	68±10	0.65
Anti-hypertensive drug distribution			
Total anti-HTN drugs	4±0.3	5±0.2	0.02
Thiazide diuretic, %	88 (22)	91 (17)	0.25
Aldosterone receptor inhibitor, %	11.4 (3)	9.3 (2)	0.39
β-blockers, %	81.8 (20)	71.4 (13)	0.42
Angiotensin-converting enzyme inhibitors, %	48.0 (12)	72.0 (14)	0.03
Angiotensin receptor blocker, %	40.4 (10)	63.5 (12)	0.04
Calcium channel blocker, %	60.9% (15)	85.5 (16)	0.03
Centrally acting anti-hypertensive drug, %	12.2 (3)	15.1 (3)	0.37

Values are means±SD: except anti-hypertensive drug distribution that are percentage (n); Statistical significance (p<0.05); WC: white-coat; RH: resistant hypertension; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; ABPM: ambulatory blood pressure monitoring.

RESULTS

The general characteristics of the study groups are listed in table 1. No differences were observed between the RH with WC and RH without WC groups regarding age, body mass index or gender. The RH without WC group received more anti-hypertensive drugs than RH with WC group (5.1±0.2 *versus* 4.1±0.3, respectively) (Table 1). Considering the total population of this study, the prevalence of WC response in RH individuals was 40%, similar to other previous studies[4-6].

The RH without WC group demonstrated higher office and ABPM SBP, ABPM DBP, as well as pulse pressures (PP) compared to RH with WC group (Table 1).

No differences regarding LF nu, HF nu and LF/HF were found between both groups during daytime. However, there were significant differences regarding the same parameters during nighttime between RH with WC and RH without WC groups (LF nu: 58.9±20.9 *versus* 39.8±22.9, p<0.01; HF nu: 40.8±21.3 *versus* 60.1±23.0, p<0.01; LF/HF: 3.53±3.0 *versus* 1.09±1.2, p=0.006, respectively) (Table 2).

In the RH with WC group, both LF nu and HF nu during day and night were similar (78.7±12.8 *versus* 58.9±20.9 and 21.6±13.2 *versus* 40.8±21.3, respectively - p>0.05) whereas in the RH without WC group, these parameters were different

Table 2. Heart rate variability in resistant hypertension patients

HRV variable	RH with WC (n=25)	RH without WC (n=19)	*p*-value
Day			
LF nu	79±13	76±17	0.59
HF nu	22±13	24±17	0.61
LF/HF	5±3	4±2	0.60
Night			
LF nu	59±21	40±23	<0.01
HF nu	41± 21	60±23	<0.01
LF/HF	3±3	1±1	0.006

Values are expressed as means±SEM; Statistical significance ($p<0.05$); WC: white-coat; RH: resistant hypertension; LF nu: low frequency in normalized units from the power spectra of HRV by computer analysis using Fast Fourier Transformation (FFT); HF nu: high frequency in normalized units from the power spectra of HRV by computer analysis using FFT; LF/HF: LF to HF ratio.

(76.3±16.8 *versus* 39.8±22.9 and 23.6±16.8 *versus* 60.1±23.0, respectively - p<0.05). Moreover, RH with WC group had the nighttime LF nu correlated positively with office SBP and office pulse pressure (PP) (r=0.57, p=0.002 and r=0.55, p=0.003, respectively). Also in the same group, nighttime HF nu correlated negatively with office SBP and office PP (r=-0.57, p=0.002 and r=-0.55, p=0.003, respectively).

DISCUSSION

The present study demonstrated that the two sub-groups of RH (with or without the white-coat response) hold different profiles of the autonomic circadian rhythm beyond the already known differences in the blood pressure. Not only the RH with WC group demonstrated greater autonomic imbalance than the RH without WC group during nighttime, but it demonstrated a pattern of autonomic circadian disruption due its sympathetic overactivity compared to the parasympathetic tone during nighttime. Moreover, the nighttime LF nu (sympathetic activity) correlated positively with the morning office SBP and office PP in the RH with WC group. The contribution of this study is the inedited profiling of the circadian autonomic disturbances of RH with WC and RH without WC groups and the correlation of the nighttime autonomic disturbance (sympathetic overactivity) of the RH with WC group with the office BP and PP surge in the morning.

The WC phenomenon is more prevalent in women and older persons[6] and occurs when BP is increased temporarily through an autonomic neural reaction triggered by the process of BP measurement in the office[7]. These cases must be necessarily confirmed with 24-hour ABPM[8]. Thus, patients can be diagnosed as truly hypertensive, but still present the WC response.

Considering the influence of autonomic imbalance, evidence indicates the involvement of increased activity of the sympathetic nervous system (SNS) in the pathogenesis of HTN[9]. Not only the sympathetic overactivity is related to the low amplitude of the alert reaction of WC response, but early alterations of the parasympathetic system were demonstrated to influence it[10].

Clinically relevant, SNS overactivity is associated with increased cardiovascular outcomes during the early morning hours[11]. Moreover, elevated PP is widely being recognized as a risk factor for cardiovascular events, particularly in coronary disease[12] and during the morning period[13]. During the pre-wake and wake periods, the sympathetic system has its activity raised provoking heart rate increasing[14]. Furthermore, circumstances of medical assistance such as frequent unfamiliar doctors measuring ambulatory BP lead to higher sympathetic activity during the visit and also stay high with a slow rate of disappearance after the doctor´s departure[15].

Our results demonstrated that RH with WC group had higher sympathetic activity during nighttime than the RH without WC group. In addition, it was shown that sympathetic activity during nighttime correlated with the morning office BP and PP in the same subgroup. Due to the importance of sympathetic overactivity in the genesis of HTN, circumstantial BP and PP increases, it is possible to infer that the overactivity during nighttime may not only influence the prevalent non-dipper pattern of RH but also contribute to the BP morning surge perceived as the WC response during our morning ambulatory medical appointments (strictly scheduled between 8:00 and 10:00 a.m. in our service).

The percentage of β-blockers, aldosterone receptor inhibitors and centrally acting antihypertensive drugs was similar in both RH groups. These data suggest that classes of antihypertensive drugs which interfere with sympathetic activity cannot be directly responsible for the observed differences in autonomic imbalance observed in RH with WC group.

Our main limitation was the reduced sample size of RH patients due to the diligent exclusion of pseudo-resistance hypertension patients in order to minimize, as much as it is possible, known factors that could skew the results.

Another confounding factor regarding the evaluation of the autonomic function in RH patients is the high prevalence of OSA. It is known that patients with sleep disorders such as OSA have increased sympathetic activation and also present faster heart rates during resting wakefulness, suggesting their increased cardiac sympathetic drive[16]. Inasmuch as RH patients are associated with sympathetic activation and OSA, only RH patients classified as "low risk" (Berlin sleep questionnaire) of OSA diagnosis were included in this study.

In addition to the limitations of studying the autonomic system, inferences concerning the autonomic imbalance cannot be reductionist due its complexity. For instance, the sympathetic activation is not uniformly distributed over the cardiovascular system in metabolic syndrome patients[17]. Considering that all patients enrolled in this study had some degree of autonomic imbalance and most of them had metabolic disorders, cautious interpretation of autonomic assessments should be adopted. It is still matter for future studies if the autonomic circadian nuances such as what we have found have significant clinical importance for predicting the WCE among RH patients.

In conclusion, the presence of white-coat phenomenon in RH patients implies a worse autonomic imbalance than in its absence. Moreover, white-coat phenomenon is associated with

autonomic circadian disruption during the nighttime and holds a positive correlation with the morning office and pulse blood pressure surge.

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Competing interests

Leandro Boer-Martins is an employee of Novartis Pharmaceuticals Corporation (East Hanover, NJ, USA). Other authors declare no conflict of interest.

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