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EFEITO DO AVENTAL BRANCO NA HIPERTENSÃO RESISTENTE: PARTICIPAÇÃO DA DISFUNÇÃO AUTONÔMICA E LESÕES DE ÓRGÃOS ALVO

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Tese de Doutorado apresentada à Pós-Graduação da Faculdade de Ciências Médicas da Universidade Estadual de Campinas - UNICAMP para obtenção de título de Doutor em Farmacologia. Sob orientação do Prof. Dr. Heitor Moreno Junior.

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"O único lugar onde o sucesso

vem antes do trabalho é no dicionário."

Albert Einstein

SUMÁRIO

LISTA DE ABREVIATURAS E SIGLAS

ARA	Antagonistas dos receptores de angiotensina
AINES	Anti-inflamatórios não esteroidais
ALLHAT	*Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial*
AOS	Apneia obstrutiva do sono
LDLc	Colesterol de lipoproteína de baixa densidade
DM	Diabetes *mellitus*
DRC	Doença renal crônica
EAB	Efeito do avental branco
FC	Frequência cardíaca
HA	Hipertensão arterial
HAR	Hipertensão resistente
HAB	Hipertensão do avental branco
HVE	Hipertrofia ventricular esquerda
ICC	Insuficiência cardíaca congestiva
IM	Infarto do miocárdio
IMC	Índice de massa corporal
LOA	Lesão de órgão alvo
MA	Microalbuminúria
MAPA	Monitoração ambulatorial da pressão arterial
MRPA	Monitoração residencial da pressão arterial
NA	Noradrenalina

PA	Pressão arterial
PAD	Pressão arterial diastólica
PAS	Pressão arterial sistólica
SNA	Sistema nervoso autônomo
SNP	Sistema nervoso parassimpático
SNS	Sistema nervoso simpático
SRAA	Sistema renina angiotensina aldosterona
VFC	Variabilidade da frequência cardíaca

LISTA DE ILUSTRAÇÕES

RESUMO

A definição de hipertensão arterial resistente (HAR) inclui pacientes cuja pressão arterial (PA) 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, excluída a pseudo-resistência. A hiperatividade do sistema nervoso simpático está criticamente envolvida na patogênese da hipertensão arterial, correlacionando-se positivamente com a gravidade da hipertensão arterial e maior variabilidade da frequencia cardíaca, estando ainda envolvida no efeito do avental branco (EAB). Ademais, os distúrbios do sono frequentemente associam-se à HAR. **Objetivos:** Avaliar se a presença do EAB associa-se a maior proporção (adicional) de lesões de órgão alvo em HAR; avaliar se a disfunção do sistema nervoso autônomo, quantificada através da variabilidade da frequência cardíaca, correlaciona-se com diferentes níveis de PA nestes pacientes e verificar se o risco para apneia obstrutiva do sono e qualidade do mesmo está associado ao EAB. **Casuística e Métodos: subestudo 1 -** Foram incluídos 121 pacientes diagnosticados como hipertensos resistentes em seguimento no ambulatório de Hipertensão Resistente do HC-FCM/UNICAMP e divididos em 2 grupos: HAR+EAB (n=66) e HAR-EAB (n=61). Foram realizados estudos para investigação do remodelamento cardiovascular (Ecocardiografia), da função renal (microalbuminúria e *Clearance* de creatinina); **subestudo 2** - foram incluídos 44 pacientes diagnosticados como hipertensos resistentes em seguimento no ambulatório de Hipertensão Resistente do HC-FCM/UNICAMP e divididos em 2 grupos: HAR+EAB (n=25) e HAR-EAB (n=19). Foram realizados estudos para investigação da avaliação da variabilidade da frequência cardíaca (sistema não invasivo – Holter 24 horas), bem como responderam ao Questionário índice de qualidade do sono de Pittsburgh e Questionário de Berlim (avaliação do risco para apneia obstrutiva do sono). **Resultados: subestudo 1**- os dois subgrupos eram semelhantes em distribuição de gênero, idade e índice de massa corporal. Os valores de PA observados foram: consultório= 169,8±15,8/95,1±14,0 (HAR+EAB) e 161,9±9,0/90,1±10,4 mmHg (HAR-EAB) e MAPA= 143,0±12,8/86,1±9,9 (HAR+EAB) e 146,1±13,6/85,1±14,9 mmHg (HAR-EAB). Não houve diferença significativa entre os 2 subgrupos quanto ao IMVE (HAR+EAB= 132±38; HAR-EAB= 125±32 g/m^2), clearance de creatinina (HAR+EAB= 78±38; HAR-EAB=

80±28 ml/min/m^2) e microalbuminúria (HAR+EAB= 44±68; HAR-EAB= 49±53 mg/g Cr); **subestudo 2** - os dois subgrupos eram semelhantes em distribuição de gênero, idade e índice de massa corporal. A despeito da alta prevalência de risco para apneia obstrutiva do sono e qualidade de sono ruim ter sido observada em ambos os subgrupos, o subgrupo HAR+EAB apresentou atividade simpática aumentada durante o período noturno (HAR+EAB=58,9±20,9 e HAR-EAB=39,8±22,9, $p<0,05$). **Conclusão: subestudo 1 -** demonstramos que nesta amostra de pacientes com HAR, o EAB não se associou a maior proporção de lesões em órgãos alvo (quando avaliados rins e coração); **subestudo 2** - a hiperativação simpática durante o período de sono ocorreu somente em hipertensos resistentes com EAB, apesar da influência semelhante de distúrbios do sono e da qualidade do mesmo em ambos os grupos.

Palavras chave: hipertensão, órgãos alvo, sistema nervoso simpático.

ABSTRACT

Background: The revised definition of resistant hypertension (RHTN) 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. White coat effect (WCE) originates from an alerting reaction by the patient while being examined in a medical environment and is frequently associated with an increase in heart rate and blood pressure (BP). It is known that high prevalence of obstructive sleep apnea in resistant hypertension (RH) and its subsequently nighttime sympathetic overactivation. **Objectives: substudy 1**- the relationship between occurrence of WCE and target organ damage (TOD) has not yet been assessed in true RHTN; **substudy 2** –
the aim of the study was to investigate the influence of the pattern of autonomic activity in the circadian rhythm in true resistant hypertension with and without WCE and its relationship with quality of sleep and sleep disorders. **Methods: substudy 1-** one hundred twenty-seven RHTN patients were identified with WCE (WCE) (66) and without WCE (non-WCE) (61).All patients were submitted to office BP measurement, ABPM, echocardiography and renal function evaluation; **substudy 2** - consecutive stable patients with RHTN (44 in number) were evaluated for the risk of obstructive sleep apnea by the Berlin Questionnaire, sleep quality by the Pittsburgh Sleep Questionnaire Index and were submitted to office BP measurement, ABPM and 24-hour Holter monitoring. **Results: substudy 1-** Office BP were 169.8 ± 15.8 / 95.1 ± 14.0 (WCE) and 161.9 ± 9.0 / 90.1 ±10.4 mmHg (non-WCE), ABPM = 143.0 ± 12.8 / 86.1 ± 9.9 (WCE) and 146.1 ± 13.6 / 85.1 ± 14.9 mmHg (non-WCE). No statistical differences were observed between WCE and non-WCE subgroups with respect to left ventricular mass index (WCE= 131 ± 4.7; non-WCE= 125 ± 2.9 g/m^2), creatinine clearance (WCE = 78 ± 4.7; non-WCE= 80 ± 3.6 ml/min/m^2) and microalbuminuria (WCE= 44 ± 8.4; non-WCE= 49 ± 6.8 mg/g Cr); **substudy 2** - RHTN patients were identified with WCE (WCE) (25) and without WCE (non-WCE) (19). Office BP was 170.7±17.2/94.8±14.0 (WCE) and 161.7±08.6/90.3±11.4 mmHg (non-WCE), daytime ABPM = 144.0±13.4/77.3±17.3 (WCE) and 146.2±15.6/84.0±15.0 mmHg (non-WCE). Despite of the similar results regarding quality of sleep and risk of OSA in both groups, significant differences were observed between WCE and non-WCE subgroups

regarding low frequency in normalized units (LF nu) during night time (WCE=58.9±20.9 and non-WCE 39.8±22.9, $p<0.05$). **Conclusion: substudy 1-** this finding may suggest that WCE is not associated with additional increase of TOD in true RHTN subjects; **substudy 2** - the sympathetic overactivation during the nighttime prior the medical appointment occurred in RH patients with WCE despite of the influence of sleep disorders.

Key-words: hypertension, target organs, sympathetic nervous system.

1.INTRODUÇÃO

1.1 Aspectos preliminares

O conceito de que a origem da hipertensão essencial depende grandemente das alterações da homeostase do controle adrenérgico da pressão arterial (PA) foi desenvolvido há algumas décadas e recebeu continuamente evidências robustas de estudos experimentais e clínicos [1-2].

Nos últimos anos, novas descobertas em relação ao papel do sistema nervoso simpático (SNS) na fisiopatologia da hipertensão arterial foram feitas. Entre elas, incluem-se a ativação simpática no desenvolvimento da hipertensão arterial (HA) não apenas nos estágios iniciais da doença, mas na sua manutenção e agravamento com o surgimento de lesões de órgão alvo (LOA) tais como hipertrofia ventricular esquerda (HVE), disfunção diastólica do ventrículo esquerdo e enrijecimento e remodelamento arteriolares [3-7].

Adicionalmente, foram descobertas fortes associações entre o SNS, as alterações hemodinâmicas (aumento da resistência vascular periférica, diminuição da distensibilidade arterial e redução da perfusão tecidual) e metabólicas (resistência insulínica, obesidade e dislipidemia), frequentemente encontradas no paciente hipertenso [8-13].

Logo, diante do acúmulo de evidências do comportamento da atividade simpática na doença hipertensiva associada a várias outras condições mórbidas como insuficiência cardíaca, obesidade e síndrome metabólica, o conceito de "reforço neuroadrenérgico" surgiu na literatura científica [1-2]. Este conceito visa demonstrar que a hiperativação simpática prepondera na doença hipertensiva com complicações clínicas [1-2], correlacionando-se positivamente com a gravidade da HA [14], estando ainda envolvida no efeito do avental branco (EAB) [15-16].

O EAB é definido como uma elevação persistente e clinicamente importante da PA medida no ambiente médico, quando comparado a outros métodos de medida de PA fora do mesmo, como monitoração ambulatorial da pressão arterial (MAPA) [17]. A MAPA possui algumas vantagens, entre outras, de atenuar o efeito do observador e do ambiente sobre a pressão arterial [18]. Teorias têm sido propostas sugerindo que o fenômeno do avental branco está significativamente relacionado à hiper-reatividade emocional por parte do sujeito ao ser examinado em ambiente médico [19]. Assim, o EAB pode estar relacionado a uma reação de alerta mediada pelo SNS, a qual se associa maior variabilidade da PA e diminuição da variabilidade da frequência cardíaca (VFC) [20].

A VFC pode ser usada para avaliação dos distúrbios autônomos, sendo inclusive um bom marcador prognóstico de mortalidade [21]. Assim, as medidas da VFC nos domínios do tempo e da frequência têm sido utilizadas com sucesso para avaliação do tônus simpático e parassimpático [22]. Embora haja ainda diferenças nos valores de referência da VFC entre diversos estudos, há consenso de que menores valores destes índices referentes à função vagal estão associados, prospectivamente, à morte e incapacidade física [23]. A atividade parassimpática e a VFC estão associadas à disfunção imunológica e inflamação que estão, direta ou indiretamente, relacionadas à grande gama de doenças cardiovasculares e ao diabetes [24-25].

Diante da forte associação entre a atividade do sistema nervoso autônomo (SNA), órgão alvo e o EAB na hipertensão resistente (HAR), os estudos que se seguem como capítulos desta tese de doutorado (modelo alternativo) visam à identificação da associação entre EAB e disfunção do SNA, e suas possíveis consequências em LOA na HAR.

1.2 Hipertensão arterial resistente

Apesar da grande disponibilidade de fármacos efetivos para o tratamento da hipertensão arterial, o relatório do National Health Nutrition Education Survey revelou que somente 34% da população americana de adultos hipertensos têm a pressão controlada (<140/90 mmHg), o restante não atinge as metas recomendadas pelo consenso [26-27]. Embora a baixa adesão [28] e/ou regimes de tratamento inadequados, medidas incorretas da PA e outras causas de pseudo-hipertensão possam explicar em parte esse insucesso no controle da PA, há um percentual ainda significativo de pacientes que, mesmo excluídos esses fatores, apresentam real resistência ao tratamento anti-hipertensivo, sendo considerados hipertensos resistentes. Por definição, segundo a *American Heart Association,* a HAR é aquela em que os níveis de PA mantêm-se acima da meta pressórica mesmo com o uso de três classes diferentes de anti-hipertensivos em uma combinação racional de doses máximas, sendo um deles um diurético. Ainda, os pacientes que estão com a PA controlada, mas que necessitam de quatro ou mais anti-hipertensivos também foram incluídos como resistentes ao tratamento nessa diretriz [29].

Apesar da prevalência exata da HAR não ser determinada, evidências indiretas de estudos populacionais e clínicos sugerem que este é um problema clínico relativamente comum. Por exemplo, somente 48 % do total de pacientes tratados, participantes do *Framingham Heart Study*, e menos de 40 % dos pacientes idosos estavam com a pressão controlada [30]. Em outro exemplo, somente 66 % dos pacientes de alto risco do estudo *Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)* atingiram as metas pressóricas de < 140/90 mmHg [31]. Estudos menores mostram uma prevalência para a HAR de 5% na prática clínica geral a 50 % em clínicas de nefrologia

[32]. Em resumo, a prevalência de HAR varia de acordo com a população estudada e as ferramentas diagnósticas e terapêuticas utilizadas.

De acordo com as diretrizes da *American Heart Association* para HAR [33], baseando-se em dados demográficos e resultados dos estudos de Framingham e ALLHAT, os maiores preditores de ausência de controle pressórico são a idade avançada, pressão arterial demasiadamente elevada na avaliação inicial, obesidade, excesso de ingestão de sódio, diabetes *mellitus* (DM) e doença renal crônica (DRC). O envelhecimento e sua interface com a ativação do SNS estão bem documentados [34-38]. Vários estudos demonstraram que a atividade nervosa simpática está diminuída com o envelhecimento e alguns índices de atividade simpática, especialmente a atividade simpática muscular, estão mais relacionadas à pressão arterial nas idades avançadas [34, 39].

Além do envelhecimento, obesidade, excesso de aldosterona, DM e apneia obstrutiva do sono (AOS) cobrem uma grande área do mosaico de características dos pacientes hipertensos resistentes [33, 40]. Em coortes com pacientes com HAR, a média do índice de massa corporal (IMC) foi maior do que 32 kg/m², a prevalência de hiperaldosteronismo foi de aproximadamente 20% e os casos de AOS diagnosticados ou suspeitos foram de alta prevalência [41-42]. Ademais, entre os pacientes com HAR, o hiperaldosteronismo foi mais prevalente nos pacientes com diagnóstico de AOS confirmado do que nos pacientes com baixo risco desta comorbidade. Os dados existentes reforçam que a AOS, o excesso de aldosterona e a obesidade são comorbidades frequentes nos pacientes hipertensos resistentes e influenciam a atividade simpática (Figura 1).

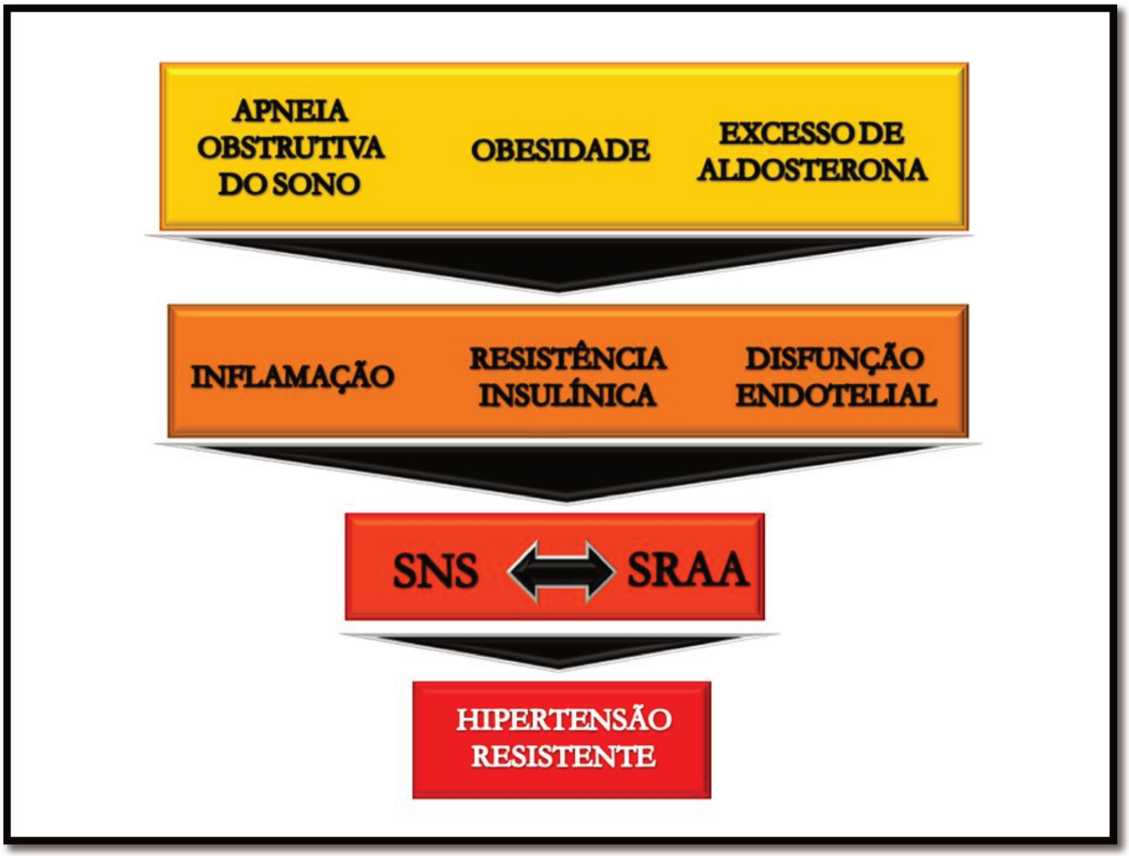

Figura 1. Fisiopatologia da HAR relacionada à hiperatividade simpática (Modificado de Tsioufis, Kordalis ET al.) [40]. Condições como AOS, obesidade e excesso de aldosterona são fatores desencadeantes de inflamação, resistência insulínica e disfunção endotelial. Como consequência, há hiperativação do SNS e sistema renina angiotensina aldosterona (SRAA) que possuem, por suas vezes, a propriedade de hiperativação recíproca podendo incorrer em HAR.

O prognóstico dos pacientes com HAR comparado aos pacientes com HA de mais fácil controle não foi avaliado profundamente até o momento. Presumivelmente, o prognóstico é menos favorável, visto que estes pacientes possuem um histórico prolongado de HA não controlada somada a outros fatores de risco cardiovascular como diabetes, AOS, hipertrofia do ventrículo esquerdo e doença renal crônica. O grau de redução dos riscos cardiovasculares ao tratamento da HAR também é desconhecido [33].

A estratégia terapêutica na HAR visa bloquear todos os mecanismos possíveis para a elevação da pressão arterial. A terapia combinada com diurético permanece como “pedra

angular" do tratamento atual [40]. Ademais, há consenso de que o tratamento da HAR necessitará da administração de três ou mais fármacos [43].

Estudos clínicos têm sugerido que a adição de espironolactona ou eplerenone aos regimes terapêuticos de pacientes hipertensos resistentes proporciona reduções pressóricas significativas [33, 43-44]. Também é digno de nota que as reduções pressóricas foram similares em pacientes com e sem hiperaldosteronismo primário e que não foram preditas pelos níveis basais plasmáticos ou urinários (24 horas) da aldosterona, atividade plasmática de renina ou relação aldosterona/renina [45].

Com relação às opções terapêuticas para a hiperatividade do SNS, além do bloqueio periférico dos receptores adrenérgicos com o uso de alfa e beta-bloqueadores, faz-se necessário mencionar as emergentes evidências da atividade simpatoinibitória dos antagonistas dos receptores de angiotensina II (ARAII) e mineralocorticóide [46-48].

Agentes de ação central são efetivos como anti-hipertensivos na HAR, mas possuem alta incidência de eventos adversos e falta de evidências de desfecho cardiovascular primário [33]. Entretanto, resultados promissores têm sido alcançados com recentes estudos intervencionistas de inibição simpática através da ativação de barorreceptores carotídeos com estímulos elétricos [49] e desnervação simpática renal seletiva [50].

A resistência à terapia anti-hipertensiva é usualmente multifatorial [51], porém, pseudo-resistência, fatores contribuintes e hipertensão secundária são fatores que têm um papel importante na caracterização da HAR (Quadro 1).

Quadro 1. Fatores que contribuem para caracterização da hipertensão arterial resistente

Pseudo-resistência • Fenômeno do avental branco • Mensuração inadequada da PA • Falta de adesão ao tratamento • Inércia terapêutica
Fatores contribuintes • Expansão volêmica Ingestão excessiva de sódio Retenção hídrica causada por doença renal crônica Terapia diurética inadequada • Obesidade/resistência insulínica • Substancias exógenas Anti-inflamatórios não-hormonais Anticoncepcionais orais Álcool Corticosteroides Esteroides anabólicos Agentes simpatomiméticos Cafeína Ciclosporina Eritropoetina Agentes quimioterápicos Antidepressivos
Causas secundárias de HA • Hiperaldosteronismo • Apneia obstrutiva do sono • Doença renal cônica • Estenose de artéria renal • Feocromocitoma • Coarctação da aorta • Doenças da tireoide

Adaptado do Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [26].

1.2.1 Causas de pseudo-resistência

Pseudo-resistência é a aparente falta de controle pressórico causada por verificação incorreta da pressão arterial, escolha de doses e medicamentos inapropriados, não adesão à

terapia prescrita ou fenômeno do avental branco [52], e costuma ser erroneamente diagnosticada como HAR.

1.2.1.1 Adesão ao tratamento

A adesão ao tratamento pode ser caracterizada pelo grau de coincidência entre a prescrição médica e o comportamento do paciente. O controle inadequado da pressão arterial, fato frequentemente observado, pode estar relacionado à falta de adesão do paciente ao tratamento [53]. Pesquisadores consideram que a adesão pode ser caracterizada como a extensão em que o comportamento do indivíduo, em termos de tomar o medicamento, seguir a dieta recomendada, realizar mudanças no estilo de vida e comparecer às consultas médicas, coincide com o conselho médico ou de saúde [54]. A não adesão ao tratamento é uma das maiores dificuldades no controle da hipertensão arterial. Algumas medidas simples podem ser utilizadas na avaliação da adesão, como a contagem de comprimidos e os auto-relatos. É necessário otimizar a adesão ao tratamento, utilizando-se anti-hipertensivos com o menor efeito colateral possível, terapia combinada de baixa dose, diminuindo o número de tomadas diárias, controlando precocemente a pressão arterial, evitando a polifarmácia, diminuindo o custo do tratamento e educando o paciente a respeito de sua doença e de seu tratamento [55]. Cabe ressaltar que a má adesão é subestimada e subdiagnosticada [56].

1.2.1.2 Inércia terapêutica

A "inércia terapêutica" é a não capacidade do médico assistente em agir para o alcance das metas pressóricas propostas, contribuindo para as altas prevalências de hipertensão não controlada, devido a não prescrição correta de fármacos em doses individualizadas ou a não prescrição de novas classes e medicamentos, sendo que o mesmo percebe a necessidade para realizar tais modificações, mas não as modifica, geralmente por insegurança [57]. A presença de comorbidades pode influenciar a conduta terapêutica do médico quanto à hipertensão arterial [58]. Alguns pacientes são especialmente suscetíveis a determinados medicamentos, manifestando efeitos colaterais que levam à intolerância ao fármaco e abandono do tratamento, sendo eventualmente rotulados como HAR.

1.2.1.3 Fenômeno do avental branco

A elevação da pressão arterial em ambiente médico é chamada de fenômeno do avental branco e envolve duas situações: **Hipertensão e Efeito do avental branco** [19, 59].

A hipertensão do avental branco (HAB) é um fator comum de pseudo-resistência [60]. Caracterizada por níveis pressóricos elevados em medidas isoladas no consultório (≥ 140 x 90 mmHg) e normais na MAPA realizada durante o período de vigília (≤ 135 x 85 mmHg) [61].

O efeito do avental branco também é caracterizado por pressão arterial medida em consultório elevada em relação à média de pressão de vigília na MAPA, porém, sem haver alteração do diagnóstico, seja de hipertensão ou de normotensão, com prevalência de aproximadamente 27% quando se considera aumento ≥ 20 mmHg na pressão arterial sistólica (PAS) e/ou ≥ 10 mmHg na pressão arterial diastólica (PAD) [61].

Este fenômeno é conhecido desde os primórdios da moderna esfigmomanometria. Scipione Riva-Rocci já alertava sobre essa possibilidade: "O estado mental do paciente tem um efeito transitório, mas considerável na pressão sanguínea. Falar com o paciente, convidá-lo a ler ou olhar de repente para ele, assim como um barulho repentino, faz a pressão subir". E acrescentava: "Quando o paciente estiver acomodado da melhor maneira possível (sentado ou no leito), em repouso e absolutamente calmo, pois mesmo as mais leves emoções podem causar apreciáveis modificações no nível da pressão arterial, é o melhor momento para a medida" [62].

O efeito do avental branco ocorre, quando os valores de pressão arterial medidos pelo profissional de saúde no consultório são significativamente elevados comparados com os valores obtidos em outros locais como, por exemplo, por MAPA ou monitoração residencial da pressão arterial (MRPA). A prevalência do efeito do avental branco varia de 20% a 40% entre a população geral de pacientes hipertensos e pode ser ainda maior na HAR [63]. A ocorrência do EAB é mais comum em mulheres e idosos. Estudos prospectivos não têm definido a história natural ou morbi-mortalidade associadas à hipertensão do avental branco não-tratada, mas estudos secionais cruzados [64] sugerem que, quando comparados com indivíduos normotensos, os pacientes com hipertensão do avental branco têm maior hipertrofia ventricular, índices mais altos de colesterol de lipoproteína de baixa densidade (LDLc) e maior rigidez arterial, podendo ser considerados potencialmente de maior risco cardiovascular. Da mesma forma, como na população hipertensa em geral, os pacientes com HAR que apresentam o fenômeno do "avental branco" manifestam dano em órgãos alvo menos severo, e parecem ter menor risco cardiovascular comparados com aqueles pacientes com hipertensão persistente durante a MAPA [29].

A hipertensão do avental branco deve ser suspeitada em pacientes que permanecem resistentes ao tratamento na ausência de lesões de órgão alvo, que manifestam sintomas de supermedicação e/ou que relatam valores de pressão arterial domiciliares significativamente mais baixos que os valores medidos no consultório. Como essa entidade é relativamente comum, todos os pacientes com hipertensão devem ser encorajados a medir a sua pressão em casa ou fora do ambiente hospitalar em condições adequadas. Nessa situação, a MAPA de 24 horas e a MRPA são úteis em estabelecer o diagnóstico. Embora as diferentes diretrizes de tratamento não tenham definido a conduta mais adequada para esses pacientes, um seguimento cuidadoso associado a modificações do estilo de vida é recomendado. Em casos particulares, principalmente na presença de lesão de órgãos alvo, o tratamento farmacológico é recomendado [65].

O diagnóstico da verdadeira hipertensão resistente/hipertensão do avental branco é importante porque evita tratamento, efeitos adversos e custos desnecessários, e também, em algumas vezes, investigação invasiva para hipertensão secundária. Portanto, recomenda-se que todos os pacientes suspeitos de hipertensão resistente devam ser submetidos a MAPA [51]. Infelizmente, em muitos países como o Brasil, os recursos em cuidados de saúde são limitados e a MAPA ou MRPA não estão disponíveis para todos os pacientes. Portanto, o médico frequentemente necessita decidir no consultório o início da investigação diagnóstica sem a utilização da MAPA [66].

Teorias têm sido propostas sugerindo que o efeito do avental branco está significativamente relacionado à hiper-reatividade emocional por parte do paciente ao ser examinado em ambiente médico [19]. Assim, o EAB pode estar relacionado a uma reação de alerta mediada pelo SNS, a qual se associa maior variabilidade da PA e da FC [20].

1.3 Modulação do sistema nervoso autônomo

O SNA, através das divisões simpáticas e parassimpáticas, modula diversas funções do sistema cardiovascular [67]. Tanto o SNS quanto o sistema nervoso parassimpático (SNP) estão continuamente ativos. A intensidade de ativação destes sistemas pode aumentar ou diminuir por ação do sistema nervoso central, de acordo com as necessidades momentâneas do organismo [68].

O balanço simpato-vagal é modulado pela interação de pelo menos três principais fatores: interação neural central, mecanismos reflexos inibitórios e, mecanismos reflexos excitatórios [68]. A FC depende de pulsos intrínsecos do nodo sinusal e da integração entre os SNS e SNP. A noradrenalina (NA) é o neutransmissor liberado pelo ramo simpático, denominado via adrenérgica, enquanto a acetilcolina é liberada pelo ramo parassimpático, denominado via colinérgica [67].

A VFC é amplamente dependente da modulação vagal devido à velocidade de dissipação do neutransmissor no nodo sinusal. O nodo sinusal é rico em acetilcolinesterase, a qual rapidamente hidrolisa a acetilcolina, tornando, portanto, o efeito de qualquer impulso vagal breve [23].

Dessa desigualdade entre as velocidades de transmissão nas vias adrenérgicas e colinérgicas resultam diferenças na frequência de modulação destes dois sistemas no nodo sinusal. O efeito resultante dessas influências autonômicas é a variabilidade batimento a batimento, da frequência cardíaca, instantaneamente [69]. A VFC é determinada por variações do SNA sobre o nodo sinusal [70]. Vários mecanismos atuam nessa variação, incluindo os centros cerebrais, reflexos barorreceptores e a respiração [71].

1.4 A avaliação do sistema nervoso autônomo em pacientes hipertensos

Os métodos clínicos para avaliação regional da função do SNS em pacientes hipertensos são três: a eletrofisiologia (utilizando-se a microneurografia), a neuroquímica (utilizando-se a dosagem da diluição plasmática de isótopos de noradrenalina em veias de órgãos específicos como o coração e o rim) e a utilização da eletrocardiografia ambulatorial, para análise da variabilidade do sinal elétrico, batimento a batimento, para avaliação da VFC [2] (Figura 2).

A microneurografia é uma técnica que permite o estudo dos disparos nervosos em fibras simpáticas subcutâneas distribuídas na pele e no músculo esquelético. A técnica envolve a inserção de eletrodos de tungstênio posicionando-os sobre as fibras simpáticas, mais comumente, os nervos fibular ou mediano. Registros na forma de *bursts* da atividade nervosa autonômica, sincronizados com os batimentos cardíacos, são gerados [72].

A dosagem das taxas de NA liberada pode ser avaliada clinicamente utilizando-se medidas radioisotópicas de noradrenalina plasmática nos órgãos dos indivíduos. Como os métodos microneurográficos são incapazes de avaliarem a atividade dos nervos simpáticos dos órgãos internos, a dosagem de NA orgânica regional pode ser utilizada. Através da infusão de NA tritiada e as dosagens locais do plasma do seio coronário e das veias renais, é possível estimar o grau de liberação do neurotransmissor no coração e nos rins [73-75].

Embora a investigação clínica tenha aumentado o nosso conhecimento sobre a função do SNS e seu envolvimento na fisiopatologia de várias doenças cardiovasculares, incluindo a HA, não há nenhuma recomendação para a estimativa da atividade adrenérgica na HAR. Apesar das avaliações da função adrenérgica feitas com a microneurografia da atividade simpática muscular e as medidas de NA plasmática em órgãos específicos terem

sido realizadas em estudos clínicos, nenhuma técnica pode ser classificada como "padrão ouro" e as metodologias descritas acima são basicamente utilizadas como ferramentas de investigação clínica para estudos científicos [76]. A frequência cardíaca em repouso e ao estímulo são reguladas não apenas pelo sistema nervoso simpático, mas pelo SNP, que é também dependente dos receptores cardíacos adrenérgicos. Ademais, a modulação autonômica em repouso na posição supina denota limitada correlação com outros índices da atividade simpática como a NA plasmática e atividade simpática muscular [77]. Com relação à excreção urinária de catecolaminas em 24 horas, a inabilidade de avaliação dinâmica da atividade do SNS e a dificuldade de se determinar se a origem das catecolaminas é sistêmica ou renal são dignas de nota [78]. Especificamente com relação aos níveis de NA plasmática, constituem-se limitações substancias à análise e interpretação dos dados a sua baixa reprodutibilidade, baixa sensibilidade e a incapacidade de discriminação se os níveis de NA são decorrentes do aumento da secreção ou diminuição do *clearance* dos níveis elevados de neurotransmissores circulantes [76, 79].

A análise do poder espectral da frequência cardíaca é comumente aplicada como alternativa não-invasiva do estudo da atividade simpática do coração [80-81]. O ramo simpático do sistema nervoso aumenta a frequência cardíaca, implicando em intervalos mais curtos entre batimentos. Por sua vez, o ramo parassimpático desacelera o ritmo cardíaco, resultando em intervalos maiores entre os batimentos. Assim, a variabilidade da frequência cardíaca pode ser medida com base nos intervalos entre batimentos, os quais são mais facilmente calculados como sendo os períodos entre ondas R consecutivas, ou intervalos RR [82]. A VFC pode ser usada para avaliação dos distúrbios autônomos, doenças e mortalidade geral [21]. As medidas da VFC nos domínios do tempo e da frequência têm sido utilizadas com sucesso para avaliação do tônus simpático e

parassimpático [22]. Embora haja ainda diferenças nos valores de referência da VFC em diversos estudos, há consenso de que menores valores destes índices referentes à função vagal estão associados, prospectivamente, à morte e incapacidade [23]. A atividade parassimpática e a VFC estão associadas à disfunção imunológica e inflamação que estão, direta ou indiretamente, relacionadas à grande gama de doenças cardiovasculares e ao diabetes [24-25].

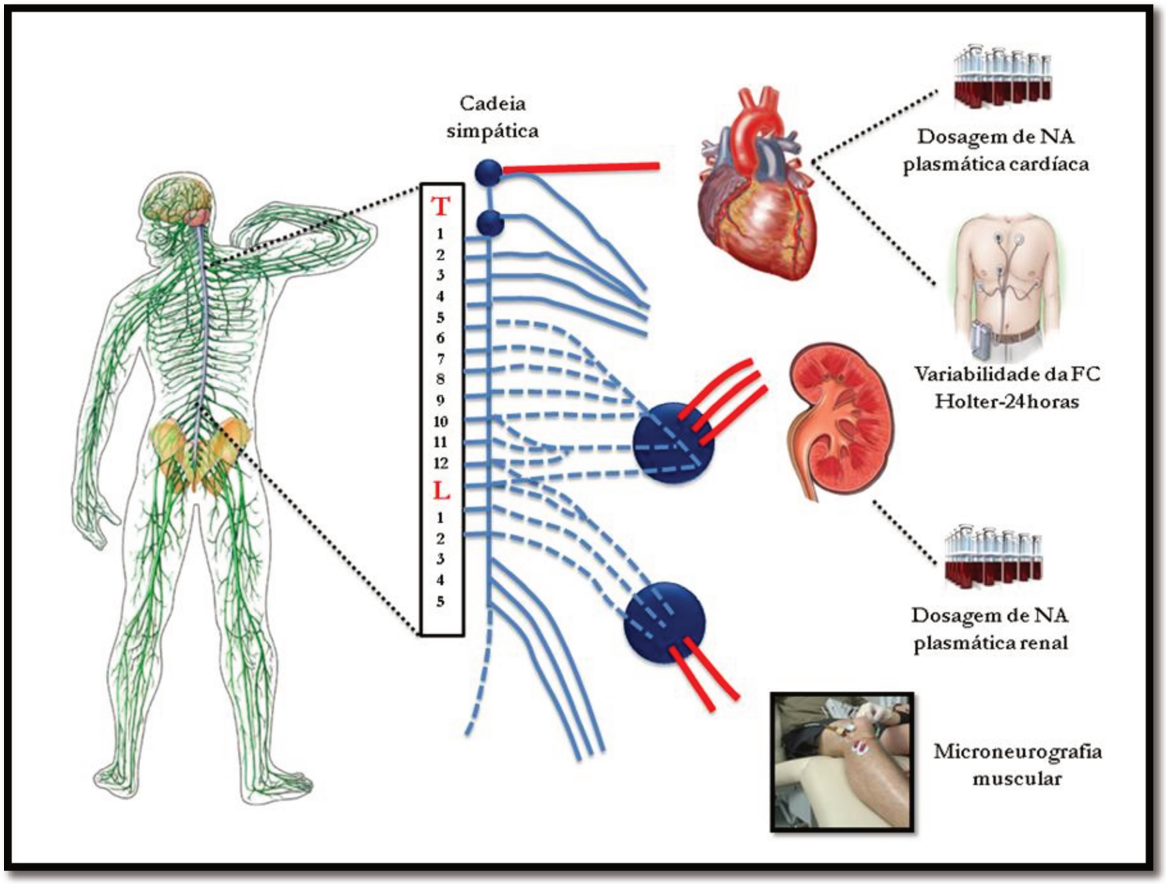

Figura 2. Métodos para avaliação da atividade simpática em pacientes hipertensos (Modificado de Esler) [2]. A dosagem plasmática de noradrenalina em órgãos como o coração e rim, a microneurografia do nervo fibular e a análise da variabilidade da frequência cardíaca pela eletrocardiografia ambulatorial (Sistema Holter) são métodos utilizados para avaliação do sistema nervoso simpático em pacientes hipertensos.

1.5 O ritmo circadiano e o sistema cardiovascular

A atividade do sistema nervoso autônomo não se encontra, porém, dissociada do meio ambiente [83]; a vida no planeta Terra demanda a existência de um relógio biológico sincronizado com os ciclos regulares de nosso planeta no Sistema Solar [83]. O relógio biológico localizado essencialmente no sistema nervoso central no núcleo hipotalâmico supraquiasmático integra-se, por mecanismos ainda não bem compreendidos, com o relógio biológico de cada célula periférica de todo o organismo [84]. Esta adequação não é exclusiva dos seres humanos e o comportamento do relógio biológico de roedores, insetos, plantas, algas, fungos e até mesmo bactérias também está programado para ciclos de 24 horas [85-92].

A fisiologia cardiovascular e a homeostase do organismo estão relacionadas ao ritmo circadiano em ciclos endógenos com duração de aproximadamente 24 horas [93], adaptando-se perfeitamente à média do dia solar [94]. A frequência cardíaca, pressão arterial, função endotelial e a secreção de hormônios relacionados ao metabolismo glicídico e lipídico demonstram variações durante o dia [95].

Entretanto, o estilo de vida ocidental tem sido modificado intensamente nas últimas décadas levando os seres humanos à ruptura do ritmo circadiano por três comportamentos preocupantes: a hiperalimentação, principalmente com alimentos gordurosos, o sedentarismo e o encurtamento do período de sono, principalmente pela disponibilidade de luz artificial e a necessidade de agendamento de atividades laborais e recreativas durante o período noturno [96]. Esses comportamentos são influenciadores epigenéticos conhecidos como zeitgebers -"guardadores do tempo" – que têm a propriedade de promover o reset dos

relógios biológicos podendo levar à dessincronização do ritmo circadiano que é conhecida como "ruptura do ritmo circadiano" [97] (Figura 3).

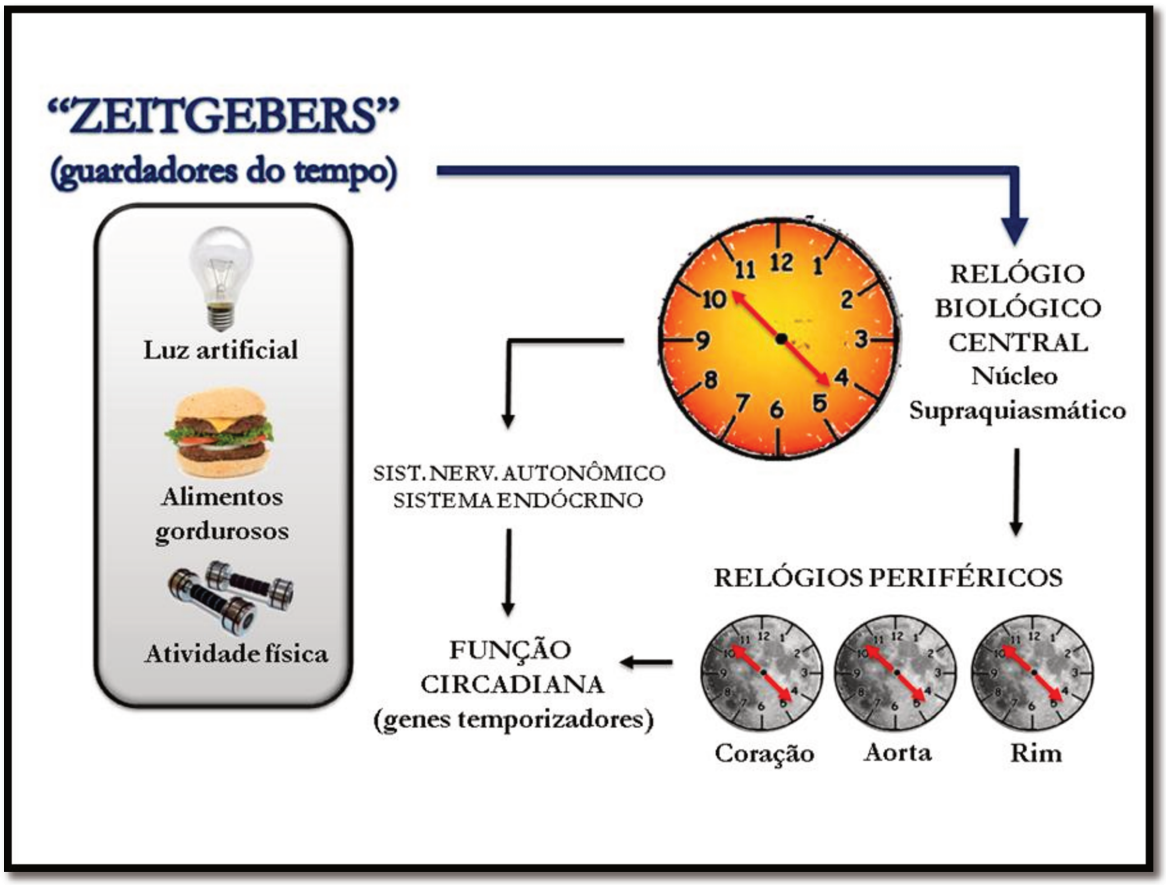

Figura 3. A ruptura do ritmo circadiano (Modificado de Maury, Ramsey ET al.) [84]. Fatores conhecidos como *zeitgebers* (luz artificial, alimentos gordurosos e atividade física) influenciam o relógio biológico central localizado no núcleo supraquiasmático do hipotálamo reprogramando-o (*reset*) para a função diurna. As células periféricas também possuem um relógio biológico que se harmoniza com o relógio biológico central. Quando não há harmonização entre os relógios biológicos (central e periférico), há ruptura do ritmo circadiano.

A ruptura do ritmo circadiano tem consequências fisiopatológicas de curto e longo prazo [84]. Na ocorrência da dessincronização destes ritmos há maior propensão de lesão de órgãos alvo cardiovasculares (Figura 4).

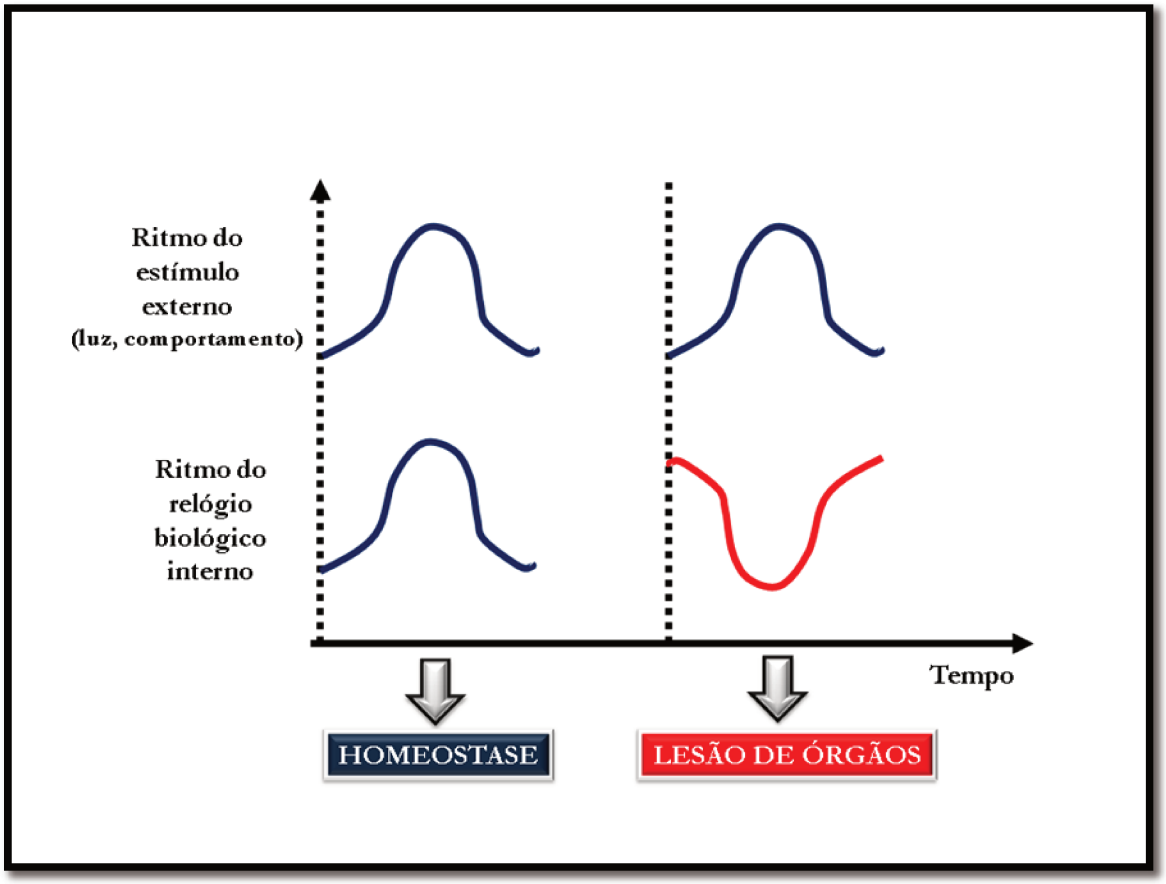

Figura 4. Ruptura do ritmo circadiano e complicações cardiovasculares (Modificado de Maury, Ramsey et al.) [84].

1.6 Lesões de órgãos alvo na hipertensão arterial resistente

Lesões de órgãos alvo, tais como doença renal crônica e hipertrofia ventricular esquerda, reforçam o diagnóstico de hipertensão mal controlada e em caso da DRC irá influenciar o tratamento em termos de classes de fármacos anti-hipertensivos.

1.6.1 Hipertrofia Ventricular Esquerda

A HVE é a resposta cardíaca à sobrecarga pressórica e/ou volumétrica crônica, e sua prevalência e incidência elevam-se de acordo com a progressão de níveis de pressão arterial [98]. Essa adaptação está associada à maior morbidade e mortalidade dos seus portadores. É possível que o mecanismo adaptativo esteja acompanhado de alterações intrínsecas dos miócitos cardíacos ou de outras células miocárdicas, predispondo a um déficit contrátil e instabilidade elétrica do coração. Com relação ao aumento da massa do ventrículo esquerdo, os resultados do Framingham Heart Study demonstraram de forma inequívoca o valor prognóstico da detecção de hipertrofia ventricular esquerda na estratificação de risco para doença cardiovascular, morbidade e mortalidade [99-100]. Estudos epidemiológicos têm implicado HVE como fator de risco para o infarto do miocárdio (IAM), insuficiência cardíaca congestiva (ICC) e morte súbita [101]. Estudo englobando HAR demonstrou maior HVE nos pacientes portadores de resistência aos fármacos anti-hipertensivos em relação aos hipertensos controlados e ao grupo controle de normotensos [102]. Além disso, mais recentemente foi evidenciado que o subgrupo de hipertenso resistente não controlado apresentou maior índice de massa ventricular esquerda comparado aos indivíduos portadores de HARC [103].

1.6.2 Doença renal crônica

Insuficiência renal crônica é uma causa comum de HAR e uma consequência de inadequado controle da PA. Retenção de líquido, ativação excessiva do SRAA e uso de medicamentos concomitantes, tais como AINEs, estão relacionados à resistência do tratamento em pacientes com insuficiência renal. Todos os pacientes com HAR devem ter

seu *clearance* de creatinina avaliado, principalmente em idosos, seja por dosagem em urina de 24h ou através da creatinina plasmática, utilizando-se a fórmula de Crockroft-Gault, que leva em consideração a idade, o sexo e o peso, apresentada a seguir [104]. Em mulheres, o resultado deve ser multiplicado por 0.85, que corrige para a menor massa muscular no sexo feminino.

Albuminúria e proteinúria devem ser avaliadas. A detecção da microalbuminúria (MA) é uma importante ferramenta na identificação de pessoas que apresentam um risco elevado para eventos cardiovasculares, progressão de doença renal e indivíduos que necessitam de uma terapia mais agressiva comparada com indivíduos com uma taxa de excreção de albumina normal [105]. A MA tem sido tradicionalmente definida como excreção de albumina urinária (UAE – urinary albumin excretion) de 20 a 200 μg/min, correspondendo a 30 a 300 mg/24h ou alternativamente, pela relação albumina / creatinina (ACR - Albumin Creatinine Ratio) de 30 a 300 μg/mg (10–25 mg/mmol) [106]. Não obstante, a presença de microalbuminúria em pessoas com hipertensão essencial é um fator de risco independente para falência orgânica e insuficiência renal [107-108]. O bloqueio do SRAA em pacientes com DRC reduz o risco cardiovascular, melhora o controle da PA, reduz proteinúria e progressão para doença renal em estágio final [109].

O EAB não implica em aumento de risco cardiovascular para hipertensos de forma geral [110], havendo inclusive estudos que o associam a menores taxas de risco de mortalidade para todas as causas [111]. Entretanto, é desconhecido se pacientes com HAR que apresentam efeito do avental branco têm mais lesões em órgãos alvo quando comparados com indivíduos portadores de HAR que não manifestam tal fenômeno.

2.OBJETIVOS

2.1 Subestudo 1

Avaliar se a presença de efeito do avental branco associa-se a maior proporção (adicional) de lesões de órgão alvo em hipertensos resistentes.

2.2 Subestudo 2

O objetivo primário do segundo estudo foi avaliar se a disfunção do SNA, quantificada através da variabilidade da frequência cardíaca, correlaciona-se com o efeito do avental branco.

O objetivo secundário do segundo estudo foi avaliar se o risco para apneia obstrutiva do sono e qualidade do mesmo está associado ao efeito do avental branco.

3.CONCLUSÕES

3.1 Subestudo 1

1. Demonstramos que nesta amostra de pacientes com HAR, o efeito do avental branco não se associou a maior proporção de lesões em órgãos alvo (quando avaliados rins e coração).

(Trabalho submetido à revista ***Medicina Clinica***)

3.2 Subestudo 2

1. Observamos maior atividade simpática durante a noite em pacientes hipertensos resistentes com efeito do avental branco em comparação aos que não apresentaram esse efeito.
2. Não observamos associação associação entre presença do EAB e maior frequência de distúrbios do sono.

(Trabalho submetido à revista ***Arquivos Brasileiros de Cardiologia***)

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CAPÍTULO I

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PROF. DR. M. VILARDELL

EDITOR-IN-CHIEF

MEDICINA CLINICA

Dear Professor M. Vilardell

Please find enclosed our original manuscript "**White coat effect is not associated with additional increase of target organ damage in true resistant hypertension**". The paper hereby submitted follows some important publications of our group in resistant hypertension and we would like to publish it in the **MEDICINA CLINICA** due its relevance this syndrome.

This manuscript is original and is not under consideration by any other journal.

All authors have approved the submission of the present study in this journal and there are no financial or other relationships that might lead to a conflict of interest.

Yours sincerely,

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White coat effect is not associated with additional increase of target organ damage in true resistant hypertension

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ABSTRACT

The revised definition of resistant hypertension (RHTN) 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. White coat effect (WCE) (i.e., the difference between office blood pressure [OBP] and awake ambulatory blood pressure monitoring [ABPM]) may be present in hypertensive individuals. The relationship between occurrence of WCE and target organ damage (TOD) has not yet been assessed in true RHTN. RHTN patients were identified with WCE (WCE) (66) and without WCE (non-WCE) (61). Office BP were 169.8 ± 15.8 / 95.1 ± 14.0 (WCE) and 161.9 ± 9.0 / 90.1 ±10.4 mmHg (non-WCE), ABPM = 143.0 ± 12.8 / 86.1 ± 9.9 (WCE) and 146.1 ± 13.6 / 85.1 ± 14.9 mmHg (non-WCE). No statistical differences were observed between WCE and non-WCE subgroups with respect to left ventricular mass index (WCE= 131 ± 4.7; non-WCE= 125 ± 2.9 g/m^2), creatinine clearance (WCE = 78 ± 4.7; non-WCE= 80 ± 3.6 ml/min/m^2) and microalbuminuria (WCE= 44 ± 8.4; non-WCE= 49 ± 6.8 mg/g Cr). This finding may suggest that WCE is not associated with additional increase of TOD in true RHTN subjects.

Keywords: resistant hypertension, white coat effect, left ventricular hypertrophy, renal dysfunction.

INTRODUCTION

Resistant hypertension (RHTN) is defined as being present when a therapeutic plan, including attention to lifestyle modification and the prescription of at least three antihypertensive agents of different classes in adequate doses, fails to lower systolic blood pressure (SBP) and diastolic blood pressure (DBP) sufficiently [1]. In addition, patients whose blood pressure (BP) is controlled but who require four or more medications to reach the goal (of which is BP < 140 / 90 mmHg) should be considered resistant to treatment [1]. Ambulatory blood pressure monitoring (ABPM) is one of the valid methods to differentiate "isolated office resistant hypertension" (or pseudo-resistant hypertension) from "true resistant hypertension", providing higher prognostic value than office BP measurements in the evaluation of subjects with resistant hypertension [2-6].

The BP measurement at the physician's office can lead to a high office BP when compared with other out-of-clinic measurements, such as ABPM in hypertensive patients [7]. This is known as the 'white coat effect' (WCE) [8-9]; some theories have been put forward suggesting that it is significantly related to mental stress [10], emotional hyperresponsiveness or hyperreactive response on the part of the patient while being examined by the physician [11-12]. Thus, WCE may be related to an alerting reaction mediated by the sympathetic nervous system that is associated with greater variability in BP [10]. Moreover, sustained hypertension is associated with sympathetic predominance or decrease in parasympathetic activity, which has an influence on heart rate as well as BP [13-14]. Some authors have found that WCE does not entail increased cardiovascular (CV) risk [15] to hypertensive subjects, being associated with decreased hazard ratios for all-cause mortality [16].

The prognostic significance of WCE in RHTN patients is unclear [17]. It is known that pseudo RHTN patients with manifesting WCE have less severe target organ damage (TOD) when compared to those with true RHTN during ambulatory monitoring [6], meaning that the latter have a poorer prognosis than the former. However, no study has evaluated the influence of WCE on TOD in true RHTN. The aim of the present study was to assess whether WCE is associated with TOD in true RHTN.

METHODS

Patient population

We evaluated patients referred to the Resistant Hypertension Service of the University of Campinas for difficult-to-control hypertension. All individuals completed a medical history questionnaire and were submitted to physical examinations,

electrocardiography and laboratory tests. Patients with secondary forms of hypertension, liver disease, coronary heart disease, strokes, peripheral vascular disease or any other major diseases, as well as smoking patients, were excluded. Patients were evaluated concerning adherence to treatment [18-20] and underwent clinical optimization of antihypertensive therapy [21]. Daytime ABPM (Spacelabs 90207, Spacelabs Inc, Redmon, WA, USA) is an auxiliary method to characterize RHTN and in our study it was used to exclude causes of pseudoresistance, including white coat hypertension. After a 6-month period (five to six visits), 127 patients were identified with "true" RHTN and included in the study. They were divided into two groups: with WCE (WCE, n=66) and without WCE (non-WCE, n=61). This study was approved by the Research Ethics Committee of the University of Campinas, São Paulo, Brazil and written informed consent was obtained from each patient before study participation.

Study design

Nonpharmacologic therapies were optimized, including dietary salt control, which were confirmed by the measurement of urinary sodium excretion (< 100 mEq/24h). All patients were submitted to office BP measurement, ABPM, echocardiography and renal function evaluation in three visits. WCE was defined as measurement of systolic blood pressure (BP) >20mmHg and/or diastolic BP >10mmHg, in the physician's office, in comparison with daytime ABPM [8].

Measurements

Office blood pressure

With the patients in a seated position with the arm comfortably placed at heart level, BP level after resting for 5 min and office BP level were obtained according to American Heart Association [21]. Office BP was measured three times from each patient using a digital BP monitor (HEM-907 XL Omron) [22]. We used the mean value of the two last measurements as the final office blood pressure level.

Ambulatory blood pressure monitoring

All participants underwent 24-hour ABPM on a usual working day. They were instructed to act and work normally [23]. The Spacelabs 90207 ambulatory blood pressure monitor (Spacelabs Inc, Redmon, WA) was used[24]. The appropriate size cuff was placed around the nondominant arm. 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. Ambulatory blood pressure parameters included mean daytime systolic and diastolic blood pressures. All participants were instructed to

write the sleep period in a personal diary. Also, white coat hypertension was extensively excluded as cause of pseudoresistance by ABPM, allowing that only "true" RHTN patients were included in this study.

Echocardiography

Measurements of left ventricle (LV) dimensions were performed according to the American Society of Echocardiography (ASE) recommendations [25], using a two-dimensional targeted M-mode echocardiography. LV mass was calculated by the recommended ASE formula [26]. LV mass index (LVMI) was calculated dividing the LV mass by the body surface. Left ventricle hypertrophy (LVH) was defined as left ventricle mass index > 115 g/m² for men and > 95 g/ m² for women. Echocardiography measurements were evaluated by two blinded investigators.

Laboratory assessment

Baseline blood samples for measurement of glycemia (mg/dL), total cholesterol (mg/dL), LDL cholesterol (mg/dL), triglycerides (mg/dL) and creatinine (mg/dL) were collected at 8 a.m. after overnight fasting, during which time individuals rested in the supine position for eight hours, followed by one hour in an upright position in an air-conditioned room (22-24ºC). Urinary sodium (mEq/24h), creatinine clearance (mL/min/1,73m^2) and microalbuminuria (MA) (mg/g Cr) rate were evaluated in 24-hour sterile urine. The glomerular filtration rate was also calculated through the Cockroft-Gault formula (140-age x weight/creatinine x 72 for men and for women, multiplied by the correction factor of 0.85). The U-Alb level was measured as the albumin to creatinine excretion ratio (mg/g Cr) in the urine. Microalbuminuria was defined as U-Alb level between 30 and 300 mg/g Cr.

Statistical analysis

The Statistical Analysis System, version 8.02 (SAS Institute Inc., Cary, NC, USA), was used for all statistical analyses. The statistical analysis was performed descriptively and interpreted in an explorative way. Significant differences between the study subgroups were determined using the Student t test. A value of $P < 0.05$ indicated significance. Sample size was calculated to fit statistical power of 0.80 and two-tailed significance level of 0.05 for all studied variables. All values are expressed as mean ± SD (standard deviation).

RESULTS

The general characteristics of the two RHTN subgroups are listed in table 1. No differences were observed between the WCE and non-WCE groups regarding age, body

mass index or gender. The mean ages were 55.0 ± 9.1 and 57.9 ± 10.5 years in WCE and non-WCE patients (p>0.05). Women represented 64.1 and 69.2% of the patients in these groups, respectively.

As shown in table 1, both subgroups registered similar values in office systolic BP (169.8 ± 15.8 *vs.* 161.9 ± 9.0 mmHg) and diastolic BP (95.1 ± 14.0 *vs.* 90.1 ± 10.4 mmHg; p>0.05 in WCE and non-WCE groups, respectively). The BP delta values (i.e., difference between physician's office and daytime ABPM) registered were 28 ± 4 vs. 16 ± 3 mmHg for SBP and 16 ± 5 vs. 7 ± 2 mmHg for DBP in WCE and non-WCE groups, respectively.

WCE patients received more anti-hypertensive drugs than non-WCE (5.2 ± 0.3 *vs*. 4.1 ± 0.2, respectively) (Table 2).

Left ventricular hypertrophy (LVH) was present in 75% of RHTN, with no significant differences between WCE and non-WCE groups. Left ventricular mass index (LVMI) was similar in both groups (131.7 ± 4.7g/m^2 and 125.9 ± 2.9 g/m^2 in WCE and non-WCE patients, respectively (p>0.05) (Fig. 1).

Renal function measured by creatinine clearance was similar in both groups (78.5 ± 4.7 and 80.6 ± 3.6 ml min 1.73m^{-2} in WCE and non-WCE patients, respectively) (Table 1), as well as microalbuminuria levels, i.e. 44.6 ± 8.4 mg/g Cr and 49.8 ± 6.8 mg/g Cr in WCE and non-WCE patients, respectively (p>0.05) (Fig. 2).

DISCUSSION

In the present study, we compared left ventricular hypertrophy and renal dysfunction in two true RHTN subgroups: those with and without white coat effect. The main finding of this study is that TOD, evaluated by left ventricular hypertrophy, creatinine clearance and microalbuminuria, were similar.

WCE is an alerting reaction caused by the visit to the physician's office, being frequently observed [27] in hypertensive subjects undergoing ABPM and HBPM. In the present study, we found a higher prevalence of WCE in RHTN individuals (52%) in comparison with other authors (20 to 30%) [5]. This difference may be due to the stricter inclusion criteria for RHTN used in our study. Most studies define RHTN as office BP >140 / 90 mmHg and 24-h BP <135 / 85 mmHg [1, 5, 28]. Our study group was only comprised of RHTN patients who had both increased daytime ABPM and office BP levels. This observation is important because the proportion of patients with clinical target-organ damage is greater in subjects with true RHTN than in those with white coat resistant hypertension (WCRH) (pseudoresistant hypertension) [29]. The first finding was expected, since it is known that

there is greater variability in systolic than in diastolic hypertension as well as in other grades, and even in normotensive individuals [1], but usually WCE is more common in female patients [6].

Left ventricular hypertrophy, creatinine clearance reduction and microalbuminuria were similar in the two RHTN subgroups. First of all, white coat hypertension should not be confused with white coat effect. White coat effect means the difference between the office and daytime ambulatory blood pressures and occurs in patients with white coat hypertension, as well as in those with treated or untreated sustained hypertension [30].

Several measures of target organ damage, including left ventricular mass and microalbuminuria, have been compared among normotensives, white-coat hypertensives, and sustained hypertensives. In general, target organ damage in white coat hypertension is less than that in sustained hypertension [31], but the white coat effect is not associated with increased target organ involvement [32]. Conversely, Hérnandez del Rey and col. have shown a higher proportion of patients with clinical target organ damage with true resistant hypertension than those with pseudoresistant hypertension (WCRH) [29]. This difference may be explained because we included in this study only RHTN patients characterized by increased BP levels in both ABPM and office BP. Thus, in these truly RHTN subjects, the presence of WCE was not associated with a higher degree of left ventricular hypertrophy or renal damage.

We found that LVH was present in 75% of RHTN, with no significant differences between WCE and non-WCE groups. It is well known that the extent of BP rise seems to be independently associated with left ventricular hypertrophy and left ventricular mass in hypertensive patients [33] and long-term antihypertensive treatment may induce reductions in left ventricular mass index and in the clinic-daytime differences for systolic and diastolic BP; however, no significant relationship between these two parameters was found when tested by multiple regression analysis [34]. This study provided the first longitudinal evidence that clinic-daytime differences in BP have no substantial value in predicting the regression of target organ damage, such as left ventricular hypertrophy, which has prognostic relevance in RHTN [35]. In addition, CV risk is more tightly correlated with out-of-office BP than clinic BP [36] and among patients with RHTN. Twenty-four-hour ABPM is an independent predictor of CV morbidity and mortality, whereas office BP has been found to have no prognostic value [35]. Therefore, based on our own and other authors' findings, the occurrence of WCE is not responsible for higher LVH in RHTN. However, more research needs to be undertaken.

One interesting observation is that all the patients who took part in this study were overweight or grade I obese. Recently, we have demonstrated that body mass index is higher in uncontrolled RHTN subjects than in controlled ones, and also it is associated with greater left ventricular hypertrophy [37]. Hypertensive patients with white coat phenomenon have greater sympathetic activation compared with normotensive subjects [38-40] and hypertensive patients [13]. The development of a particularly resistant form of hypertension in metabolic individuals can be partially attributed to vasoconstriction from increased sympathetic activation. In general, the sympathetic predominance in hypertension is associated with deleterious effects on target organs, predicting the development of cardiovascular complications [41]. Our results reinforce the relevance of obesity and a possible enhanced sympathetic activation in the determination of the increased cardiac mass index in both RHTN subgroups, but they do not seem to be related to the occurrence of WC phenomena, which were not found associated with a higher degree of LVH.

Microalbuminuria is an important marker of TOD in patients with essential hypertension and is associated with higher rates of pressure [42]. Furthermore, other authors showed that blood pressure control appears to be fundamental for reducing microalbuminuria [43]. In our study, urine albumin excretion (UAE) was similar in both RHTN groups, suggesting that the occurrence of WCE did not aggravate microalbuminuria in RHTN, as described by other authors for general hypertension [31-32].

Microalbuminuria correlates with office BP in RHTN[44], as well as it has a significant higher prevalence in patients with true RHTN when comparing with patients with pseudo-resistant hypertension [45]. Furthermore, these authors have shown microalbuminuria and office systolic BP as the only two variables that independently predict the occurrence of true RHTN versus WCE in pseudo-resistant hypertensive patients. RHTN is a common clinical problem in older (>75 years) and obese patients which is associated with an increasing incidence of diabetes and CKD, and the prevalence of resistant hypertension can be expected to increase [46]. We found that both RHTN groups had a normal glomerular filtration rate (which is usually defined as >60 mL/min per 1.73 m^2), and low microalbuminuria probably because these patients were not as old and obese as included in other studies [47-48].

Lack of hypertension control is primarily attributable to systolic hypertension mainly in subjects with renal dysfunction [46]. The WCE subjects did not have a greater renal impairment compared with non-WCE as expected, but other factors such as the higher percentage of pleothropic antihypertensive drugs used by the former

group and lifetime duration of hypertension may be also responsible for this finding (data not available).

The WCE patients had a higher percentage of ACEIs, ARBs and CCBs, which were used by most RHTN patients. This fact should had contributed to explain the similar degree of cardiac remodeling and renal dysfunction. Also, long-term antihypertensive treatment may cause reductions in left ventricular mass index and WCE, but no significant relationship between these parameters was found when tested by multiple regression analysis [34]. We also did not find this association for RHTN subjects as well as between reduced creatinine clearance or microalbuminuria and occurrence of WCE.

Some limitations are important to note. First, this is a cross-sectional study and the potential implications of long-term crossovers between WCE and non-WCE groups do not allow us to extrapolate our results to prognostic outcomes. Second, since diabetes, smoking, dyslipidemia and all pseudo RHTN patients were excluded in order to minimize, as much as possible, any factors that could skew the results, a small number of RHTN patients were enrolled in the study. Finally, the possibility of having significant difference between the measured microalbuminuria of both groups (type II statistical error) cannot be completely discarded since we had a statistical power below the desired value (0.73) for this particular variable analysis.

Although there is no doubt that both office and ambulatory BP still have an important role in the diagnosis and follow-up of RHTN patients and can be used to classify the non-control in patients initially misdiagnosed with RHTN hypertension, we demonstrated that WCE is not associated with additional increase of TOD in true RHTN subjects. This finding suggests that future longitudinal studies need to be carried out to prove whether there is an incremental deleterious effect of WCE in TOD and which pathogenesis is involved in this effect in patients with true RHTN.

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Competing interests

Leandro Boer-Martins is an employee of Novartis Biociências S.A. (Brazil).

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Table 1. Baseline characteristics of true RH patients

	WCE **N=66**	**non-WCE** **N=61**
Clinical data		
Female gender (%)	64.1	69.2
Age (years)	55.0 ± 9.1	57.9 ± 10.5
BMI (kg/m^2)	30.5 ± 3.4	30.8 ± 2.8
Blood pressure		
Office SBP (mmHg)	169.8 ± 15.8	161.9 ± 9.0
Office DBP (mmHg)	95.1 ± 14.0	90.1 ± 10.4
Daytime SBP (mmHg)	143.0 ± 12.8	146.1 ± 13.6
Daytime DBP (mmHg)	86.1 ± 9.9	85.1 ± 14.9
Δ SBP (mmHg)	28 ± 4*	16 ± 3
Δ DBP (mmHg)	16 ± 5*	7 ± 2
Laboratory parameters		
Glycemia (mg dl^{-1})	100 ± 8.3	99 ± 7.2
Cholesterol (mg dl^{-1})	189 ± 14.1	185 ± 16.7
HDL-c (mg dl^{-1})	50.1 ± 14.2	49.9 ± 16.1
LDL-c (mg dl^{-1})	107.4 ± 18.9	110.3 ± 20.5
Triglycerides (mg dl^{-1})	119.9 ± 76.6	121.9 ± 86.2
Creatinine (mg dl^{-1})	1.1 ± 0.2	1.0 ± 0.3
eGFR (ml min 1.73m^{-2})	78.5 ± 4.7	80.6 ± 3.6
Uric acid (mg dl^{-1})	5.8 ± 1.0	6.0 ± 0.7
Sodium (mEq l^{-1})	140.9 ± 1.6	140.7 ± 2.6

Potassium (mEq l^{-1})	4.0 ± 0.2	4.1 ± 0.3

Abbreviations: N, number of patients; WCE, white coat effect; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL and HDL, low- and high-density lipoproteins, respectively; eGFR, glomerular filtration rate estimated; Δ SBP, difference between office systolic blood pressure and systolic daytime ABPM; Δ DBP, difference between office diastolic blood pressure and diastolic daytime ABPM; Values are means ± SD. (*) Statistical significance ($p<0.05$).

Table 2. Anti-hypertensive (anti-HTN) drugs distribution

Characteristic/Variable	WCE (n=66)	non- WCE (n=61)
Total anti-HTN drugs	5.2 ± 0.3*	4.1 ± 0.2
Diuretics	100% (66)	100% (61)
β-blockers	60.0% (39)	72.7% (44)
Angiotensin-converting enzyme inhibitors	70.0% (47)*	45.4% (27)
Angiotensin receptor blocker	64.7% (43)*	42.4% (26)
Calcium channel blocker	83.3% (55)*	63.6% (39)
Centrally acting anti-hypertensive drug	16.6% (11)	13.6% (8)

Abbreviations: WCE, white coat effect patients; Values are means ± SD.
(*) Statistical significance ($p<0.05$).

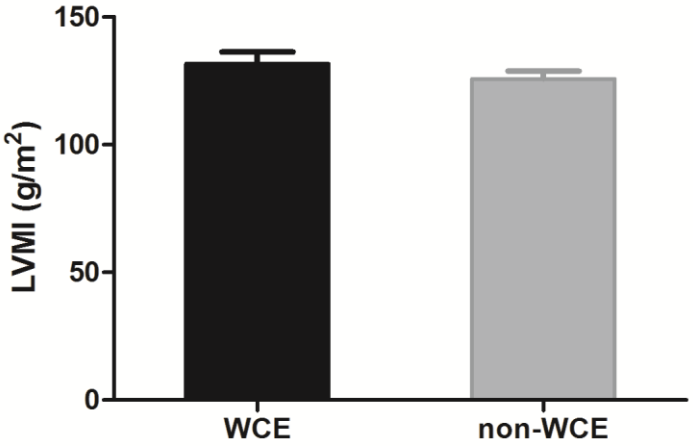

Figure 1. LVMI in WCE and non-WCE subgroups. Values expressed as means ± SD. WCE: white coat effect.

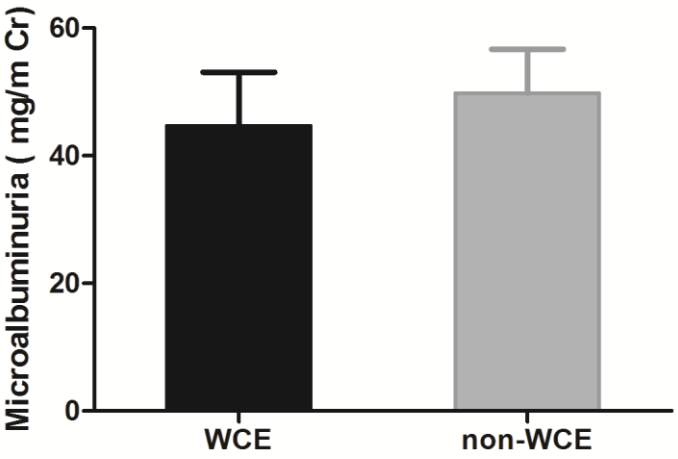

Figure 2. Microalbuminuria in WCE and non-WCE subgroups. Values expressed as means ± SD. WCE: white coat effect.

CAPÍTULO II

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PROF. DR. LUIZ FELIPE MOREIRA

EDITOR-IN-CHIEF

ARQUIVOS BRASILEIROS DE CARDIOLOGIA

Dear Prof Luiz Felipe Moreira

Please find enclosed our original manuscript "**The alerting reaction of white coat effect in resistant hypertensive patients occurs during the night time sleep prior the morning medical appointment**". The paper hereby submitted follows some important publications of our group in resistant hypertension and we would like to publish it in the Arquivos Brasileiros de Cardiologia due its relevance this syndrome.

This manuscript is original and is not under consideration by any other journal.

All authors have approved the submission of the present study in this journal and there are no financial or other relationships that might lead to a conflict of interest.

Yours sincerely,

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Title: The alerting reaction of white coat effect in resistant hypertensive patients occurs during the night time sleep prior the morning medical appointment.

Summarized title: A night sympathetic overreaction precedes the medical appointment in resistant hypertensive patients

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ABSTRACT

Study basis: White coat effect (WCE) originates from an alerting reaction by the patient while being examined in a medical environment and is frequently associated with an increase in heart rate and blood pressure (BP). It is known that high prevalence of obstructive sleep apnea (OSA) in resistant hypertension (RH) and its subsequently nighttime sympathetic overactivation. **Objectives:** The aim of this study was the evaluation if patients alerting reaction could be identified prior to the morning medical appointment during the sleep time in a high risk of OSA population such as RH patients in which the sympathetic activity is already overactivated. **Methods:** Consecutive stable patients with RHTN (44 in number) were evaluated for the risk of obstructive sleep apnea (OSA) by the Berlin Questionnaire, sleep quality by the Pittsburgh Sleep Questionnaire Index and were submitted to office BP measurement, ABPM and 24-hour Holter monitoring. **Results:** RHTN patients were identified with WCE (WCE) (25) and without WCE (non-WCE) (19). Office BP was 170.7 ± 17.2 / 94.8 ± 14.0 (WCE) and 161.7 ± 08.6 / 90.3 ± 11.4 mmHg (non-WCE), daytime ABPM = 144.0 ± 13.4 / 77.3 ± 17.3 (WCE) and 146.2 ± 15.6 / 84.0 ± 15.0 mmHg (non-WCE). Despite of the similar results regarding quality of sleep and risk of OSA in both groups, significant differences were observed between WCE and non-WCE subgroups regarding low frequency in normalized units (LF nu) during night time (WCE= 58.9 ± 20.9 and non-WCE 39.8 ± 22.9, $p<0.05$). **Conclusion:** The sympathetic overactivation during the nighttime prior the medical appointment occurred in RH patients with WCE despite of the influence of sleep disorders.

Keywords: resistant hypertension, white coat effect, sympathetic activation, sleep disorders.

RESUMO

Introdução: O efeito do avental branco (EAB) se origina de uma reação de alerta por parte do paciente ao ser examinado em um ambiente médico, sendo freqüentemente associado a um aumento da frequência cardíaca e pressão arterial (PA). Sabe-se que há uma alta prevalencia de apneia obstrutiva do sono (AOS) na hipertensão arterial resistente (HAR) e sua subsequente superativação simpática no período noturno. **Objetivos:** Avaliamos se essa reação de alerta do paciente (EAB) com HAR poderia ser identificada antes do mesmo estar em um ambiente médico, ou seja, durante o período noturno. **Métodos:** Quarenta e quatro pacientes com HAR foram avaliados por eletrocardiografia ambulatorial para análise da variabilidade da frequência cardíaca, bem como responderam ao Questionário de Berlim (risco para AOS) e de Pittsburgh (qualidade do sono). **Resultados**: Os valores de PA observados foram: consultório= 170.7 ± 17.2 / 94.8 ± 14.0 (HAR+EAB) e 161.7 ± 8.6 / 90.3 ± 11.4 mmHg (HAR-EAB) e MAPA= 144.0 ± 13.4 / 77.3 ± 17.3 (HAR+EAB) e 146.2 ± 15.6 / 84.0 ± 15.0 mmHg (HAR-EAB). A despeito da alta prevalência de risco para AOS e qualidade de sono ruim ter sido observada em ambos os subgrupos, o subgrupo HAR+EAB apresentou atividade simpática aumentada durante o período noturno (baixa freqüência em unidades normalizadas - LFnu) (HAR+EAB= 58,9 ± 20,9 e HAR-EAB= 39,8 ± 22,9, $p<0,05$). **Conclusão:** A hiperativação simpática durante o período de sono ocorreu somente em hipertensos resistentes com EAB, apesar da influência semelhante de distúrbios do sono e da qualidade do mesmo em ambos os grupos.

INTRODUCTION

Resistant hypertension (RHTN) refers to patients whose blood pressure is controlled with the use of more than three antihypertensive agents of different classes in adequate doses or patients whose blood pressure (BP) is controlled but require four or more medications to achieve blood pressure goals (of which is BP< 140 / 90 mmHg) [1].

The major regulators of blood pressure are the autonomic nervous system and hormonal factors. Activation of the sympathetic nervous system (SNS) is critically involved in the pathogenesis of hypertension [2-3] and is positively correlated with increasing severity of hypertension [4] and may be involved in white coat effect (WCE) [5-7]. WCE is defined as a persistent and clinically important elevation of BP measured in office blood pressure (OBP) compared with out-of-clinic measurements such as ambulatory blood pressure monitoring (ABPM) [8].

WCE originates from an alerting reaction by the patient while being examined by the physician [8-9] and is frequently associated with an increase in heart rate (HR) [10]. Heart rate variability (HRV) assesses 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 [11] . Variations in HRV are normally observed in association with diurnal rhythms and BP changes [12]. 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 [12].

In humans, circadian rhythms of HRV and BP [13] have been intensively studied, mainly due to the increased cardiovascular death reported during the morning hours [14]. Circadian type blood pressure rhythm refers to the daily variation of BP that is generally higher during the day than at night [15]. This phenomenon results from endogenous circadian rhythms in autonomic nervous and endocrine systems. Alterations in these intrinsic circadian rhythms can result in the absence of the nocturnal BP decline (nondipping), common in patients with essential hypertension [16]. Also, several sleep related phenomena, such as sleep-disordered breathing and high variability of nocturnal BP, have been suggested to be independent risk factors for cardiovascular events [17].

Patients with sleep disorders such as obstructive sleep apnea (OSA) have increased sympathetic activation and also have faster heart rates during resting wakefulness, suggesting that there is also an increased cardiac sympathetic drive [18]. Hypertension and OSA are linked by autonomic dysfunction; however, as far as we know, no study has evaluated the influence of the pattern of autonomic activity in the circadian rhythm in true RHTN with and without WCE and its relationship with quality of sleep and sleep disorders.

METHODS

Patient population

Forty-four RHTN subjects [1], 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 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, were properly observed and excluded [19]. Patients were evaluated concerning adherence to treatment [19-21] and underwent clinical optimization of antihypertensive therapy [22].

Ambulatory blood pressure monitoring (ABPM) was used to identify the presence or not of WCE in true RHTN. The patients were divided into two groups: with WCE (WCE, n=25) and without WCE (non-WCE, n=19). All the subjects gave written informed consent and the study was approved by the university ethics committee.

Study design

This study comprised 44 patients with true RHTN. Non-pharmacologic therapies were optimized, including dietary salt control monitored by measuring urinary sodium excretion (< 100 mEq/24h). All patients were submitted to office BP measurement, ABPM, 24-hour Holter monitoring, Berlin sleep questionnaire and Pittsburgh sleep quality index (PSQI) questionnaire. WCE was defined as measurement of systolic blood pressure (SBP) >20mmHg and/or diastolic blood pressure (DBP) >10mmHg, in the physician's office, in comparison with ABPM values [8].

Measurements

Office blood pressure

Clinical values of blood pressure were obtained three times from each patient, using a digital sphygmomanometer (Omron HEM-907 XL) [23] 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 [22]. The average of two consecutive measurements with a variation lower than 5 mmHg 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 [24]. A Spacelabs 90217 ambulatory blood pressure monitor (Spacelabs Inc, Redmon, WA, USA) was used [25]. 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. Ambulatory blood pressure parameters included mean daytime systolic and diastolic blood pressures. All participants were instructed to note their sleep period in a personal diary.

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 8 h, followed by 1 h 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. (night time period – NT) and 3 p.m. (day time period – DT). 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 [26-27]:

-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. “Day time” and “night time” were established at 3:00 p.m. and 3:00 a.m., respectively, in order to collect HRV data during wake and sleep periods.

Instruments

Pittsburgh Sleep Quality Index

Quality of sleep was measured using the Pittsburgh Sleep Quality Index (PSQI) [28]. This self-administered questionnaire assesses quality of sleep during the previous month and contains 19 self-rated questions yielding seven components: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medications and daytime dysfunction. Each component is scored from 0 to 3, yielding a global PSQI score between 0 and 21, with higher scores indicating lower quality of sleep. The PSQI is useful in identifying good and poor sleepers. A global PSQI score > 5 indicates that a person is a ‘poor sleeper’ having severe difficulties in at least two areas or moderate difficulties in more than three areas [28].

Berlin questionnaire

The presence of obstructive sleep apnea (OSA) was determined by the Berlin questionnaire,

a validated instrument designed to identify individuals with OSA [29-30]. The questionnaire includes 1 introductory and 4 follow-up questions about snoring, 3 questions about daytime somnolence (including 1 concerning sleepiness while driving), and 1 question about history of hypertension. Presence of OSA is determined by positive responses to at least 2 of the following 3 criteria: (1) persistent symptoms (>3 times per week) for at least 2 questions about snoring, (2) persistent (>3 times per week) somnolence during daytime and/or while driving and (3) history of hypertension or a body mass index >30 kg/m^2.

Statistical analysis

The Statistical Analysis System, version 8.02 (SAS Institute Inc., Cary, NC, USA), was used for all statistical analyses. The statistical analysis was performed descriptively and interpreted in an explorative way. Significant differences between the study subgroups were determined using the Student t test. Correlation analysis was performed using Pearson´s coefficient. A value of $P < 0.05$ indicated significance. All values are expressed as mean ± SD.

RESULTS

The general characteristics of the study groups are listed in table 1. No differences were observed between the WCE and non-WCE subgroups regarding age, body mass index or gender. The mean ages were 56.2 ± 8.8 and 53.1 ± 10.3 years in WCE and non-WCE patients, respectively. Women represented 56.0 and 63.1% of the patients in these groups, respectively.

As shown in table 1, both subgroups registered similar values of office SBP (170.7 ± 17.2 vs. 161.7 ± 8.6 mmHg; $p > 0.05$) and DBP (94.8 ± 14.0 vs. 90.3 ± 11.4 mmHg; $p > 0.05$ in WCE and non-WCE groups). The BP delta values (i.e., difference between physician's office and daytime ABPM) registered were 27 vs. 16 mmHg for SBP and 17 vs. 06 mmHg for DBP in WCE and non-WCE groups, respectively. Biochemical test results were very similar for both groups.

In the WCE group, both LF nu and HF nu during day and night were similar (78.7 ± 12.8 vs. 58.9 ± 20.9 and 21.6 ± 13.2 vs. 40.8 ± 21.3, respectively) ($p>0.05$) whereas in the non-WCE group, these parameters were different (76.3 ± 16.8 vs. 39.8 ± 22.9 and 23.6 ± 16.8 vs. 60.1 ± 23.0, respectively) ($p<0.05$). There were differences between WCE and non-WCE groups in frequency domain parameters (Table 2). The WCE group had night time LF nu correlated positively with office systolic BP and daytime ABPM ($r=0.45$, $p<0.05$ and $r=0.42$, $p<0.05$, respectively). Moreover, night time HF nu correlated negatively with both parameters above ($r=-0.45$, $p<0.05$ and $r=-0.46$, $p<0.05$, respectively) (fig. 1).

WCE patients received more anti-hypertensive drugs than non-WCE (5.1 ± 0.2 *vs*. 4.0 ± 0.3, respectively) (Table 3).

As shown in figure 2, both subgroups registered similar results in relation to 'poor' quality of sleep (72.0% and 57.8% in WCE and non-WCE patients, respectively [$p>0.05$]). In addition, 76.0% and 73.6% (WCE and non-WCE groups,

respectively [p>0.05]) showed a risk for obstructive sleep apnea.

DISCUSSION

The present study demonstrates that there is an autonomic imbalance due to sympathetic overactivity during night time in WCE patients compared to the non-WCE group. Interestingly, both groups demonstrated a similar pattern of sympathetic and parasympathetic tones during day time. Quality of sleep and risk for obstructive sleep apnea were similar in both subgroups. Night time LF nu (sympathetic activity) correlated positively with morning office mean sitting systolic blood pressure (msSBP) and day time ABPM in the WCE group. As far as we know, this is the first time that circadian disruption (CD) has been evaluated in RHTN in order to better understand its role in the pathogenesis of WCE in this kind of population.

WCE is more prevalent in women and older persons [31] and occurs when blood pressure is increased temporarily through an autonomic neural reaction triggered by the process of BP measurement in the office [32]. These cases must be confirmed with 24-hour ambulatory blood pressure monitoring [33]. Thus, patients can be diagnosed as truly hypertensive, but still demonstrate a significant white coat effect. In the present study, we found a higher prevalence of WCE in HRTN individuals (56%) in comparison with other authors (20 to 30%) [34]. An important point in this study is that our study group was only comprised of RHTN patients who had both increased ABPM and office BP levels (home BP ≥ 135 or 85 mmHg and office BP ≥ 140 or 90 mmHg) in contrast with these authors in which patients had normal daytime BP (≤ 135/85 mmHg).

Hyperaldosteronism is prevalent in patients with resistant hypertension [35]. In the present study, all patients were screened with the cut-off ratio plasma aldosterone concentration (PAC)/plasma renin activity (PRA) (ARR < 20 ng dl^{-1} per ng ml^{-1} per h) to avoid secondary causes of hypertension. Gonzaga et al demonstrated that resistant hypertension patients with hyperaldosteronism, had also been previously diagnosed with OSA [36]. However, it is unclear if aldosterone excess is the cause or consequence of untreated OSA [37].

OSA is an important sleep-related breathing disorder characterized by recurrent obstruction of the upper airway leading to repeated breathing pauses either complete or partial. Increased sympathetic nervous system activity secondary to intermittent hypoxemia and increased upper airway resistance plays a major contributing role as well as renin-angiotensin-aldosterone system (RAAS) activation, oxidative stress and endothelial dysfunction [38]. Therefore, OSA is very common in RHTN individuals (prevalence of 83%) [39]. As expected, this study showed the proportion of 75% of RHTN classified as “high risk” for OSA by the Berlin sleep questionnaire with no significant difference between WCE and non-WCE groups. In accordance with previous evidence of the relationship between OSA and autonomic imbalance, both groups (WCE and non-WCE) demonstrated a similar pattern of autonomic dysfunction. Moreover, OSA should be strongly

suspected in resistant hypertension, non-dipper subjects and in those with symptoms suggestive of OSA (such as poor sleep quality and excessive daytime somnolence) [40].

Corroborating the evidence above, we found that poor sleep quality was present in 65% of RHTN, with no significant differences between the WCE and non-WCE groups. It is well known that poor sleep quality is related to a non-dipping pattern [41] and OSA due to sleep fragmentation [40, 42].

Considering the influence of autonomic imbalance, evidence indicates the involvement of increased activity of the sympathetic nervous system (SNS) in the pathogenesis of hypertension [43]. Moreover, SNS overactivity is associated with the increased cardiovascular outcomes during the early morning hours [14]. During the pre-wake and wake periods, there is an increased sympathetic activity and consequently increased heart rate [44-45].

Our results demonstrated that patients with RHTN with WCE had higher sympathetic activity during night time than the group without WCE. In addition, it was shown that the sympathetic activity correlates with the morning office BP.

Due to the importance of sympathetic overactivity in the genesis of hypertension or isolated BP increases, it is possible to infer that the overactivity during night time not only influences the non-dipper pattern of RHTN but also on the BP morning surge and the WCE assessed in morning medical appointments, strictly scheduled between 8:00 and 10:00 a.m.

It was previously demonstrated that WCE is an alert reaction of low amplitude in which there is an early alteration of the parasympathetic system [46]. Further , 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 [6].

However, the inferences concerning the autonomic imbalance cannot be reductionist. Since all the patients enrolled in this study had autonomic imbalance, it would be expected that the whole study population had WCE during medical assistance. That was not what we found.

This interesting lack of WCE in patients who also have autonomic imbalance highlights that this disturbance displays a plurality of actions on the cardiovascular system.

Recently, this hypothesis was first evaluated demonstrating that in metabolic syndrome the sympathetic activation is not uniformly distributed over the cardiovascular system [47]. This information is of great value for an adequate comprehension of WCE since our study population was comprised of patients with a higher prevalence of metabolic disorders than in earlier stages of hypertension.

Despite the fact that many components of metabolic disorders may influence the fashion diversity of sympathetic activity over the cardiovascular system [47], this study demonstrated that a circadian aspect of the autonomic imbalance is strongly associated with WCE which is the sympathetic overactivity during night time. A number of potential limitations have to be considered. First, because of technical limitations, we could not perform Holter monitoring and

ambulatory BP monitoring simultaneously. Second, since diabetes, smoking, dyslipidemia and all pseudo RHTN patients were excluded in order to minimize, as much as possible, any factors that could skew the results, a small number of RHTN patients were enrolled in the study. And finally, there was no polysomnography for diagnosis of OSA.

In conclusion, the alerting reaction, identified by the sympathetic overactivation during the nighttime prior the medical appointment, occurred in RH patients with WCE despite of the baseline influence of sleep disorders on sympathetic activity.

COMPETING INTERESTS

Leandro Boer-Martins is an employee of Novartis Biociências S.A. (Brazil). Other authors declare no conflict of interest.

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Table 1. Characteristics of the study population

	WCE group (N=25)	non-WCE group (N=19)
Clinical data		
Female gender (%)	56.0	63.1
Age (years)	56.2 ± 8.8	53.1 ± 10.3
BMI (kg/m^2)	29.0 ± 5.3	30.8 ± 6.2
Heart rate		
Day time (bpm)	84.7 ± 8.5	86.3 ± 14.2
Night time (bpm)	68.3 ± 9.9	67.4 ± 10.4
Blood pressure		
Office SBP (mmHg)	170.7 ± 17.2	161.7 ± 8.6
Office DBP (mmHg)	94.8 ± 14.0	90.3 ±11.4
Day time SBP (mmHg)	144.0 ± 13.4	146.2 ± 15.6
Day time DBP (mmHg)	77.3 ± 17.3	84.0 ± 15.0
Δ SBP (mmHg)	27*	16
Δ DBP (mmHg)	16*	6
Night time SBP (mmHg)	122.2 ± 15.1	122.9 ± 9.4
Night time DBP (mmHg)	72.9 ± 10.1	71.0 ± 10.2
Laboratory parameters		
Glycemia (mg dl^{-1})	100 ± 9.3	99 ± 8.2
Cholesterol (mg dl^{-1})	187 ± 13.1	186 ± 15.7
HDL-c (mg dl^{-1})	50.1 ± 15.2	49.9 ± 16.5

LDL-c (mg dl^{-1})	108.3 ± 18.8	111.4 ± 19.5
Triglycerides (mg dl^{-1})	120.9 ± 75.6	121.6 ± 85.3
Creatinine (mg dl^{-1})	1.1 ± 0.3	1.0 ± 0.2
Uric acid (mg dl^{-1})	5.9 ± 0.9	6.0 ± 0.8
Sodium (mEq l^{-1})	140.8 ± 1.5	140.7 ± 2.4
Potassium (mEq l^{-1})	4.1 ± 0.2	4.1 ± 0.2
PRA (ng ml^{-1} per h)	1.4 ± 0.5	1.5 ± 0.5
PAC (ng dl^{-1})	7.5 ± 3.7	8.5 ± 5.8
ARR (ng dl^{-1} per ng ml^{-1} per h)	5.5 ± 3.1	5.7 ± 3.8

WCE - white coat effect; BMI - body mass index; SBP - systolic blood pressure; DBP - diastolic blood pressure; Δ SBP - difference between office systolic blood pressure and systolic daytime ABPM; Δ DBP - difference between office diastolic blood pressure and diastolic daytime ABPM; LDL and HDL - low- and high-density lipoproteins, respectively; MA - microalbuminuria; ARR - aldosterone–renin ratio; PAC - plasma aldosterone concentration; PRA - plasma renin activity; Values are means ± SD; (*) Statistical significance ($p<0.05$).

Table 2: Heart rate variability in resistant hypertension patients

HRV variable	WCE group (n=25)	Non-WCE group (n=19)	*p*-value
Day			
LF nu	78.7 ± 12.8	76.3 ± 16.8	0.59
HF nu	21.6 ± 13.2	23.6 ± 16.8	0.61
LF/HF	5.47 ± 3.4	4.47 ± 2.4	0.60
Night			
LF nu	58.9 ± 20.9*	39.8 ± 22.9	< 0.01
HF nu	40.8 ± 21.3*	60.1 ± 23.0	< 0.01
LF/HF	3.53 ± 3.0*	1.09 ± 1.2	0.006

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; values are expressed as means ± SD; (*) Statistical significance ($p<0.05$).

Table 3: Anti-hypertensive (anti-HTN) drug distribution

Characteristic/Variable	WCE group (n=25)	non- WCE group (n=19)
Total anti-HTN drugs	5.1 ± 0.2*	4.0 ± 0.3
Diuretics	100% (25)	100% (19)
β-blockers	71.4% (18)	81.8% (15)
Angiotensin-converting enzyme inhibitors	72.0% (18)*	47.3% (9)
Angiotensin receptor blocker	63.5% (16)*	40.4% (7)
Calcium channel blocker	85.5% (21)*	60.9% (11)
Centrally acting anti-hypertensive drug	15.1% (4)	12.2% (2)

WCE - white coat effect patients; values are expressed as means ± SD;
(*) statistical significance ($p<0.05$).

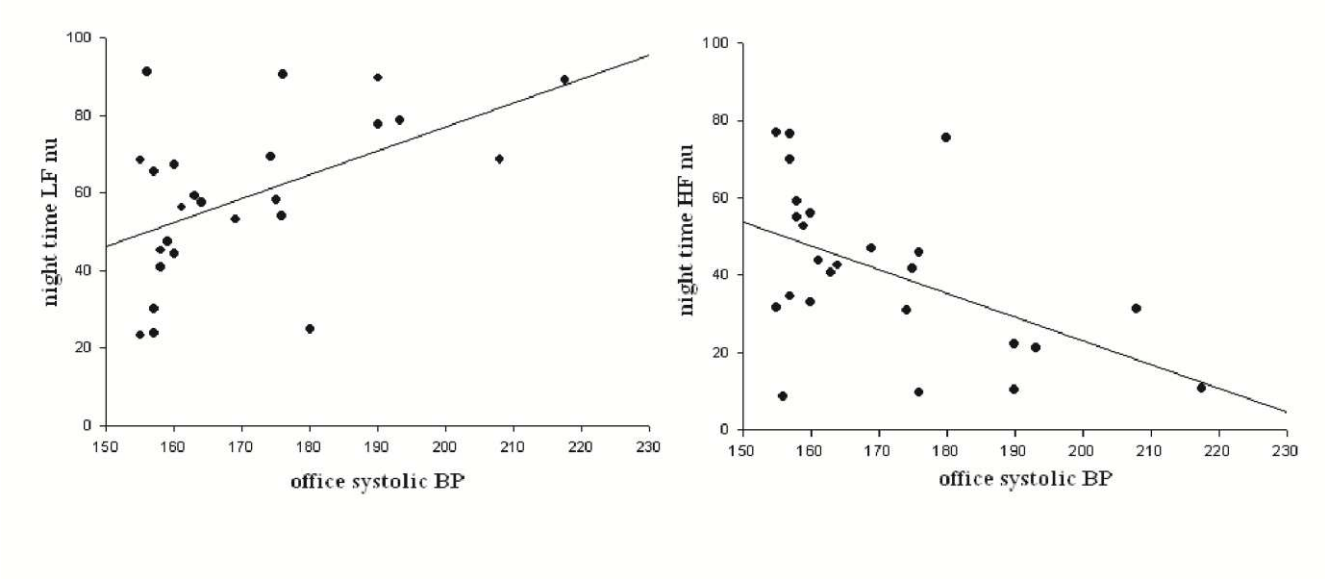

Figure 1: A: Correlation between night time LF nu and office systolic BP in WCE patients (r=0.45; p<0.05); B: Correlation between night time HF nu and office systolic BP in WCE patients (r=-0.45; p<0.05).

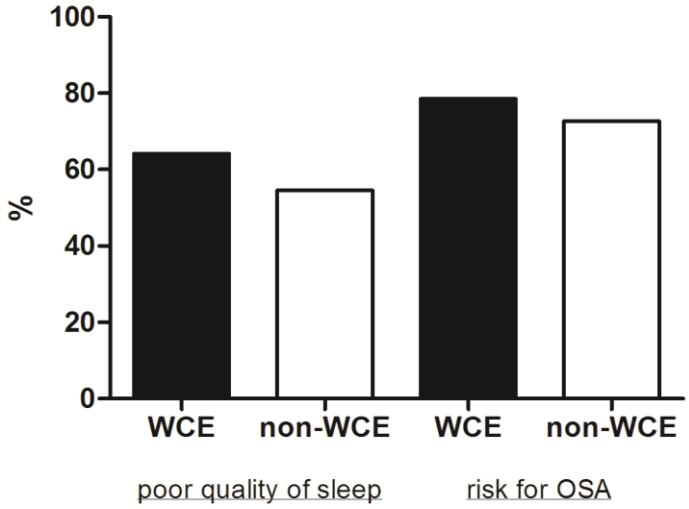

Figure 2: Poor quality of sleep and risk for obstructive sleep apnea (OSA) in WCE and non-WCE subgroups. Results expressed as percentage. WCE: white coat effect patients.

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