RODRIGO GIMENEZ PISSUTTI MODOLO

FATORES ASSOCIADOS À ISQUEMIA MIOCÁRDICA NA HIPERTENSÃO ARTERIAL RESISTENTE

PREDICTORS OF MYOCARDIAL ISCHEMIA IN RESISTANT HYPERTENSION

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Orientador: Prof. Dr. Heitor Moreno Junior

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Tese de Doutorado apresentada ao Programa de Pós-Graduação em Farmacologia da Faculdade de Ciências Médicas da Universidade Estadual de Campinas para obtenção de título de Doutor em Farmacologia.

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Dedico

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(Marthin Luther King)

INTRODUÇÃO: A hipertensão arterial é o mais prevalente e significante fator de risco modificável para doença arterial coronariana (DAC). Uma parte destes pacientes com hipertensão descontrolada é classificada como sendo portadora da Hipertensão Arterial Resistente (HAR). A incidência da isquemia miocárdica e da DAC aumenta juntamente com a ascensão dos níveis pressóricos. No entanto, a prevalência de isquemia miocárdica em pacientes com HAR é desconhecida, bem como os fatores associados à primeira.

MÉTODOS: Analisamos 129 pacientes com HAR verdadeira, seguidos regularmente em nosso ambulatório especializado. Foi realizada cintilografia de perfusão miocárdica em repouso e após stress farmacológico por dipiridamol nestes indivíduos. Os pacientes eram então divididos em dois grupos: com (I-HAR, n=36) e sem (SI-HAR, n=93) isquemia miocárdica. Ecocardiograma, MAPA-24h (para inclusive análise de efeito do jaleco branco), e vasodilatação mediada por fluxo (VMF) também foram realizados.

RESULTADOS: Trinta e seis pacientes (28%) tinham isquemia miocárdica e 49% apresentavam o efeito do jaleco branco (EJB). O EJB esteve associado com alta prevalência de isquemia miocárdica (49,2% vs. 7,6%, p<0,001). Não houve diferença entre os grupos no que concerne à idade, sexo, parâmetros bioquímicos, pressão arterial de consultório e na MAPA. Pacientes no grupo I-HAR eram mais diabéticos (31 vs. 11%, p<0,05) e obesos (75 vs. 40%, p<0,001). Ajustando-se para idade e IMC, a regressão logística múltipla mostrou que diabetes (OR 6,5; 95%CI: 1,06-40,1, p=0,04), VMF (OR 0,18; 95%CI: 0,07-0,41, p<0,001), frequência cardíaca (OR 1,23; 95%CI: 1,11-1,36, p<0,001), índice de massa ventricular esquerda (OR 1,02; 95%CI: 1,01-1,04, p=0,04), e microalbuminúria (OR 1,02; 95%CI: 1,01-1,04, p=0,002) foram considerados preditores independentes de isquemia. Em outro modelo de regressão logística, ajustando-se para as mesmas variáveis, ainda tendo

isquemia miocárdica como variável dependente, o EJB também foi considerado preditor independente de isquemia (OR=14,7, CI95% 4,8-44,8; p<0,001).

CONCLUSÃO: Há uma alta prevalência de isquemia miocárdica em pacientes com HAR. Microalbuminúria, frequência cardíaca, disfunção endotelial, massa ventricular esquerda e a presença do efeito do jaleco branco podem ser úteis para guiar a investigação de isquemia miocárdica em pacientes assintomáticos para DAC, neste grupo de pacientes de alto risco – HAR.

Palavras-chave: Hipertensão arterial resistente, lesão de órgãos-alvo, isquemia miocárdica, doença arterial coronariana, efeito do jaleco branco.

BACKGROUND: Hypertension is the most prevalent and significant modifiable risk factor for coronary heart disease. A portion of patients with uncontrolled hypertension is considered to have resistant hypertension (RHTN). Myocardial ischemia incidence increases along with blood pressure (BP) levels. However, the prevalence of myocardial ischemia in patients with RHTN is unknown, as well as the factors associated with it.

METHODS: We enrolled 129 patients with true RHTN regularly followed in our specialty hypertension clinic and evaluated then by resting and dipyridamole pharmacological stress myocardial perfusion scintigraphy. Patients were then divided in two groups: with (I-RHTN, n=36) and without (NI-RHTN, n=93) myocardial ischemia. Echocardiography, 24h-ABPM (for analysis of white-coat effect -WCE) and flow-mediated dilation (FMD) were also evaluated.

RESULTS: Thirty-six (28%) patients had myocardial ischemia and 49% presented the WCE. WCE was associated with higher prevalence of myocardial ischemia (49.2% vs. 7.6%, $p<0.001$) There was no difference between groups regarding age, gender, biochemical parameters, office and 24h-ABPM levels. Patients in the I-RHTN group were more likely diabetic (31 vs. 11%, $p<0.05$) and obese (75 vs. 40%, $p<0.001$). Adjusting for age and BMI, multiple logistic regression showed that diabetes (OR 6.5; 95%CI: 1.06-40.1, $p=0.04$), FMD (OR 0.18; 95%CI: 0.07-0.41, $p<0.001$), heart rate (OR 1.23; 95%CI: 1.11-1.36, $p<0.001$), left ventricular mass index (OR 1.02; 95%CI: 1.01-1.04, $p=0.04$), and microalbuminuria (OR 1.02; 95%CI: 1.01-1.04, $p=0.002$) were independent predictors of ischemia. On another model of logistic regression, using the same adjustments and myocardial ischemia as dependent variable, the WCE wasconsidered an independent predictor of ischemia as well (OR=14.7, CI95% 4.8-44.8; $p<0.001$).

CONCLUSIONS: In conclusion, there is a high prevalence of myocardial ischemia in patients with RHTN. Increased microalbuminuria, heart rate, endothelial dysfunction, LV mass and the presence of the white-coat phenomenon can be useful to guide the investigation for myocardial ischemia in these high risk patients.

Keywords: Resistant hypertension, target organ damage, myocardial ischemia, coronary artery disease, white-coat effect.

AHA	American Heart Association
AOS	Apneia obstrutiva do sono
DAC	Doença arterial coronariana
DE	Disfunção endotelial
DM	Diabetes *mellitus*
ECA	Enzima conversora da angiotensina
EJB	Efeito do Jaleco Branco
ESC	European Society of Hypertension
ESC	European Society of Cardiology
HAS	Hipertensão arterial sistêmica
HAR	Hipertensão arterial resistente
HARC	Hipertensão arterial resistente controlada
HARNC	Hipertensão arterial resistente não controlada
HVE	Hipertrofia ventricular esquerda
IMC	Índice de massa corpórea
IMVE	Índice de massa ventricular esquerda
JNC VII	Seventh Report of the Joint National Committee
LOA	Lesões de órgãos-alvo
MA	Microalbuminúria
MAPA	Monitoração ambulatorial da pressão arterial
MRPA	Monitoração residencial da pressão arterial

NO	Óxido nítrico
PA	Pressão arterial
PAD	Pressão Arterial Diastólica
PAS	Pressão Arterial Sistólica
SNS	Sistema nervoso simpático
SRAA	Sistema renina angiotensina aldosterona
VMF	Vasodilatação mediada por fluxo

1 INTRODUÇÃO

1.1 Considerações Gerais

Estima-se que em 2025, mais de 1,5 bilhão de pessoas no mundo terão hipertensão arterial sistêmica (HAS). Esta condição será responsável por até 50% do risco de doença cardíaca e 75% do risco de acidentes vasculares cerebrais (1). Há várias décadas, é bem conhecido que a redução da pressão arterial (PA) com modificação do estilo de vida, medicamentos, ou ambos, podem reduzir substancialmente o subsequente risco do paciente hipertenso (2). Para cada redução de 10 mm Hg na PA sistólica (PAS), o risco de mortalidade por doença cardíaca e por acidente vascular cerebral diminui em 30% e 40%, respectivamente (3).

A HAS é o maior fator de risco modificável para doença arterial coronariana (DAC), sendo fortemente associada à esta afecção. Uma variação de apenas 10 mmHg na PA de um indivíduo chega a reduzir a incidência de coronariopatia em 37% (4). Apesar dos claros benefícios, em análise transversal dos dados da maior coorte cardiovascular (Framingham Heart Study), apenas 48% dos pacientes hipertensos e menos de 40% dos idosos conseguem controle da PA (5, 6). Existem muitas causas para o controle ineficaz da PA além de estilo de vida inapropriado, não adesão à medicação (7, 8) e falha em intensificar a terapêutica pelo médico assistente (inércia clínica) (9, 10). Estudos aleatorizados comparativos demonstram que, para reduções semelhantes da PA, há redução semelhante na incidência de morbidade e mortalidade cardiovascular mesmo com classes diferentes de anti-hipertensivos (11). Dentro deste grupo de pacientes com dificuldade de controle da PA com aumento do número de drogas anti-hipertensivas prescritas estão os hipertensos resistentes.

A hipertensão arterial resistente (HAR), estudada há décadas, apesar de já ter diversas alterações fisiopatológicas conhecidas, ainda mantém sua definição extremamente simples e baseada apenas em níveis pressóricos e uso de medicamentos anti-hipertensivos. A HAR persiste como uma condição sem definição universalmente aceita, sendo ainda a real prevalência também muito variável (12). Paciente com HAR é definido como aquele hipertenso que apresenta PA descontrolada à despeito do uso de 3 diferentes classes de anti-hipertensivos em doses ótimas, sendo uma das classes idealmente um diurético; ou os indivíduos que necessitam 4 classes para obter o controle pressórico (13). Este controle é obtido trazendo os valores pressóricos aos níveis pré-definidos em Diretrizes de Hipertensão Arterial (<140x90 mmHg para a população em geral e <130x80 mmHg para os portadores de diabetes mellitus ou doença renal crônica) (2).

Hipertensos resistentes apresentam mais lesões de órgãos-alvo (LOA) e seus marcadores, como disfunção endotelial, microalbuminúria (MA) e hipertrofia ventricular esquerda (HVE) (14-16). Lesões de órgão-algo acarretam maior incidência de eventos cardiovasculares, como infarto agudo do miocárdio (17) que podem ser devido à: (i) envelhecimento e diabetes (14) e (ii) mais placas ateroscleróticas (18).

Assim, os médicos clínicos precisam estar atentos para a presença de isquemia miocárdica silenciosa (sem sintomas cardiovasculares) para o diagnóstico precoce desta patologia a fim de evitar evolução desfavorável de coronariopatia sem tratamento adequado. A cintilografia de perfusão miocárdica com (99m)tc-sestamibi faz o diagnóstico preciso de isquemia miocárdica e coronariopatia em pacientes assintomáticos com hipertensão arterial (19, 20). No entanto, uma vez que estes pacientes são assintomáticos, a avaliação de fatores preditores de isquemia miocárdica neste subgrupo de hipertensos pode

ajudar a evitar gastos extras guiando melhor a avaliação de isquemia e tratamento adequado.

1.2 Hipertensão Arterial Resistente

No Brasil, a HAS apresenta prevalências entre 22,3% e 43,9% (21, 22). Embora existam diversos medicamentos anti-hipertensivos disponíveis, estudos revelam apenas 19,6% de controle adequado da PA nos pacientes hipertensos (22, 23). A falta de cumprimento das metas terapêuticas deve-se, em parte, à má aderência ao tratamento anti-hipertensivo (24), seja ele composto somente por mudanças no estilo de vida, principalmente com a redução de ingesta de sal e álcool, perda de peso e realização de atividade física regular ou acrescido à terapêutica medicamentosa, tratamento prescrito inadequado, medidas incorretas de PA e outras causas de pseudo-hipertensão. Entretanto, existe um grupo de pacientes o qual, apesar da adequada realização das orientações e administração de medicamentos, os níveis pressóricos mantém-se elevados, sendo chamados de hipertensos resistentes.

1.2.1 Definição

A HAR persiste como uma condição sem definição universalmente aceita. Segundo o *Seventh Report of the Joint National Committee (JNC VII)* (2) e a *European Society of Hypertension / European Society of Cardiology (ESH/ESC)* (25), HAR é definida quando a PA mantém-se em níveis acima das metas recomendadas com o uso de, no mínimo, três fármacos anti-hipertensivos com ações sinérgicas em doses máximas ou toleradas, sendo um deles idealmente um diurético. Entretanto, a *American Heart Association* (AHA), em

seu *"Scientific Statement"* especificamente sobre HAR, incluiu pacientes em uso de quatro ou mais fármacos anti-hipertensivos, em dosagens otimizadas, com controle adequado de PA também como hipertensos resistentes (13). Dessa maneira estes dois grupos hoje são considerados conjuntamente como hipertensos resistentes.

Existe contudo, controvérsia se todos estes pacientes deveriam ser colocados em conjunto, sendo uma nova terminologia proposta, na qual deveriam ser separados em dois subgrupos: resistentes e refratários (26-28). Esta nova classificação ainda está em discussão, não sendo totalmente aceita (29), existindo contudo, dados novos consistentes de que estes grupos seriam distintos e deveriam ser separados (30).

No entanto, a simples divisão em pacientes controlados e não controlados já é consagrada e torna os grupos reconhecidamente diferentes. Uma análise epidemiológica de 90 pacientes com diagnóstico de HAR segundo a AHA, divididos em dois grupos de acordo com os níveis pressóricos, os controlados (com, no mínimo 4 fármacos) e os não controlados mostrou que no grupo de não controlados, níveis pressóricos (tanto PAS quanto PAD), pressão de pulso, índice de massa corporal, atividade de renina plasmática, concentração de aldosterona plasmática e relação aldosterona/renina são significativamente maiores, quando comparados ao grupo controlado (31). Além disso, o grupo não controlado apresentou maior espessura íntima-média, velocidade de onda de pulso, HVE (15, 31), disfunção endotelial e menor queda noturna dos níveis pressóricos que os controlados (32). É digno de nota que 20% dos pacientes controlados foram excluídos porque apresentavam uso de fármacos em doses não otimizadas, mantendo-se apenas os verdadeiramente resistentes controlados (31). Com isso, demonstrou-se que existem diferenças importantes

entre os indivíduos controlados e não controlados, o que justifica a elevada morbimortalidade deste último grupo.

1.2.2 Pseudorresistência

É de extrema importância para avaliação diagnóstica, definir a presença de pseudorresistência entre os indivíduos hipertensos resistentes. Essa entidade é descrita como o aparente não controle pressórico, que na verdade, é devido a medidas inadequadas da PA, escolha terapêutica, tanto de fármacos quanto de dosagens inapropriados, falta de aderência ao tratamento e efeito jaleco branco (33). Conforme comprovação prévia, uma intensiva monitorização de aderência ao tratamento, possibilita a identificação dos pacientes hipertensos "verdadeiramente" resistentes (34).

1.2.3 Prevalência

A prevalência desta patologia ainda é incerta e varia conforme a especialização do centro e o tipo de análise epidemiológica. Estudos iniciais sobre hipertensão arterial, entre as décadas de 70 e 80, estimaram prevalências oscilando entre 3% e 13% do total de pacientes hipertensos usando até terapia quádrupla (12, 35, 36). Mais recentemente, demonstrou-se incidência de 1,9% de HAR em pacientes em seguimento por 18 meses (37). Relatos que descrevem uma prevalência maior que essas, normalmente não excluem pacientes com avaliação de pressão ambulatorial normal ou não submetem os pacientes a uma avaliação sistematizada para o diagnóstico de HAR, envolvendo exclusão de causas secundárias ou removíveis e pseudorresistência (38, 39). Em relação à prevalência, o estudo de Framingham mostrou 52% de pacientes sem controle adequado de PA (6). Entretanto,

estes altos índices estão acrescidos de má aderência e tratamento inadequado. O estudo ALLHAT (*Design The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial*), no qual havia diversidade étnica importante e o tratamento dos pacientes era mais adequado e controlado, após 5 anos de seguimento, aproximadamente 50% dos indivíduos necessitavam de 3 ou mais classes de fármacos para o tratamento (40). Contudo, este valor pode estar superestimado, devido aos regimes terapêuticos restritos permitidos neste estudo, além das principais associações terapêuticas utilizadas, como diuréticos tiazídicos, inibidores da ECA e bloqueadores de canais de cálcio, não serem encorajadas (41). Uma análise dos pacientes do *National Health and Nutrition Examination Survey*, entre 2003 e 2008, classificou em hipertensos resistentes 12,8% dos indivíduos tratados HAS (42). Talvez, o estudo mais criterioso para tal fim seja o da Universidade do Alabama (Birmingham) (43), onde os pacientes eram encaminhados com hipertensão de difícil controle e acompanhados por pelo menos 6 meses antes de considerados verdadeiros hipertensos resistentes. Destes, 9,5% permaneceram refratários ao tratamento (43). Outros estudos corroboram estes dados, mostrando uma prevalência aceita entre 5 e 15% (44), demonstrando inclusive, um aumento na prevalência ao longo das duas últimas décadas, de 5,5% para 8,5% e, então, 11,8% entre 2005 e 2008 (43, 45, 46).

1.2.4 Fisiopatologia

A HAR apresenta uma fisiopatologia multifatorial, que evidencia pior prognóstico quando comparada a HAS, sendo que os mecanismos de resistência ao tratamento não são totalmente conhecidos. O fato da definição de HAR basear-se estritamente em níveis pressóricos e número de drogas dificulta ainda mais o estabelecimento de mecanismos

fisiopatológicos para a doença. Dados demográficos do estudo de Framingham mostram que a falência de controle pressórico está associada a valores extremamente elevados de PA já na avaliação inicial (6). Obesidade também é preditor de insucesso no controle da PA, porém os mecanismos são complexos e não totalmente elucidados, mas incluem excreção deficiente de sódio, aumento da atividade simpática e ativação do SRAA (31, 47, 48). Adicionalmente, diabetes *mellitus* também dificulta a redução dos níveis pressóricos sanguíneos (31, 41, 49).

Algumas características são comuns à maioria dos pacientes: hiperativação do sistema nervoso simpático e sistema renina-angiotensina-aldosterona (SRAA) (50-52), excesso de aldosterona (53, 54), expansão volêmica (55), disfunção endotelial (15, 56) (57), e elevação da resistência vascular periférica (58). Recentemente, hipoxemia intermitente cíclica (59), resistência à insulina (60) e alterações na função de adipocinas (61) também têm sido associadas à fisiopatologia da doença (Figura 1).

A sobrecarga de volume parece justificar, em grande parte, a fisiopatologia da doença (55) (acompanhada por um balanço positivo de sódio corporal). Um dos principais fatores determinantes da PA – e da composição aquosa do corpo – é o equilíbrio entre ingestão hídrica oral, e perdas renal e extra-renal. Este balanço é regulado pelo SRAA, peptídeo natriurético atrial e os receptores atriais e renais de pressão (62). A patogenia desta característica é diversa: nefrosclerose hipertensiva e/ou disfunção renal estabelecida; uso de vasodilatadores diretos e simpatolíticos periféricos (que promovem reabsorção renal hídrica em resposta a uma vasodilatação sistêmica); diminuição da perfusão renal (e filtração glomerular) resultante do uso intensivo de anti-hipertensivos; sobrecarga de sódio na dieta; obesidade e síndrome metabólica; níveis elevados de aldosterona plasmática; e uso

inadequado de diuréticos (41, 58, 63).

Figura 1: Fisiopatologia da HAR relacionando os principais mecanismos envolvidos (Modificado de *Tsioufis, Kordalis et al.*)(64). Condições como apneia obstrutiva do sono (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 a propriedade de hiperativação recíproca, podendo incorrer em HAR.

O fato da sobrecarga de volume ser um componente frequente incita o uso de diuréticos. Estudos de intervenção apresentam resultados favoráveis ao uso intensivo de diuréticos, apesar de alguma controvérsia. Alguns demonstram que a resposta pode não ser satisfatória (43) enquanto a maioria traz resultados promissores: por meio do bloqueio nefrológico sequencial (65) ou simplesmente pela intensificação do uso – embora sob o risco de piora da função renal (58). Os fatores contribuintes para a HAR são sumariamente

listados na Tabela 1.

1.2.4.1 Padrão Hemodinâmico da HAR

Alguns autores sugerem no entanto, que o aumento da resistência vascular periférica total e/ou do débito cardíaco, seriam mais importantes que a sobrecarga de volume. Essa conclusão é sugerida pelo fato de não haver supressão dos níveis de aldosterona ou de atividade de renina plasmática – resultados esperados na sobrecarga de volume – em hipertensos refratários, quando comparados a resistentes controlados. Além disso, estes pacientes refratários apresentariam frequência cardíaca persistentemente mais elevada que o último grupo; sugerindo uma maior influência do sistema nervoso simpático para a resistência ao tratamento (43).

Tabela 1: Fatores contribuintes para hipertensão arterial resistente

Fatores contribuintes
Expansão volêmica
Terapia diurética inadequada
Retenção hídrica causada por doença renal crônica
Ingestão excessiva de sódio
Obesidade/resistência insulínica
Substâncias exógenas
Anti-inflamatórios não-esteroidais
Contraceptivos orais
Álcool
Corticosteroides
Esteroides anabólicos
Agentes simpatomiméticos
Cafeína

	Ciclosporina
	Eritropoetina
	Agentes quimioterápicos
	Antidepressivos

Adaptado do Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (2).

Ademais o aumento da resistência vascular periférica total tende a ser acentuado e persistente na evolução da doença hipertensiva (66). Geralmente atribuído a um aumento no tônus vascular (67), o mecanismo é comum aos hipertensos em geral, nos quais após um aumento inicial do débito cardíaco, eleva-se a resistência vascular periférica total progressivamente, independentemente da classificação da hipertensão. Ocorre precocemente aos esforços e, com a progressão da doença, passa a ocorrer ao repouso; efeito este demonstrado em longas coortes de até vinte anos de seguimento (68). A grande influência do estímulo simpático tem servido de base racional para os recentes e crescentes estudos intervencionistas de denervação renal para o tratamento da HAR, com resultados promissores (69, 70).

1.2.5 Lesões de órgãos-alvo

As lesões de órgãos-alvo apresentam alta correlação com a HAR e são divididas em vasculares, cerebrais, cardíacas e renais. As alterações vasculares podem estar presentes já nos estágios iniciais da doença, se associando a maior grau de disfunção endotelial, avaliada por vasodilatação dependente de endotélio e aumento de biomarcadores inflamatórios. Isto leva ao aumento da rigidez vascular, avaliado pela velocidade de onda

de pulso (15, 31, 71). O sistema nervoso central também pode estar acometido precocemente e é o órgão que mais se beneficia de redução dos níveis pressóricos. Estenoses de carótidas, aterosclerose intracraniana e arco aórtico e lesões cardíacas estão entre os responsáveis por fenômenos tromboembólicos isquêmicos. A hipertensão não controlada pode, com o passar do tempo, levar a formação de pequenos aneurismas cerebrais que, ao romper, causam hemorragias cerebrais ou subaracnóideas (72).

A HVE é a principal lesão cardíaca e, apesar de relatos de prevalência de 16% nos pacientes hipertensos resistentes acometidos (49), no Brasil encontramos relatos de 83,3%, diagnosticada pelo ecocardiograma (48). Nestes pacientes, a presença de alterações eletrocardiográficas com padrão de *strain* (inversão de onda T e depressão do segmento ST nas derivações V_5 e V_6) correlacionam-se a pior prognóstico (73, 74). Esta alteração constitui-se fator de risco independente cardiovascular, aumentando em até 1,5 vezes a mortalidade (75, 76). A HVE se associa à aumento da circulação de mediadores inflamatórios e aldosterona e reduz a reserva coronariana, levando à aterosclerose mais acentuada, rigidez arterial, insuficiência cardíaca, arritmias e disfunção endotelial (15, 31, 48, 77). Quando analisamos alterações funcionais induzidas pela HVE, a disfunção diastólica do ventrículo esquerdo é a mais comum das morbidades, acarretando um risco aumentado de progressão para a insuficiência cardíaca (78). Seu diagnóstico é baseado em alterações eletrocardiográficas e aumento de massa ventricular esquerda indexada para a superfície corpórea ao ecocardiograma (79).

As alterações renais também ocorrem precocemente e são comuns, levando a um quadro de nefroesclerose caracterizada por arterioloesclerose e arterioesclerose, hialinose e lesões túbulo-intersticiais e glomeruloesclerose segmentar e focal. Nas formas de

hipertensão mais malignas, a hiperplasia miointimal e necrose fibrinóide são descritas como lesões principais.

1.2.6 Disfunção Endotelial

O endotélio pode ser considerado um órgão endócrino ativo que, em respostas a estímulos humorais, neurais e mecânicos, sintetiza e libera substâncias vasoativas que modulam tônus, calibre vascular e fluxo sanguíneo, desempenhando papel fundamental na regulação da circulação e na proliferação e migração das células do músculo liso vascular e adesão de leucócitos (80, 81).

Quando exposto aos fatores de risco, como HAS, o endotélio apresenta alterações funcionais, denominadas genericamente de disfunção endotelial (DE) (82) caracterizada por diminuição na biodisponibilidade de óxido nítrico (NO) secundário ao estresse oxidativo aumentado (83). A disfunção endotelial é uma condição patológica sistêmica (84) na qual existe um desequilíbrio entre substâncias vasodilatadoras, antimitogênicas e antitrombogênicas (fatores relaxantes derivados do endotélio (85)) e substâncias vasoconstritoras, pró-trombóticas e com propriedades proliferativas (fatores constrictores derivados do endotélio, como catecolaminas, angiotensina II e endotelina-1 (86)).

As células endoteliais estão disfuncionais em várias doenças cardiovasculares e na HAS. Usualmente, essa disfunção é expressa como ‘alteração do relaxamento dependente do endotélio’ causada, principalmente, por redução da liberação e/ou ação dos fatores dilatadores derivados do endotélio, podendo também ocorrer liberação de fatores constritores derivados do endotélio, contribuindo dessa forma, para DE. Portanto, a DE constitui um marcador precoce e é elemento-chave na patogênese das doenças

cardiovasculares (87). Grandes evidências indicam que pacientes hipertensos, inclusive com HAR, apresentam disfunção endotelial, tanto em distritos vasculares periféricos como em coronarianos (88). Em estudo foi relatado que a função endotelial está claramente reduzida nos hipertensos não controlados em relação aos sujeitos normotensos (57). Além disso, mais especificamente, foi demonstrado em estudo recente que, em relação aos subgrupos da HAR, pacientes resistentes não controlados (HARNC) apresentam piora da função endotelial quando comparados ao subgrupo resistente controlado (HARC) (89).

1.2.7 Diagnóstico

Segundo o 1º Posicionamento Brasileiro sobre a HAR, o diagnóstico exige inicialmente o afastamento da pseudorresistência como causa. Isto deve ser feito comprovando-se a aderência tanto da terapia farmacológica quanto não farmacológica e uso de fármacos na posologia otimizada, ou seja, a máxima permitida ou tolerada (41). Em seguida, excluindo-se a hipertensão do jaleco branco – com comprovação de elevados níveis pressóricos não só no consultório médico, mas também durante o restante do dia e/ou da noite – através de MAPA ou MRPA (90). Após a comprovação da hipertensão, deve-se pesquisar causas secundárias de HAR, cujas principais então listadas na tabela 2.

Tabela 2: Principais causas de hipertensão secundária.

Frequentes:
Apneia Obstrutiva do Sono
Doença Renal Parenquimatosa
Estenose de Artéria Renal
Hiperaldosteronismo Primário

Raras:
Feocromocitoma
Doença de Cushing
Hiperparatireoidismo
Coarctação de Aorta
Tumor Intracraniano

Adaptado de Calhoun et al (41).

1.2.8 Hipertensão Secundária

Apneia obstrutiva do sono é caracterizada por qualquer grau de obstrução das vias aéreas superiores, limitando ou impedindo o fluxo normal respiratório durante o sono (33), sendo causa frequente de hipertensão secundária associada HAR (91-93). Em estudo clínico com 125 pacientes avaliados quanto a motivos conhecidos de resistência, 64% apresentavam AOS (93). O diagnóstico deve ser realizado através de polissonografia.

A doença renal parenquimatosa é consequência de inadequado controle pressórico ao longo dos anos. Esta patologia está associada a retenção hídrica, ativação excessiva do SRAA e uso de anti-inflamatórios não esteroidais. Todos os pacientes com HAR devem ser avaliados quanto à função renal (94).

Estenose de artéria renal é uma patologia renovascular de etiologia predominantemente aterosclerótica (90%), cuja prevalência aumenta com a idade (94). O diagnóstico sempre deve ser pesquisado através de exames de imagem, como ultrassom de artérias renais, cintilografia ou tomografia computadorizada.

O hiperaldosteronismo primário foi primeiro descrito por Conn em 1955 (95). Na ocasião, uma paciente do sexo feminino apresentava-se com hipertensão resistente, hipocalemia e alcalose metabólica, devido à presença de um adenoma produtor de

aldosterona. Atualmente, essa síndrome inclui o aumento dos níveis de aldosterona, sem necessariamente apresentar adenomas, mas hiperplasia adrenal bilateral (33, 96). Estudos mostram incidência em torno de 8% a 13% de hiperaldosteronismo em pacientes hipertensos (97, 98). Quando avaliamos a prevalência entre os hipertensos resistentes esta relação se torna maior, com valores de 17% a 23% (99-102). Acredita-se que esta doença aumente o risco cardiovascular através da elevação dos mediadores inflamatórios levando a lesões cardíacas e vasculares (103, 104), exemplificadas por HVE (105), doença renal crônica (106), disfunção endotelial (107) e aumento da razão íntima-média (108). O diagnóstico não necessita da presença de hipocalemia. A razão da concentração de aldosterona/atividade plasmática de renina ≥20 sugerem o diagnóstico, que deve ser confirmado pelo aumento na excreção urinária de aldosterona em 24 horas. Outra maneira é confirmando-se a falta de supressão da secreção de aldosterona através de expansão volêmica (infusão de soro fisiológico ou dieta rica em sal) ou bloqueio do SRAA com inibidores da ECA (109). Com as positividades, faz-se necessário a realização de uma ressonância nuclear magnética de cortes finos para a pesquisa de tumores adrenais (94).

1.2.9 Resistência e Refratariedade

O termo Resistente foi inicialmente usado na literatura médica em 1960 por Vandyne et al. (110), praticamente no mesmo momento que seu termo coincidente – refratário – utilizado por Lee et al. (111) em 1958. Com relação à terminologia, o *Webster´s Dictionary* define resistente como algo "incapaz de ser afetado" e refratário como algo "que não responde ao tratamento" (112).

Desde o início estes termos foram usados sem distinção para classificar este tipo de hipertensão que não respondia bem ao tratamento, mantendo níveis pressóricos elevados a despeito do uso de múltiplas medicação anti-hipertensivas. Apesar do uso concomitante destes termos nos últimos 50 anos, na última década, autores têm proposto subdivisões dentro do grupo dos hipertensos resistentes, na tentativa de cunhar um novo subgrupo de hipertensos refratários. A tabela 3 mostra a evolução nestes últimos anos das definições propostas para este subgrupo.

Tabela 3: Evolução cronológica das definições propostas para Hipertensão Refratária.

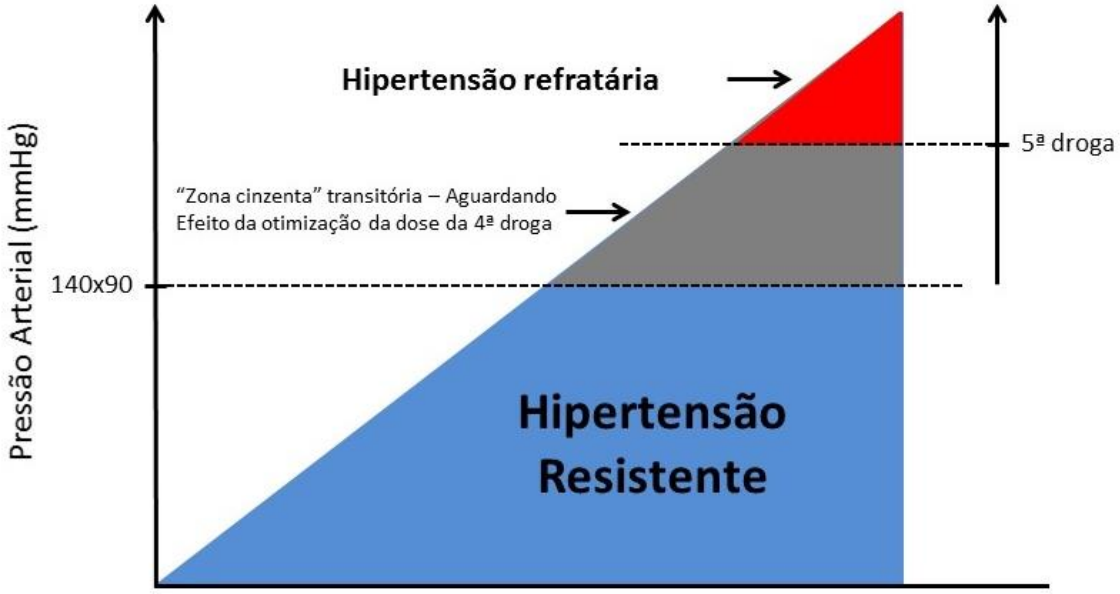
Autor	Ano	Definições
Martell(113)	2003	Refratário e Resistente usados ainda como sinônimos.
Ram(114)	2006	
Silverstein(115)	2008	
Sander(116)	2011	Refratário definido como Resistente descontrolado apesar do uso de 4 ou mais drogas anti-hipertensivas.
Acelajado(117)	2012	Refratário definido como Resistente descontrolado.
Moreno(118)	2012	
Calhoun(119)	2013	Refratário definido como Resistente que se mantém descontrolado com uso de 5 ou mais drogas.

Mais recentemente, pesquisadores classificaram este novo subgrupo de maior risco. As últimas definições foram propostas por:: (i) Acelajado et al. – Hipertensão refratária é aquela resistente onde não há controle pressórico após pelo menos 3 visitas em clínica

especializada (117), e (ii) Calhoun et al. – Hipertensão refratária é aquela resistente que se mantém acima da meta pressórica com uso de no mínimo 5 drogas anti-hipertensivas (119) (Figura 2).

Esta subdivisão evidencia diferenças importantes entres os grupos. Com relação às lesões de órgãos alvo, o grupo de hipertensos refratários apresenta maior massa ventricular esquerda (179±49 *vs.* 142±30 g/m^2, p<0,05) e rigidez arterial(VOP – 12,9±1,7 *vs.* 9,1±1,1 m/s, p<0,05) (14), além de maior prevalência de hipertrofia ventricular esquerda, microalbuminúria e disfunção renal quando comparados com resistentes (119). Apesar das diferenças clínicas, as variáveis antropométricas – IMC, idade e sexo – destes grupos são similares (120),(117). Com relação à raça, a negra apresenta maior prevalência nos refratários em comparação aos resistentes (119).

Figura 2. Representação gráfica da evolução do atendimento para caracterizar Hipertensão Refratária.



1.2.10 Prognóstico

Para uma melhor avaliação de prognóstico, estudos como coortes prospectivas se fazem necessários. Pelos critérios diagnósticos relativamente recentes e necessidade de protocolo restritivo para um adequado seguimento, além de amostras limitadas, não há ainda disponibilidade destes estudos. Presumivelmente ele é menos favorável, avaliando-se que o risco de complicações cardiovasculares se eleva linearmente com o incremento dos níveis pressóricos (121). Estes indivíduos também apresentam diversos fatores de risco cardiovasculares associados, como idade avançada, obesidade, diabetes e doença renal crônica (122), além de lesões de órgãos-alvo, como HVE e marcadores de risco como o aumento da espessura íntima-média(123). Em estudo prévio, demonstrou-se risco relativo de 1,47 em hipertensos resistentes (37). O grau de redução desses riscos com o tratamento da HAR também é desconhecido (41). Atualmente, o nosso grupo de pesquisa iniciou avaliação retrospectiva dos pacientes de nossa clínica especializada com o intuito de avaliar prognóstico e fatores associados aos desfechos clínicos.

1.2.11 Tratamento

1.2.11.1 Não Farmacológico

Como já é parte dos critérios diagnósticos, o tratamento com múltiplas medicações – ao contrário da HAS – já é regra na HAR. No entanto, como qualquer doença crônico-degenerativa do sistema cardiovascular, as atitudes de mudança de estilo de vida e medidas não farmacológicas são de extrema importância como terapia adjuvante (41).

Pacientes com HAR devem ser orientados quanto à importância da prática de exercícios físicos regulares, redução de sal na dieta, perda de peso e limitação do consumo de bebidas alcoólicas à pequenas doses (41, 121).

Apesar da dieta hipossódica reduzir os níveis pressóricos moderadamente, os pacientes com HAR são especialmente sensíveis ao sal. Em estudo prévio mostrou-se que um consumo diário de até 2,5g de sal por dia reduz em 23x9 mmHg a PA (63), mostrando a importância da redução desta ingesta, mesmo sendo uma meta de difícil alcance. Recomenda-se, pela Organização Mundial de Saúde, um consumo diário de 1,2g de sal por dia (121).

O consumo de álcool está intimamente ligado à elevação da PA. Homens que consomem mais de 4 doses de álcool por dia têm 50% mais chance de apresentar valores pressóricos fora das metas (6). A abstinência de álcool em grandes bebedores reduziram os níveis de PAS e PAD em 7,2 e 6,6 mmHg, respectivamente, além da prevalência de hipertensão entre os participantes ter reduzido de 42% para 12% (124). O consumo alcoólico deve ser ≤20g de etanol por dia ou abstinência total, se possível (121).

A redução de peso diminui a PA de forma significativa, devido à melhora da retenção hídrica, da AOS e melhora da estimulação do sistema nervoso simpático (41, 93, 125). Pacientes com IMC ≥30 apresentam chance 50% maior de apresentar PA não controlada em comparação a pessoas com IMC normal (6, 31). Com isso, a perda de peso deve sempre ser estimulada e buscada entre os indivíduos com HAR (44).

Existe um benefício claro entre atividade física e redução da PA (41, 126). A prática de exercícios físicos regulares, além de reduzir os níveis pressóricos, também melhora o

perfil metabólico, tanto com exercícios de resistência quanto aeróbicos (126). Assim, estes pacientes dever ser encorajados a realizar atividade física leve a moderada (121).

1.2.11.2 Farmacológico

A terapêutica na HAR não apresenta estratégia definida e/ou universalmente aceita. Mesmo para o tratamento das HAS – em que existe consenso de especialistas e diretrizes para orientação – a ordem das prescrições são diferentes entre os consensos diversos como o europeu, brasileiro e americano (25, 127, 128). Preconiza-se atingir a meta pressórica de PA de consultório ou MRPA de 130/80mmHg ou 125/75mmHg na MAPA (129).

O esquema anti-hipertensivo deve almejar o bloqueio de todos os possíveis mecanismos envolvidos na HAS. Logo, a associação de um diurético tiazídico com bloqueador do SRAA (inibidor da ECA, ou antagonista do receptor de angiotensina II) e um antagonista dos canais de cálcio dihidropiridínico é considerada a melhor combinação tripla, mais eficaz, sinérgica e muito bem tolerada (130).

Em relação ao uso de um quarto fármaco, não há consenso sobre sua escolha, tendo em vista que faltam estudos comparativos entre as classes demonstrando superioridade em potência anti-hipertensiva e proteção cardiovascular (44). Segundo o estudo ASCOT (*Anglo-Scandinavian Cardiac Outcomes Trial*), a adição de espironolactona, um bloqueador de receptores mineralocorticoides, ao esquema tríplice tradicional apresentou quedas de 21,9 mmHg de PAS e 9,5 mmHg da PAD após 1,3 ano de tratamento (131). Outro estudo realizado em 2009, com pacientes hipertensos resistentes controlados e não controlados também mostrou resultados semelhantes (48). Esta redução é independente da presença de hiperaldosteronismo primário e não relacionada aos níveis plasmáticos ou

urinários basais iniciais de aldosterona, atividade plasmática de renina ou relação aldosterona/renina (132, 133).

A escolha de fármacos que sejam adicionados ao esquema quádruplo deve ser individualizada (121) de acordo com a experiência de cada médico e de outras comorbidades que o paciente possa ter. Inibidores adrenérgicos, incluindo beta e alfa-bloqueadores e inibidores de ação central, vasodilatadores e inibidores de renina, também são muito importantes como opções terapêuticas aos pacientes com HAR (44). Entretanto, seu uso está mais condicionado a situações especiais, como a necessidade de redução de frequência cardíaca, em relação ao uso de betabloqueadores. Além disso, apresentam maior incidência de efeitos adversos (41, 121).

Recentemente, uma nova classe de fármaco foi testada no tratamento anti-hipertensivo: os inibidores de fosfodiesterase-5 (134, 135). No entanto, apesar de algum grau de sucesso ter sido demonstrado, estudos prospectivos a longo prazo são necessários para obter resultados mais conclusivos.

1.2.11.3 Outros Tratamentos

Existem ainda, novas modalidades terapêuticas que estão em desenvolvimento para ajudarem o tratamento farmacológico no controle pressórico dos pacientes resistentes.

A estimulação dos barorreceptores presentes no seio carotídeo estimula o sistema nervoso parassimpático, propiciando, além de bradicardia, aumento na excreção renal de sódio e água. A hipervolemia é um dos principais mecanismos envolvidos na resistência da hipertensão destes pacientes, sendo que o aumento da diurese é um alvo terapêutico importante a ser atingido. As tentativas de reduzir a hiperatividade do sistema nervoso simpático para reduzir os níveis pressóricos arteriais remontam ao início do século 20

(136). A estimulação tanto aguda quanto crônica do seio carotídeo para a redução da hipertensão arterial começou a mostrar resultados positivos nos anos 1960. No entanto, na ocasião, os aparelhos responsáveis pela estimulação eram grandes e com baterias de pouca duração (137). Nos dias de hoje, esta terapia está novamente em desenvolvimento, com técnicas novas de implantação, que reduzem seus efeitos colaterais, utilizando aparelhos mais modernos, menores e de duração maior. Estudos recentes têm demonstrado benefício da estimulação crônica como adjuvante ao tratamento da HAR, inclusive com redução do número de fármacos administrados diariamente (138, 139).

Outro tratamento que vem ganhando destaque é a denervação simpática renal. Os nervos simpáticos renais contribuem para o surgimento e manutenção da HAS, por meio de liberação de renina, retenção de sódio e aumento da volemia (140). Entre os anos 1920 e 1930, a simpatectomia radical era um dos tratamentos utilizados para reduzir a PA em hipertensos graves. Contudo, este procedimento apresentava altos índices de complicações (141). Recentemente, novas técnicas intervencionistas com bloqueio da ação simpática aferente e eferente por radiofrequência têm mostrado redução significativa na HAS, sem maiores complicações descritas (142). Os estudos SIMPLICITY HTN-1 (*Catheter-based renal sympathetic denervation for resistant hypertension*) e SIMPLICITY HTN-2 (*Renal sympathetic denervation in patients with treatment-resistant hypertension*) trouxeram grande promessa à comunidade científica com grande diminuição pressórica e da necessidade de medicamentos após o procedimento (69, 70). A grande crítica se devia ao fato dos estudos não serem controlados. Há dois meses, no entanto, tornou-se público o primeiro estudo controlado sobre denervação renal – SIMPLICITY HTN-3 (*A controlled trial of renal denervation for resistant hypertension)* – que ao comparar o procedimento

com o *sham procedure* (intervenção fictícia) de maneira cega, mostrou-se ineficaz em baixar a pressão arterial (143).

1.3 Hipertensão / Efeito do Jaleco Branco

Hipertensão do jaleco branco é um fator comum de pseudorresistência (144). O efeito do jaleco branco (EJB) 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 monitoração ambulatorial da pressão arterial (MAPA) ou monitoração residencial da pressão arterial (MRPA). Este fenômeno tem sido relatado em 20% a 40% dos pacientes com hipertensão não-tratada (145) e apresenta alta prevalência dentre os pacientes com HAR (20-52%) (146, 147). A ocorrência do EJB tem sido atribuída ao estresse mental, resposta hiperativa do paciente em presença de algum profissional de saúde (especialmente o médico), e hiperatividade simpática (148, 149).

A definição do EJB pode ser um pouco confusa. A diferença desta para a hipertensão do jaleco branco é que a última é um fenômeno onde pacientes não tratados apresentam PA elevada perante um profissional de saúde (consultório) enquanto a aferição ambulatorial como por MAPA mostra níveis pressóricos normais. Já no EJB a "queda" pressórica vista no período de vigília da MAPA pode ocorrer também em tratados e não necessariamente normaliza a PA (150).

Na hipertensão do jaleco branco, o risco cardiovascular não está aumentado, sendo menor quando comparado com pacientes com hipertensão mascarada ou mantida (151). A hipertensão do jaleco 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. Recomenda-se que todos os pacientes suspeitos de hipertensão resistente devam ser submetidos a MAPA (152). 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 (153).

1.4 Doença arterial coronariana e isquemia miocárdica

Isquemia miocárdica é definida como o desequilíbrio entre a oferta e o consumo de oxigênio pelo miocárdio. Está intimamente relacionada à doença arterial coronariana (DAC) obstrutiva, devido à limitação ao fluxo sanguíneo imposta por esta patologia. A DAC, em conjunto com outras doenças cardiovasculares, tem sido grande responsável por morbidade e mortalidade em diversas regiões do mundo (154, 155).

A isquemia silenciosa – onde a isquemia miocárdica ocorre na ausência de qualquer sintomatologia típica – é a apresentação mais frequente da coronariopatia crônica, descrita inicialmente em 1981 por Cohn *et al.* (156). A presença de infradesnivelamento do segmento ST sem *angina pectoris* durante o teste de esforço tem sido frequentemente descrito em pacientes com hipertensão arterial essencial, sem história pessoal de DAC, infarto do miocárdio ou sintomas (157). Essa presença de isquemia silenciosa relaciona-se a

maior risco de morte e eventos cardíacos (158-160), chegando a verificar-se mortalidade até três vezes maior (24% *vs*. 8%) em relação àqueles sem evidência de isquemia (161). Assim, torna-se de fundamental importância sua detecção precoce, de maneira a atuar sobre os fatores de risco passíveis de modificação e/ou tratamento, evitando a progressão da doença, mesmo antes de suas complicações e manifestações clínicas.

No entanto, ainda permanece obscuro quais fatores estão associados e/ou são responsáveis pela ocorrência da isquemia silenciosa, havendo influência das estenoses das artérias coronárias, disfunções do endotélio e dos fatores de consumo de oxigênio, principalmente nos pacientes em uso de medicações anti-hipertensivas (162-164).

A cintilografia de perfusão miocárdica com (99m)tc-sestamibi destaca-se entre os diversos métodos capazes de determinar a repercussão funcional das lesões obstrutivas das artérias coronárias. O método possui grande acurácia para detectar isquemia miocárdica, além de ser uma importante ferramenta para prever o risco de eventos coronarianos futuros, possibilitando melhor estratificação dos pacientes e orientação de uma melhor conduta terapêutica (165, 166).

A cintilografia de perfusão miocárdica com (99m)tc-sestamibi faz o diagnóstico preciso de isquemia miocárdica e coronariopatia em pacientes assintomáticos com hipertensão arterial (19, 20). No entanto, uma vez que estes pacientes são assintomáticos, a avaliação de fatores preditores de isquemia miocárdica no grupo de hipertensos resistentes pode ajudar a evitar gastos extras guiando uma melhor avaliação de isquemia.

2 JUSTIFICATIVA DO ESTUDO

A isquemia miocárdica é grande responsável por morbidade e mortalidade cardiovasculares, especialmente em pacientes com fatores de risco – dentre eles a hipertensão. No entanto, até o presente momento, pouco se sabe em relação à prevalência desta alteração especificamente no grupo de pacientes hipertensos resistentes – um nicho *per se* com pior prognóstico e mais acometido por lesões de órgãos alvo e marcadores de lesão cardiovascular.

Além disso, também são desconhecidos os fatores que estão associados à esta alteração nos pacientes com HAR.

Como os pacientes que apresentam isquemia silenciosa não apresentam sintomatologia – ou seja, não indicam ao seu clínico atendente a necessidade de investigação específica para o quadro de isquemia – é prudente que um grupo de alterações identificáveis ao exame clínico e propedêutico seja identificado a fim de guiar uma melhor e mais direcionada investigação desta patologia, para melhorar morbidade e mortalidade cardiovasculares neste grupo de pacientes.

3 OBJETIVOS

1- Objetivamos com este estudo avaliar a presença de isquemia miocárdica silenciosa em uma população de hipertensos resistentes, comparando variáveis clínicas, laboratoriais e lesões de órgãos-alvo de pacientes com e sem isquemia miocárdica.

2- Com estas variáveis que diferem entre os grupos, visamos encontrar os fatores que podem ser classificados preditores de isquemia neste subgrupo de pacientes.

4 CAPÍTULO I

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Modolo R, Ruggeri Barbaro N, de Faria AP, Rodrigues Sabbatini A, Paganelli MO, Fontana V, Moreno H.
Blood Press. 2014 Feb 26. [Epub ahead of print]

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Blood Pressure, 2014; Early Online: 1–5

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ORIGINAL ARTICLE

The white-coat effect is an independent predictor of myocardial ischemia in resistant hypertension

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Abstract

White-coat hypertension (WCH), commonly found in pseudoresistant hypertension, does not pose higher cardiovascular risk than hypertensive status. However, when the decrease of the out-of-office blood pressure does not reach normal levels – the white-coat effect (WCE) – the repercussions are still obscure. We investigated the repercussions of the WCE in myocardial perfusion in resistant hypertension (RHTN). We enrolled 129 asymptomatic RHTN subjects – divided into WCE ($n = 63$) and non-WCE ($n = 66$) – to perform rest and stress myocardial perfusion scintigraphy and biochemical tests. Groups were equal regarding age, gender and body mass index. There was a high prevalence of WCE (49%). WCE was associated with higher prevalence of myocardial ischemia (49.2% vs 7.6%, $p < 0.001$), microalbuminuria (60.3% vs 36.4%, $p = 0.01$) and higher heart rate (72 [64–80] vs 64 [60–69], $p < 0.001$), compared with non-WCE patients. On an adjusted logistic regression, heart rate was considered a predictor of WCE (OR = 1.10, 95% CI 1.04–1.15; $p < 0.001$), but not MA (OR = 1.8, 95% CI 0.8–3.9; $p = 0.15$). On a second model of adjusted logistic regression, WCE was an independent predictor of myocardial ischemia (OR = 14.7, 95% CI 4.8–44.8; $p < 0.001$). We found a high prevalence of WCE in RHTN, and this effect may predict silent myocardial ischemia in this subset of hypertensive patients. In this group of hypertensives special attention should be given to the WCE.

Key Words: *Myocardial ischemia, resistant hypertension, white-coat effect*

Introduction

Cardiovascular disease (CVD) is still the major cause of overall mortality in most of Western countries. Coronary heart disease (CHD) is responsible for 16% of all deaths, and causes one heart attack about every 34 s and one death every minute, in the USA alone (1). Hypertension is a major risk factor for CVD, where an increase of 10 mmHg can almost triple the relative risk of CHD (2). However, only 53% of the known hypertensive subjects are at their blood pressure (BP) goal (1). A small but significant number of these uncontrolled patients (varying from 8.9% to 14.5%) (3–5) are considered to have resistant hypertension (RHTN) (6), presenting worse cardiovascular outcomes (7).

The white-coat effect (WCE – a phenomenon where the patient has a lower out-of-office BP than that measured in the clinic) poses a high prevalence in RHTN (20-52%) (8,9). Its occurrence has been attributed to mental stress, hyperactive response of the patient in the presence of a healthcare professional and sympathetic hyperactivity (10,11). Although the absence of a link between white-coat hypertension (WCH) and CHD has already been settled, little is known between the WCE and myocardial ischemia, especially in RHTN patients – with high prevalence of this condition. We aimed to investigate WCE in RHTN and assess myocardial ischemia in this group of subjects.

Methods

This study was approved by the Research Ethics Committee of the local Medical School Institution

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(University of Campinas – Campinas, Brazil). All patients provided written informed consent before participation, and the study was carried according to the Declaration of Helsinki.

Study population

In this cross-sectional study, 129 patients regularly followed at the Outpatient Specialized Resistant Hypertension Clinic of the University of Campinas were enrolled. The subjects had to be completely characterized as having true RHTN according to the accustomed guidelines (6). All subjects were followed for at least 6 months to exclude pseudoresistance (due to non-adherence or non-optimal doses of antihypertensive therapy) (12,13) and secondary causes of hypertension (12,13). Patients with a moderate to high risk of obstructive sleep apnea (OSA) by the Berlin questionnaire or with diagnosed OSA were excluded (14).

For the analysis, subjects were divided into two groups according to the differences in BP levels in ambulatory BP monitoring (ABPM) and office BP. If the difference between 24-h ABPM and office BP measurements was higher than 20 mmHg in the systolic or higher than 10 mmHg in the diastolic BP, they were considered as having WCE ($n = 63$) (9,15). Patients not meeting these criteria were put in the non-WCE group ($n = 66$).

Blood pressure measurements

Office BP measurements were performed three times in each office clinic visit in the right upper arm. The patient was put in a calm environment, and measurements assessed after a 10-min rest in the sitting position with a validated digital sphygmomanometer (Omron HEM-711DLX, OMRON Healthcare Inc., Bannockburn, IL, USA), according to international guidelines (16).

Assessment of 24-h ABPM was performed with a validated automatic device (Spacelabs 90217, Spacelabs Inc, Redmon, WA, USA) (17), and measurements were taken every 20 min. Patients were oriented to maintain their usual daily activities. The parameters measured were: average 24-h systolic, diastolic, mean and pulse pressures, and heart rate. Data were only analyzed if there were at least 70% satisfactory measurements completed (18).

Myocardial perfusion scintigraphy imaging

Image acquisition at rest began 45 min after 925–1480 MBq of Tc-99m sestamibi injection. A dual-headed camera (Millenium MG, GE Medical Systems, Milwaukee, WI) with a high-resolution collimator rotated in a 180° orbit was used and acquired 64 projections (20 s/projection). Vasodilator stress was then induced by dipyrimidole and new images were acquired and interpreted by two experienced observers through a semi-quantitative visual interpretation of myocardial perfusion was in short-axis and vertical long-axis tomograms (19). Myocardial perfusion defects were described after a quantitative evaluation with a 17-myocardial segment approach, where each segment is graded through a 5-point scoring system (19). Images were compared at rest and after stress, and perfusion abnormalities were considered as having: (i) myocardial scarring when the perfusion defects were maintained on the two phases and (ii) myocardial ischemia if the perfusion defects appeared or increased after stress tomograms (19,20).

Statistical analysis

The analyses were performed using SigmaPlot software (Systat Software, Inc.v.12, Chicago, IL, USA). Data are shown as mean± standard deviation, or median (interquartile range) depending on data distribution, and categorical data were presented as percentages. Comparisons of groups were performed with Student's *t*-test or Mann–Whitney *U*, and categorical variables were compared by chi-square. Binary logistic regression was used to assess the prediction of myocardial ischemia by independent variables. The level of significance (α) accepted was 0.05.

Results

Patients enrolled had been diagnosed with RHTN for 17 ± 9 years and had a follow-up of 7 ± 2 years. Thirty-six patients (28%) had myocardial ischemia in the scintigraphy. There were no differences in age, gender, presence of risk factors and medication use between groups (Table I).

The WCE group presented: (i) higher prevalence of myocardial ischemia (49.2% vs 7.6%, $p < 0.001$), (ii) more microalbuminuria (MA; 60.3% vs 36.4%, $p = 0.01$), and (iii) higher 24-h ABPM heart rate (72 [64–80] vs 64 [60–69], $p < 0.001$), compared with those subjects without WCE. The differences between office BP and ABPM measurements, both systolic and diastolic, correlated with MA ($r = 0.34$, $p < 0.001$ and $r = 0.28$, $p = 0.001$) and heart rate ($r = 0.36$, $p < 0.001$ and $r = 0.18$, $p < 0.03$), respectively (Figure 1).

On a binary logistic regression, adjusting for body mass index (BMI), age and gender, heart rate was a predictor of WCE (OR = 1.10, 95% CI 1.04–1.15; $p < 0.001$), but MA was not (OR = 1.8, 95% CI 0.8–3.9; $p = 0.15$). On a second model of logistic regression, adjusting for the same variables, the presence of WCE was considered an independent predictor of

Table I. Characteristics of resistant hypertension (RHTN) patients with white-coat effect (WCE) and without (non-WCE).

Variables	WCE ($n = 63$)	non-WCE ($n = 66$)	p-value
Clinical characteristics			
Age (years)	53 ± 12	55 ± 9	0.30
Gender (female) (%)	45 (71%)	44 (67%)	0.69
BMI (kg/m^2)	31 ± 6	31 ± 7	0.90
Obesity (BMI > 29.9 kg/m^2) (%)	35 (56%)	29 (44%)	0.25
Duration of hypertension (years)	16 ± 8	18 ± 10	0.21
Current smoking habit (%)	10 (16%)	12 (18%)	0.90
Diabetes (%)	11 (17%)	10 (15%)	0.91
Dyslipidemia (%)	13 (21%)	15 (23%)	0.94
Family history of premature CHD (%)	18 (29%)	12 (18%)	0.23
Physical inactivity (%)	14 (24%)	23 (35%)	0.16
Left ventricular hypertrophy (%)	53 (84%)	53 (80%)	0.73
Myocardial ischemia, n (%)	31 (49)	5 (8)	< 0.001
24-h ABPM heart rate (bpm)	72 (64–80)	64 (60–69)	< 0.001
Antihypertensive drugs (%)			
Number of drugs	4.8 ± 0.7	5.1 ± 0.8	0.12
Diuretics (%)	96	97	0.96
ACEI (%)	49	43	0.55
ARA II (%)	76	73	0.80
Beta-blockers (%)	49	53	0.79
Calcium-channel blockers (%)	45	53	0.42
Laboratory parameters			
Cholesterol (mg/dl)	183 ± 27	192 ± 23	0.37
LDL-c (mg/dl)	110 ± 14	107 ± 17	0.25
HDL-c (mg/dl)	47 ± 12	50 ± 9	0.11
Triglycerides (mg/dl)	112 ± 58	125 ± 66	0.24
Fasting blood glucose (mg/dl)	104 ± 17	109 ± 19	0.12
Glycated hemoglobin HbA_1c (%)	7.3 ± 0.9	7.5 ± 0.8	0.18
Urea (mg/dl)	30 ± 15	34 ± 16	0.15
Serum creatinine (mg/dl)	1.0 ± 0.2	1.0 ± 0.3	0.37
MA (mg/g)	60 (16–124)	20 (10–63)	0.004
Patients with MA (%)	38 (60)	24 (36)	0.01
Serum potassium (mEq/dl)	4.0 ± 0.5	4.2 ± 0.4	0.16

BMI, body mass index; CHD, coronary heart disease; ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin-converting enzyme inhibitors; ARA II, angiotensin II receptor blockers; LDL-c, low-density lipoprotein-cholesterol; HDL-c, high-density lipoprotein-cholesterol; MA, microalbuminuria. Values are expressed as mean ± SD and median (interquartile range).

myocardial ischemia (OR = 14.7, 95% CI 4.8–44.8; $p < 0.001$).

Discussion

We assessed myocardial ischemia and WCE in a population of true resistant hypertensive subjects. Our main findings were that there is a high prevalence of the WCE in RHTN (49%), and that in these patients the presence of myocardial ischemia is higher than in those without WCE. Indeed, the renal target organ damage assessed by MA and heart rate were also greater in WCE. Thus, the WCE was predicted by elevated heart rate and was considered an independent predictor of myocardial ischemia in patients with RHTN.

The definition of WCE can be a little confusing. The difference from WCH is that the latter is a phenomenon where the untreated patient presents an elevated office BP level that normalizes in 24-h ABPM – being a hypertensive status due to the presence of a healthcare professional. Conversely, WCE occurs when there is a decrease in awake BP levels on the 24-h ABPM compared with office BP evaluation but not necessarily normalizing it (15).

The importance of assessing BP through 24-h ABPM in hypertensive patients is well established (21–23); however, when patients present elevated BP levels (above goal) both in ABPM and office BP measurements, the impact of presenting the white-coat phenomenon is still obscure, especially in RHTN.

Differently from what studies have found regarding the decreased incidence of cardiovascular outcomes in patients with WCH compared with the masked or maintained hypertension (24), we found that MA and myocardial ischemia are more frequent in WCE. However, we analyzed patients with RHTN (therefore a more afflicted set of hypertensive patients), and those that were still considered resistant in 24-h ABPM evaluation – presenting only the phenomenon of WCE, but not the hypertension caused in the presence of a white-coat professional.

When assessing patients with WCH, it has been shown that myocardial ischemia is less prevalent than in hypertensive subjects (25). In contrast, in our

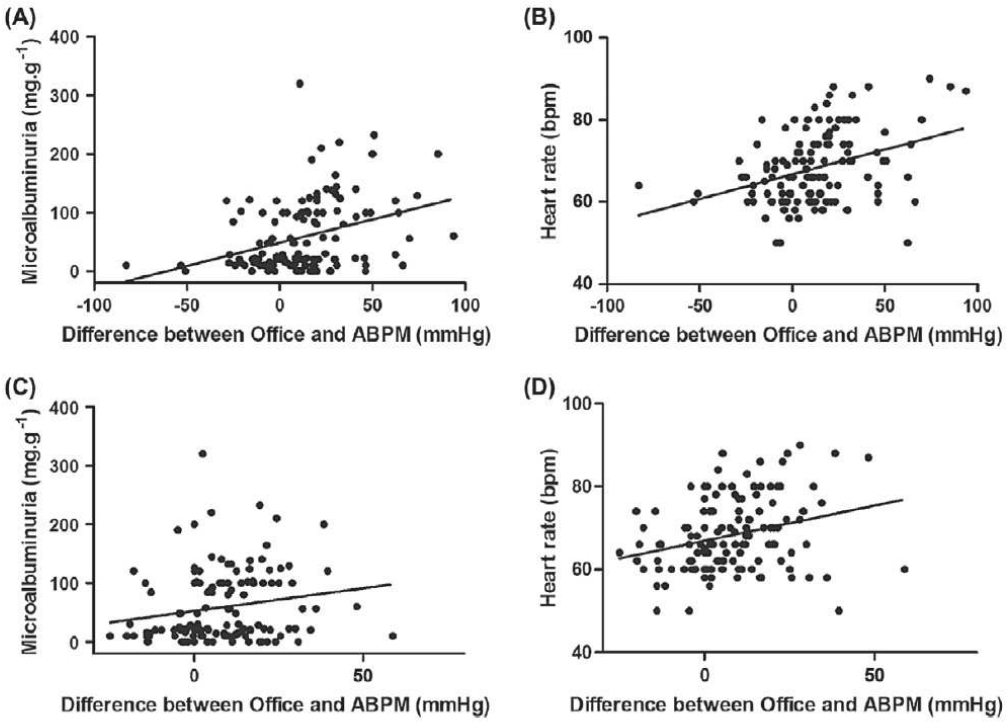

Figure 1. Correlations between the intensity of the white-coat effect (WCE), differences in office blood pressure (BP) and ambulatory BP monitoring (ABPM), and microalbuminuria and heart rate. Panels (A) and (B) systolic blood pressure. Panels (C) and (D) diastolic blood pressure.

sample, myocardial ischemia was not only more often present, but was also a predictor of WCE. This apparent difference in findings could be because our patients did not present WCH, and the WCE along with the presence of RHTN would impact more on the myocardium perfusion abnormalities.

MA was found to be associated with the WCE in our sample. Recently our research group has found that the MA was not statistically greater in patients with the WCE phenomenon (9); however, the power of the performed test at that time did not reach 80%. Even though the presence of MA was associated with WCE, MA was not considered a predictor of WCE in our sample.

In our sample, the WCE group presented higher 24-h heart rate measure, and it was even a predictor of having WCE. This can be explained due to an increased autonomic imbalance in this group of patients (26). The WCE phenomenon has been associated to occur in patients with increased sympathetic and decreased parasympathetic activities (27,28).

Myocardial ischemia was also more prevalent when WCE was present, and the occurrence of this phenomenon was considered a predictor of myocardial ischemia in RHTN. The link between coronary artery disease and that same autonomic imbalance has already been shown (29). Since this sympathetic hyperactivity may be enhanced in WCE, we can infer that the higher prevalence of myocardial ischemia in WCE may be explained by the autonomic imbalance in this group of RHTN subjects.

As a limitation to our study, this is a cross-sectional observational study, limiting causal relationship. Moreover, the myocardial ischemia evaluation in these patients, although accurate, has inherent flaws, in particular regarding false negatives because of balanced ischemia (30). Also, interpretation of the 24-h heart rate has to be taken cautiously, since the patients were not at rest, but maintaining their daily activities, which certainly differ between subjects.

In conclusion, the WCE has higher prevalence in RHTN, and its presence predicts myocardial ischemia in this specific group of patients. MA – a renal hypertensive damage – is also altered in WCE, and the intensity of the WCE correlates linearly and positively to the levels of MA. Our suggestion is that in RHTN patients with WCE, special attention should be given to CHD, in order to early diagnose any alteration and program the best therapy. Further larger and longitudinal studies should be carried out to test these findings in the settings of prognostic conclusions.

Acknowledgements

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Declaration of interest

The authors declare that they have no conflicts of interest.

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5 CAPÍTULO II

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Predictors of Silent Myocardial Ischemia in Resistant Hypertensive Patients

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BACKGROUND
Hypertension is the most prevalent and significant modifiable risk factor for coronary heart disease. A portion of patients with uncontrolled hypertension are considered to have resistant hypertension (RHTN). Myocardial ischemia incidence increases along with blood pressure (BP) levels. However, the prevalence of myocardial ischemia in patients with RHTN, as well as the factors associated with it, is unknown.

METHODS
We enrolled 129 patients with true RHTN regularly followed in our specialty hypertension clinic and evaluated them by resting and dipyridamole pharmacological stress myocardial perfusion scintigraphy. Patients were then divided into 2 groups: those with (I-RHTN; n = 36) and those without (NI-RHTN; n = 93) myocardial ischemia. Echocardiography, 24-hour ambulatory BP monitoring (ABPM), and flow mediated dilation (FMD) were also evaluated.

RESULTS
Thirty six (28%) patients had myocardial ischemia. There was no difference between groups regarding age, sex, biochemical parameters, office, and 24-hour ABPM levels. Patients in the I-RHTN group were more likely diabetic (31% vs. 11%; $P < 0.05$) and obese (75% vs. 40%; $P < 0.001$). Adjusting for age and body mass index, multiple logistic regression showed that diabetes (odds ratio [OR] = 6.5; 95% confidence interval [CI] = 1.06–40.14; $P = 0.04$), FMD (OR = 0.18; 95% CI = 0.07–0.41; $P < 0.001$), heart rate (OR = 1.23; 95% CI = 1.11–1.36; $P < 0.001$), left ventricular mass index (OR = 1.02; 95% CI = 1.01–1.04; $P = 0.04$), and microalbuminuria (OR = 1.02; 95% CI = 1.01–1.04; $P = 0.002$) were independent predictors of ischemia.

CONCLUSIONS
In conclusion, there is a high prevalence of myocardial ischemia in patients with RHTN. Increased microalbuminuria, heart rate, endothelial dysfunction, and left ventricular mass can be useful to guide the investigation for myocardial ischemia in these high risk patients.

Keywords: blood pressure; coronary artery disease; hypertension; myocardial ischemia; resistant hypertension; target organ damage.

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Hypertension is strongly associated with coronary heart disease, where a 10–mm Hg change in blood pressure (BP) reduces the risk of this condition by 37%.[1] It is imperative to effectively control BP levels to reduce the risk of cardiovascular events.[2] However, in a cross-sectional analysis of the Framingham Heart Study, only 48% of treated hypertensive patients and <40% of elderly participants were controlled to <140/90 mm Hg.[3] A significant number of these uncontrolled patients were classified as having resistant hypertension (RHTN)—defined as high BP levels despite the use of at least 3 antihypertensive agents or controlled BP with at least 4 antihypertensive drugs.[4]

Resistant hypertensive patients have a higher incidence of target organ damages (TOD) and its markers such as endothelial dysfunction, microalbuminuria, and left ventricular hypertrophy (LVH).[5,6] TOD poses greater incidence of cardiovascular events, such as myocardial infarction,[7] that might be due to (i) aging and diabetes[5] and (ii) more atherosclerotic plaques.[8] Thus, clinicians must be aware of the potential for silent ischemia and the need for early diagnostic tests for myocardial ischemia. Myocardial perfusion scintigraphy with (99m)tc-sestamibi can accurately diagnose coronary artery disease in asymptomatic patients with hypertension.[9,10] However, appropriate consideration of predictors of myocardial ischemia in this subpopulation of hypertensive subjects may help to avoid extra costs in detecting myocardial ischemia.

We investigated myocardial ischemia in resistant hypertensive subjects and compared clinical and laboratory characteristics of patients with and without scintigraphy abnormalities to define predictors of myocardial ischemic alterations in these subjects.

METHODS

This study was approved by the Research Ethics Committee of the Faculty of Medical Sciences, University of Campinas (Campinas, Brazil), and each participant provided signed

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written consent. This study was carried out according to the Declaration of Helsinki.

Study population

In this cross-sectional study, 129 consecutive subjects classified as resistant hypertensive patients according to international guidelines[4] were enrolled from the Resistant Hypertension Clinic at University of Campinas (Campinas, Brazil). All patients underwent myocardial perfusion scintigraphy with pharmacological stress for evaluation of myocardial ischemia between 2008 and 2012. According to the scintigraphy findings, they were divided into 2 groups: (i) patients with myocardial ischemia (I-RHTN; n = 36) and (ii) patients without myocardial ischemia (NI-RHTN; n = 93). The diagnosis of RHTN—defined as uncontrolled BP with the use of 3 antihypertensive drugs or controlled BP with the need for at least 4 drugs—was given after at least 6 months of follow-up, confirmation of the need for the prescribed medications, and certification of the BP levels with correctly measured office BP levels and through ambulatory BP monitoring (ABPM) to exclude white coat hypertension.[4,11] Pseudoresistance due to medication nonadherence and to secondary causes of hypertension were excluded.[12,13] Adherence was evaluated by pill count method and using the Morisky questionnaire.[14] Nonadherent subjects (with adherence rate <80% of the prescribed medication) were excluded. All BP measurements were performed according to the current guidelines.[4,11] Patients with obstructive sleep apnea previously diagnosed by polysomnography or with moderate to high risk of obstructive sleep apnea by the Berlin sleep questionnaire were also excluded.[15] Subjects with prior coronary events or who were symptomatic for coronary obstructions, such as exertional angina, were also excluded.

Myocardial perfusion scintigraphy

A dual-headed camera (Millenium MG; GE Medical Systems, Milwaukee, WI) with a high-resolution collimator rotated in a 180° orbit and able to acquire 64 projections (20 seconds per projection) was used in this study. The images were obtained after 45 minutes of Tc-99 m sestamibi infusion (925–1,480 MBq) at rest and after vasodilator stress induced by dipyridamole. Images were interpreted by 2 experienced observers, independently, and the interobserver variability was 5%. Semiquantitative visual interpretation of myocardial perfusion was performed with short-axis and vertical long-axis tomograms,[16] and correction for attenuation was performed. The myocardial perfusion defects were described regarding the extent of the lesions and the presence of the reversibility areas, intensity of the defect, and location. Quantitative analysis was performed after an evaluation of a 17-myocardial segment approach. Each segment is graded through a 5-point scoring system.[16] Images were compared at rest and after pharmacological stress. Scarring in the myocardium was considered if the perfusion defects were irreversible and ischemic when they were reversible. According to these parameters, results were given as definitive or transient hypoperfusion areas, with the transient corresponding to myocardial ischemia.[16] Patients with values >6% of transient hypoperfusion were considered as having a positive exam for myocardial ischemia.

BP measurements

Office BP measurements were recorded 3 times using a digital sphygmomanometer (Omron HEM-711DLX; OMRON Healthcare, Bannockburn, IL) on the right upper arm in the sitting position after a 10-minute rest. The average of 2 consecutive measurements was used when a variation <5 mm Hg was encountered.[17]

Twenty-four-hour ABPM was carried out with an automatic device (Spacelabs 90217; SpacelabsInc, Redmond, WA).[18] Patients were oriented to keep normal daily activities, and BP was measured at 20-minute intervals during a 24-hour period. The parameters measured were average 24-hour systolic BP, diastolic BP, mean BP, pulse pressure, and dipper status.

Endothelial function assessment

Brachial artery dilation was measured by linear vascular transducer (4–13 MHz, Siemens Acuson CV70; Siemens, Munich, Germany). The brachial artery flow-mediated dilation test was performed according to current guidelines.[19,20] All studies were initiated at 8:00 AM after overnight fasting with the subjects in a supine position in a quiet, air-conditioned room (22–24 °C). Diameter of the brachial artery was taken 5 cm above the elbow. A polyurethane cuff (Hokanson, Bellevue, WA) was placed on the forearm and inflated for 5 minutes at a 250–mm Hg pressure and quickly deflated. After 45 seconds a new diameter was recorded at the exact site of the prior assessment. Changes in the brachial artery diameter were expressed as a percentage relative to the vessel diameter before cuff inflation. The vascular function examination was performed by 2 experienced blinded examiners, and there was no significant interobserver (5%) or intraobserver (2.5%) measurement variability. No subject had baseline brachial diameter >6.0 mm.

Echocardiography

The measurements of the dimensions of the left ventricle were performed according to the American Society of Echocardiography recommendations using 2-dimensional targeted M-mode echocardiography. Left ventricular (LV) diastolic diameter (LVDD) and LV systolic diameter (LVSD), as well as the interventricular septal (IVS) thickness and LV posterior wall thickness at the end of diastole, were measured according to the QRS wave of electrocardiography. Ejection fraction was calculated by the Teicholz method, LV mass was inferred with the specific formula published elsewhere,[21] and LV mass index (LVMI) was calculated by dividing LV mass by the body surface. Doppler parameters were early mitral inflow peak (E-wave) and late diastolic peak (A-wave) velocities, in order to calculate E/A ratio.[22] Echocardiographic measurements were evaluated by 2 blinded independent investigators using cardiovascular

ultrasound machine (Siemens Acuson CV70; Siemens) with multifrequency sector transducer (2–4 MHz). The intraobserver and interobserver coefficients of variation of the LVDD, LVSD, interventricular septal thickness, and LV posterior wall thickness were <5.5% and 9.5% for LVMI.

Statistical analysis

Categorical variables were expressed as percentages (%), and continuous data were expressed as mean and SD when normally distributed or as median and interquartile range when the distribution was non-normal. Continuous variables were compared using Student *t* tests or Mann–Whitney tests according to distributions. Categorical variables were compared using χ^2 or Fisher exact tests. A multiple logistic regression model including the variables age, diabetes, body mass index, heart rate (HR), LVMI, and microalbuminuria for the presence of myocardial ischemia was performed. The level of significance (α) accepted was 0.05 (two-sided *P* value). The analyses were performed using SigmaPlot software (version 12; Systat Software, Chicago, IL).

RESULTS

The demographic and clinical characteristics of study population are shown in Table 1. The proportion of patients with uncontrolled BP was not different between I-RHTN and NI-RHTN (53% vs. 66%). Overall, the mean age of patients with RHTN was 54 ± 11 years; 39 (30%) were men. No statistical differences were observed between I-RHTN and NI-RHTN in regards to age and sex. Body mass index and diabetes frequency were higher in I-RHTN patients. Laboratory parameters were similar in both groups, except for microalbuminuria, which was higher in the I-RHTN group (Table 1). The extent of ventricular mass with reversible perfusion defects (ischemia) was 9% ± 3% among patients in the I-RHTN group according to scintigraphy findings.

Office BP and ABPM measurements were similar in both I-RHTN and NI-RHTN patients. Flow-mediated dilation was significantly lower in the I-RHTN group (Table 2). There was no difference in 24-hour ABPM dipper patterns between the 2 groups.

Echocardiography evaluation revealed no difference in ejection fraction between the groups. However, left atrial diameter, septal wall thickness, posterior wall thickness, LVDD, LV mass, LVMI, and E/A ratio were higher in the I-RHTN group when compared with the NI-RHTN group. The predominant pattern of LV hypertrophy was concentric (Table 3).

Multivariable logistic regression analysis adjusted for body mass index and age showed that diabetes (OR = 6.5; 95% CI = 1.06–40.14; $P = 0.04$), flow-mediated dilation (OR = 0.18; 95% CI = 0.07–0.41; $P < 0.001$), HR (OR = 1.23; 95% CI = 1.11–1.36; $P < 0.001$), LVMI (OR = 1.02; 95% CI = 1.01–1.04; $P = 0.04$), and microalbuminuria (OR = 1.02; 95% CI = 1.01–1.04; $P = 0.002$) were independent predictors of ischemia (Table 4). Similar results were obtained when adjusting for age and sex, with the same independent variables above. No interactions were found between all independent variables in the regression.

DISCUSSION

We assessed the presence of the myocardial perfusion abnormalities detected by scintigraphy in a population of asymptomatic RHTN patients. Our main findings were an association of the presence of myocardial ischemia with diabetes, endothelial dysfunction, HR, microalbuminuria, and LVMI. Hence, myocardial ischemia was predicted by microalbuminuria, LVMI, HR, presence of diabetes, and flow-mediated dilation.

Ischemic patients had more diabetes, in agreement with other observational studies in which diabetes is not only more prevalent in coronary disease patients but is also considered an important risk factor.[23] We found a prevalence of 28% of silent myocardial ischemia in patients with RHTN. Previous studies showed that 14% of nondiabetic patients, 26% of diabetic patients,[24] and 28% of diabetic patients with known CAD have myocardial ischemia. Also, the presence of hypertension combined with diabetes impact more myocardial ischemia than nondiabetic hypertensive patients (29% vs. 12%).[25] The high prevalence of myocardial ischemia in our asymptomatic sample shows the importance of RHTN as a risk for myocardial ischemia, comparable with the risk of diabetic patients with already diagnosed CAD.

Flow-mediated dilation, a reflection of endothelial function, was more impaired in the group of I-RHTN subjects. Endothelial dysfunction is associated with increased cardiovascular events and atherosclerosis risk factors, especially in hypertensive patients,[26] and it has been considered a predictor of coronary disease in individuals with stable angina.[27] Because flow-mediated dilation was not affected by differences in drug therapy in our sample, our findings suggest that endothelial dysfunction may be closely related to myocardial ischemia in RHTN.

There is a high prevalence of TOD in resistant hypertensive subjects.[28] The presence of TOD due to hypertension is more common and is even a predictor of vascular events and mortality in subjects with vascular disease.[29] In our specific set of patients (RHTN), who are per se more afflicted by TOD,[5] we observed a similar finding—that is, RHTN patients with myocardial ischemia presented with greater microalbuminuria and increased LV mass. Microalbuminuria, also found to be an independent predictor of myocardial ischemia in our sample, has previously been shown to be strongly associated with cardiovascular morbidity in RHTN, especially with coronary heart disease.[30] These links between altered renal protein excretion and cardiovascular morbidity can likely be explained by widespread arterial damage, endothelial dysfunction (also a predictor of ischemia in our sample), and systemic inflammation.[31]

Elevated resting HR is long known to be a risk factor for coronary artery disease.[32] We found that HR, measured by 24-hour ABPM, was higher in the patients presenting with myocardial ischemia than in those with normal myocardial perfusion. In fact, HR is increased in RHTN individuals with uncontrolled BP compared with control groups.[33] Thus, in our sample, the higher HR in the I-RHTN group could be explained by increased sympathetic activity reflecting autonomic imbalance in this subpopulation of hypertensive subjects, as previously described by our group, especially when associated with diabetes.[34]

Table 1. Characteristics of RHTN patients with (I-RHTN) and without (NI-RHTN) myocardial ischemia

Variables	I-RHTN (n = 36)	NI-RHTN (n = 93)
Demographic characteristics and cardiovascular risk factors		
Age, y, mean ± SD	52 ± 12	55 ± 10
Female sex, no. (%)	21 (59)	69 (74)
BMI, kg/m^2	33 (30–37)*	29 (26–33)
Obesity, BMI > 29.9 kg/m^2, no. (%)	27 (75)**	37 (40)
Duration of hypertension, y	14 (10–18)	17 (12–20)
Current smoking habit, no. (%)	9 (25)	13 (14)
Diabetes, no. (%)	11 (31)*	10 (11)
Dyslipidemia, no. (%)	11 (31)	17 (18)
Family history of premature CHD, no. (%)	12 (33)	18 (19)
Alcohol ingestion, no. (%)	2 (6)	7 (8)
Physical inactivity, no. (%)	10 (28)	27 (29)
Left ventricular hypertrophy, no. (%)	32 (88)	80 (86)
Antihypertensive drugs		
Number of drugs, mean ± SD	4.8 ± 0.6	5.1 ± 0.5
Diuretics, %	98	95
ACEI, %	41	45
ARA II, %	71	76
Beta-blockers, %	47	53
Calcium channel blockers, %	48	52
Direct vasodilators/central α-agonists, %	2	4
Laboratory parameters		
Cholesterol, mg/dl, mean ± SD	184 ± 16	189 ± 14
LDL-C, mg/dl, mean ± SD	112 ± 20	107 ± 18
HDL-C, mg/dl, mean ± SD	49 ± 16	50 ± 14
Triglycerides, mg/dl, mean ± SD	121 ± 86	113 ± 76
Fasting blood glucose, mg/dl, mean ± SD	109 ± 11	107 ± 8
Glycated hemoglobin HbA_1c, %, mean ± SD	7.6 ± 1.1	7.4 ± 0.7
Urea, mg/dl, mean ± SD	31 ± 17	32 ± 11
Serum creatinine, mg/dl, mean ± SD	1.0 ± 0.3	1.1 ± 0.2
eGFR, ml min/24 h, mean ± SD	94 ± 10	90 ± 8
MA, mg/g	110 (57–140)**	20 (10–56)
UNa, mg/24 h, mean ± SD	110 ± 22	109 ± 26
Serum potassium, mEq/dl, mean ± SD	4.2 ± 0.3	4.1 ± 0.3
UK, mEq/24 h, mean ± SD	47 ± 20	46 ± 18
PAC, ng/dl, mean ± SD	21.2 ± 4.2	19.5 ± 3.6
PRA, ng/mL per h, mean ± SD	1.88 ± 0.61	2.32 ± 0.73
ARR, ng/dl per ng/ml per h, mean ± SD	12.9 ± 8.5	10.3 ± 2.7

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARA II, angiotensin II receptor blockers; ARR, aldosterone–renin ratio; BMI, body mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MA, microalbuminuria; PAC, plasma aldosterone concentration; PRA, plasma renin activity; RHTN, resistant hypertension; UK, urinary potassium concentration; UNa, urinary sodium concentration.
*$P < 0.05$ vs. NI-RHTN; **$P < 0.001$ vs. NI-RHTN.

Table 2. Twenty-four-hour ambulatory blood pressure, endothelial function (flow-mediated dilation test), and nondipper status in resistant hypertension patients with and without myocardial ischemia

Variable	I-RHTN (n = 36)	NI-RHTN (n = 93)
ABPM measurements		
24-h mean SBP, mm Hg	145 (136–161)	151 (143–162)
24-h mean DBP, mm Hg	88 (83–92)	92 (88–101)
24-h mean PP, mm Hg	54 (51–69)	56 (51–66)
24-h mean HR, bpm	76±9**	65±7
Nondipper status, no. (%)	21 (58%)	44 (47%)
Office blood pressure		
Office SBP, mm Hg	154 (148–162)	157 (148–165)
Office DBP, mm Hg	97 (90–106)	100 (95–103)
Office PP, mm Hg	61±16	58±14
Uncontrolled RHTN, %	53	66
Flow-mediated dilation, %	6.9 (5.8–7.2)**	7.9 (7.0–8.8)

Abbreviations: ABPM, 24-hour ambulatory blood pressure monitoring; DBP, diastolic blood pressure; HR, heart rate; I-RHTN, resistant hypertension with myocardial ischemia; NI-RHTN, resistant hypertension without myocardial ischemia; PP, pulse pressure; RHTN, resistant hypertension; SBP, systolic blood pressure.
**$P < 0.001$ vs. NI-RHTN.

Table 3. Echocardiographic variables in patients with and without myocardial ischemia

Echocardiographic variables	I-RHTN (n = 36)	NI-RHTN (n = 93)
Ejection fraction, %	65 (60–71)	64 (60–69)
Left atrium diameter, mm	41.6±4.9*	39.7±4.2
Septal wall thickness, mm	13.1±3.4*	11.5±1.9
Posterior wall thickness, mm	12.4±2.2*	11.4±1.8
Diastolic LV diameter, mm	53 (49–55)*	49 (47–53)
LV mass, g	263 (214–331)**	218 (178–256)
LV mass index, g/m²	134 (110–160)*	124 (101–143)
E/A ratio	0.9±0.1**	1.0±0.1
LV geometric patterns		
Concentric remodeling	1 (3)	6 (6)
Concentric hypertrophy	26 (72)	62 (67)
Eccentric hypertrophy	9 (25)	25 (27)

Abbreviations: E/A, early diastolic filling velocity/atrial diastolic velocity; I-RHTN, resistant hypertension with myocardial ischemia; LV, left ventricular; NI-RHTN, resistant hypertension without myocardial ischemia; RHTN, resistant hypertension.
*$P < 0.05$ vs. NI-RHTN; **$P < 0.001$ vs. NI-RHTN.

TOD increases along with BP levels.[28] Interestingly, in our study, in the I-RHTN group the association between BP levels and TOD was not maintained, with the prevalence of TOD being higher, with no increment on the levels of BP. Explanations of this discrepancy between higher TODs without BP increases in the I-RHTN group have yet to emerge but may be related to the fact that both LVH and decreased BP may worsen myocardial ischemia by reducing perfusion pressure, as demonstrated by Mansour *et al.*[35]

In regards to the echocardiographic parameters, we also encountered significant differences in left atrial diameters and E/A ratio between groups. Although diastolic dysfunction was not completely assessed, the increase in left atrium dimensions and the lower ratio between Doppler waves E and A suggest more impaired diastolic function in the I-RHTN group.[36]

Myocardial perfusion scintigraphy was used in this study because it is a noninvasive method and provides incremental prognostic information beyond clinical and exercise electrocardiogram data.[37] Myocardial perfusion scintigraphy has the ability to detect not only epicardial obstructions but also microvascular alterations in hypertensive patients, in contrast to stress echocardiography, which has a poor ability to identify abnormalities of the microvascular coronaries.[38] The

Table 4. Multivariable logistic regression for the presence of myocardial ischemia

Variable	Odds ratio (95% confidence interval)	*P* value
Diabetes	6.52 (1.06–40.14)	0.04
LVMI	1.02 (1.01–1.04)	0.04
24-h ABPM DBP	0.95 (0.88–1.01)	0.11
HR, bpm	1.23 (1.11–1.36)	<0.001
Microalbuminuria	1.02 (1.01–1.04)	0.002
FMD, %	0.18 (0.08–0.42)	<0.001

Abbreviations: ABPM, ambulatory blood pressure measurement; DBP, diastolic blood pressure; FMD, flow-mediated dilation; HR, heart rate; LVMI, left ventricular mass index;.
[a]Adjusted for age and body mass index.

use of dipyridamole as a stress inducer is comparable with exercise.[39] Stress myocardial perfusion scintigraphy has high sensitivity (81%–96%), specificity (67%–89%), and diagnostic accuracy (83%–92%) for detecting CAD.[40] Evaluation of the accuracy of noninvasive imaging techniques for diagnosis of CAD is relevant for the appropriate management of patients with hypertension, one of the most common cardiac risk factors.[41]

To the best of our knowledge this is the first study to evaluate myocardial ischemia in resistant hypertensive patients, leading to the determination of variables associated with these myocardial perfusion abnormalities. Two previous studies have assessed silent myocardial ischemia by electrocardiogram monitoring, but not with a precise diagnose of RHTN,[42] or the study was done in essential hypertensive subjects.[43]

The main limitation of our study is that the ischemia was not investigated by coronary angiogram, which would have allowed detection of disease of the epicardial coronaries. However, this investigation was not performed for ethical issues because the majority of ischemic patients had no symptoms and small areas of ischemia, making clinical treatment the best option.[44] Another limitation might be the false-negative results provided by myocardial perfusion imaging in cases of balanced myocardial ischemia, in which the diseases on coronary arteries are distributed throughout the coronary circulation, complicating interpretation of differences in perfusion between the myocardial segments in stress and at rest.[45] As to adherence assessment, the methods used (Morisky and pill count) are indirect and may not entirely exclude nonadherent subjects. Regarding our sample, the limitation might be that it is a single-center study with a convenience sample.

Taken together, our data indicate that clinicians should be aware of predictors of silent myocardial ischemia in RHTN. Regardless of BP levels, our findings suggest that microalbuminuria, LV mass, endothelial function, presence of diabetes and increased HR play a relevant role when assessing coronariopathy and myocardial ischemia in patients with truly RHTN. The presence of these factors suggests that special attention on silent myocardial ischemia should be given to patients with RHTN. As a perspective, we feel that because the patients are asymptomatic, but carry a high risk for presenting myocardial ischemia, an individualized investigation should be performed. With the presence of these identifiable associated factors, myocardial perfusion scintigraphy would be of significant importance in screening these RHTN patients for myocardial ischemia.

DISCLOSURE

The authors declared no conflict of interest.

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6 CONCLUSÕES

1- Presença do efeito do jaleco branco, diabetes mellitus, microalbuminúria, maior massa ventricular esquerda, frequência cardíaca aumentada e disfunção endotelial estão fortemente associados à isquemia miocárdica silenciosa em pacientes com hipertensão arterial resistente.
2- Esta associação ocorreu independentemente dos valores pressóricos.
3- A presença destes fatores em pacientes com HAR deve incitar a investigação dos pacientes, mesmo que assintomáticos, para a presença de isquemia miocárdica, a fim de evitar evolução da coronariopatia nestes hipertensos.

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