Tese de Doutorado

VARIABILIDADE DA PRESSÃO ARTERIAL: DESEMPENHO DE DIFERENTES MÉTODOS DE AVALIAÇÃO E RELAÇÃO COM DESFECHOS CARDIOVASCULARES

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Cardiologia e Ciências Cardiovasculares

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Quando penso que cheguei ao meu limite,
descubro que tenho forças para ir além.

Ayrton Senna

AGRADECIMENTOS

A minha família, pois sem Deus não há vida e sem família não há base. À minha mãe Lovane, meu pai Luiz e minha irmã Carine por tudo que sou, de onde trago meus valores, minha índole, meu caráter. Muito obrigada por me apoiarem e estarem sempre ao meu lado. Amo muito vocês.

Ao meu querido marido e amor Adalberto, pelo companheirismo, paciência e compreensão pelos vários finais de semana de envolvimento com o doutorado. Obrigada anjo por completar minha vida, pela dedicação, por me incentivar e apoiar minhas escolhas.

Ao meu orientador professor Dr. Miguel Gus, o qual desde o mestrado me ensinou a fazer pesquisa, me acolhendo no ambulatório de hipertensão. Obrigada pela paciência e principalmente pelos ensinamentos.

À minha co-orientadora professora Dra Beatriz D'Agord Schaan, colaboradora e pesquisadora gerenciadora do PRADHA. Obrigada pela disponibilidade e dedicação durante todo desenvolvimento do estudo. Obrigada por assumir a posição de orientadora (conforme solicitação e consentimento do Miguel), principalmente nos momentos de cobrança de prazos e "feedback" dos artigos. A procrastinação é um mal do ser humano, e eu me incluo nisso.

Aos colegas pesquisadores e pós-graduandos e acima de tudo, companheiros de trabalho do estudo PRADHA: Priscila Ledur, Mateus Dorneles Severo, Liana Farias Leiria. E aos nossos queridos colaboradores e bolsistas (na época, hoje excelentes médicos) do projeto: Fernanda Aguiar, Alexandre Becker, Eliandra Lima obrigada pela colaboração durante várias etapas da pesquisa.

A Dra Valéria Centeno Freitas, que trabalhou arduamente na realização de todos os exames de ecografia cardíaca de nossos pacientes.

As minhas colegas colaboradoras do artigo da revisão sistemática, Dra Jeruza Lavanholi Neyeloff e Andressa da Silveira de Oliveira Schein que trabalharam arduamente nos últimos meses para que fializassemos a tempo o trabalho. Em especial a Andressa, que se dedicou e me deu forças para finalizar esta última etapa, abrindo mão dos próprios finais de semana e trabalhando noites a fio comigo, o meu muitíssimo obrigado.

À Sirlei F. Reis, com excelente competência que facilitou minha vida de pós-graduanda. Além disso, incansavelmente me deu forças e me encheu de energia para finalizar esta etapa.

Aos meus queridos e amados amigos, companheiros nas horas boas e nem tão boas, que me ampararam e me deram força nos momentos que pensei desistir e fraquejar, que compreenderam as minhas horas de ausência e distância em decorrência de minha total imersão na finalização de minha tese.

Aos funcionários da Unidade de Métodos Não-Invasivos, do Centro de Pesquisas e do Ambulatório de Hipertensão do Hospital de Clínicas de Porto Alegre que compartilharam o ambiente de trabalho e assistência com o “pessoal da pesquisa”, como nos denominavam.

Aos pacientes que participaram do estudo PRADHA se prontificando a participar da pesquisa e se disponibilizando a comparecer aos agendamentos de testes e exames.

Às instituições fomentadoras de pesquisa CNPQ, CAPES e FIPE/HCPA por acreditarem na competência e seriedade dos nossos pesquisadores.

SUMÁRIO

LISTA DE ABREVIATURAS E SIGLAS 8
RESUMO 9
1. REVISÃO DA LITERATURA 14
2.1 Monitorização Ambulatorial de Pressão Arterial de 24 horas (MAPA 24h) .. 14
2.2 Variabilidade da Pressão Arterial (VPA) 18
2.2.1 Valor preditivo da VPA para lesão subclínica em órgão alvo 20
2.2.2 Valor preditivo da VPA para eventos cardiovasculares e mortalidade . 24
2.3 Variação da pressão arterial no tempo (Índice "time rate") 28
3. JUSTIFICATIVA 34
4. OBJETIVOS 35
4.1 Objetivo geral: 35
4.2 Objetivos específicos: 35
5. REFERÊNCIAS DA REVISÃO BIBLIOGRÁFICA 36
6 ARTIGO 1- SYSTEMATIC REVIEW 47
7 ARTIGO 2- CROSS-SECTIONAL STUDY 81
8 CONCLUSÕES E CONSIDERAÇÕES FINAIS 110

LISTA DE ABREVIATURAS E SIGLAS

PA= Pressão arterial

VPA= Variabilidade da pressão arterial

PAS= Pressão arterial sistólica

MAPA 24h= Monitorização Ambulatorial da Pressão Arterial de 24 horas

MRPA= Monitorização residencial da pressão arterial

DP= Desvio padrão

PAD= Pressão arterial diastólica

CV= Coeficiente de variação

DRC= Doença renal crônica

eTFG= Taxa de filtração glomerular estimada

RR= risco relativo

IC= Intervalo de confiança

HVE= Hipertrofia do ventrículo esquerdo

ECG= Eletrocardiograma

VE= Ventrículo esquerdo

DPV= Doença dos pequenos vasos cerebrais

AVC= Acidente vascular cerebral

IMC= Índice de massa corporal

ITB= Índice tornozelo braquial

RESUMO

Admite-se que a variabilidade da pressão arterial (PA) tem correlação direta com eventos cardiovasculares e o desenvolvimento de lesão em órgãos alvo. Contudo, as evidências ainda são limitadas sobre a utilização da variabilidade da PA como objetivo terapêutico anti-hipertensivo. Além disso, permanecem lacunas a respeito da real associação, independente das médias pressóricas ou outros fatores de confusão, entre os diferentes índices de variabilidade da PA obtidos pela monitorização ambulatorial de pressão arterial de 24 horas (MAPA-24h) e dano cardiovascular, além de ainda não existir critérios de normalidade para estes índices. Por esta razão, sua aplicabilidade clínica ainda não está totalmente definida na avaliação do risco cardiovascular mesmos em indivíduos de alto risco (hipertensos e diabéticos, por exemplo).

No presente trabalho realizamos uma revisão sistemática com metanálise de estudos observacionais objetivando avaliar a associação entre a variabilidade da PA aferida por diferentes índices e métodos de monitorização da PA e a ocorrência de desfechos cardiovasculares e desenvolvemos um estudo transversal que analisou a associação entre diferentes parâmetros de variabilidade pressórica incluindo índice “time rate” aferido por MAPA-24h e parâmetros ecocardiográficos em indivíduos com hipertensão e diabetes mellitus.

A revisão sistemática e metanálise incluiu estudos prospectivos que utilizavam alguma medida de variabilidade da PA a curto prazo (nas 24h) e a muito curto prazo (batimento a batimento) obtidos pela MAPA-24h e registros

contínuos da PA. Os desfechos primordiais foram: mortalidade por todas as causas, mortalidade cardiovascular e eventos cardiovasculares, incluindo acidente vascular cerebral (AVC) e doença vascular periférica. Os desfechos substitutos escolhidos foram: hipertrofia ventricular esquerda (HVE) e comprometimento da função renal. Observou-se grande diversidade entre os estudos disponíveis nos protocolos variabilidade da PA, nos índices selecionados para quantificar a variabilidade da PA e nos desfechos utilizados para a avaliação. Os resultados vão ao encontro das recomendações da Sociedade Europeia de Hipertensão a qual preconiza que a variabilidade da PA a curto prazo dentro de 24 h pode ser considerada para a estratificação de risco em estudos populacionais e de coorte mas questões fundamentais permanecem sem resposta.

No estudo transversal avaliamos a associação entre a variabilidade da PA medida pelos índices da MAPA 24h e variáveis ecocardiográficas em 305 pacientes hipertensos e diabéticos. O índice time-rate o qual é obtido pela MAPA-24-h e indica a variação pressórica a cada medida ao longo do tempo, não se associou independentemente com variáveis ecocardiograficas no modelo linear múltiplo quando ajustado para idade, MAPA 24h, duração do diabetes e HbA1c.

INTRODUÇÃO

A elevação da pressão arterial (PA) é um dos principais fatores de risco para eventos cardiovasculares e mortalidade.[1] Evidências consistentes na literatura já demonstram uma relação log-linear com número de desfechos cardiovasculares e renais assim como com mortalidade global e que a redução da PA de consultório com tratamento anti-hipertensivo é efetiva na redução de morbidade e mortalidade.[2] O impacto da redução da pressão está ligado ao risco basal do paciente à intensidade de elevação da PA, assim como, na presença de cardiopatia isquêmica ou lesão em órgão alvo. [3] [4]

Evidências crescentes sugerem que os valores da PA por si só podem não explicar totalmente a relação fisiopatológica entre a PA e efeitos cardiovasculares adversos da hipertensão. Em diferentes estudos a variabilidade da pressão arterial (VPA) nas 24h demonstrou ser um preditor independente de incidência de eventos cardiovasculares.[5] Estudos longitudinais e observacionais indicam que a VPA a curto prazo nas 24 h pode ter uma contribuição não-marginal ao risco cardiovascular e que o aumento da VPA (curto prazo, ou a longo prazo) está associado com o desenvolvimento, progressão e severidade de doença cardíaca, vascular e lesão de órgão renal e com um aumento da incidência de morbi-mortalidade cardiovascular.[6]

Sabe-se que a PA é caracterizada por uma série de variações espontâneas. Ou seja, os valores de PA variam consideravelmente nas 24 horas, devido às alterações dia-noite, mas também por causa das diferenças entre horas, minutos e até mesmo batimento a batimento (variabilidade a curto prazo). Existem igualmente variações ao longo de ciclos (variabilidade a longo

prazo) causando diferenças presóricas entre dias, meses e estações do ano,[7] assim como a tendência da pressão arterial sistólica (PAS) aumentar ao longo dos anos.

A VPA é o resultado de interações complexas entre fatores ambientais extrínsecos e comportamentais com mecanismos de regulação cardiovascular intrínsecos (neuro-humoral central ou influências reflexas) ainda não completamente compreendidos. Desta forma, o prognóstico de pacientes hipertensos pode não depender apenas do nível de PA e sim do grau e índice da variação da PA. Portanto, avaliar como a PA varia ao longo do dia poderia fornecer informações importantes a respeito do perfil de risco cardiovascular.

A utilização de técnicas para monitoramento da PA fora do consultório como a MAPA 24h melhorou significativamente o manejo da hipertensão e tem contribuído para o entendimento sobre a importância das flutuações da PA ao longo do tempo e como esta variável poderia fornecer informações prognósticas independentemente das medidas isoladas de consultório e níveis médios ambulatoriais de PA.[8] Apesar do fato de não ser tão precisa pois não fornece medidas contínuas, tem o potencial de fornecer informações mais acuradas sobre a variação pressórica ao longo do dia.

A variabilidade a curto prazo, dentro das 24 horas, pode ser avaliada com a MAPA-24h, enquanto a variabilidade a longo prazo requer medidas repetidas de PA ao longo de dias, semanas ou meses com medições repetidas de consultório, Monitorização Residencial da PA (MRPA) ou mesmo MAPA-24h. Com base nas evidências disponíveis, a VPA de curto prazo nas 24 h pode ser considerada para a estratificação de risco em estudos populacionais e de coorte. No entanto, atualmente não representa um parâmetro rotineiro

usado na prática clínica.[9] Além disso, dependendo do método e intervalo de tempo considerados para sua análise, a significância clínica e implicações prognósticas de uma dada medida de VPA pode de fato diferir substancialmente.[8]

A partir dos registos obtidos da MAPA 24h, é possível calcular o desvio padrão (DP) da média da PAS, pressão arterial diastólica (PAD), diferenças nas médias diurnas e noturnas [10], o coeficiente de variação (CV) e, a variação da PA no tempo (índice “time rate”).[11] Outros índices têm sido propostos a fim de evitar a interferência das flutuações da PA do dia-noite nas medidas de VPA a curto prazo e estimar as alterações mais rápidas da PA: (1) Variabilidade Real Média (“Average Real Variability-ARV”);[12] (2) “VPA residual”;[13] (3) cálculo do DP “ponderado” da PA 24h;[14] (4) Variância independente da média (VIM).[15] Em comparação com DP 24h e CV, esses métodos têm se mostrado melhor correlacionados com VPA 24h [15] [16] e também sendo possivelmente melhor preditores de desfecho cardiovascular.[12] [14] [17]

Embora tenha sido sugerido que uma maior proteção cardiovascular possa ser obtida com tratamento anti-hipertensivo direcionado à normalização da VPA além de redução dos níveis absolutos da PA 24h, as evidências neste aspecto ainda são limitadas. Além disso, permanecem lacunas a respeito da real associação, independente das médias pressóricas ou outros fatores de confusão, entre os diferentes índices de VPA obtidos pela MAPA 24h e dano cardiovascular. Igualmente, inexistem critérios de normalidade para os diferentes índices de VPA e, portanto, a sua aplicabilidade clínica ainda não está totalmente definida na avaliação de indivíduos de alto risco (hipertensos e diabéticos).

Uma correlação mais consistente com eventos cardiovasculares e o desenvolvimento de lesão em órgãos alvo seria possível por meio do registro contínuo da pressão arterial (batimento a batimento), o qual não é obtido pelo método usual de registro da PA em 24 horas. Por esta razão, a IV Diretriz Brasileira do MAPA[18] não recomenda a utilização do DP das médias pressóricas ou de qualquer outro índice como indicativo da variabilidade da PA, porque, até o momento, não há critérios de normalidade para sua interpretação (Grau de Recomendação III - Nível de Evidência D).[19]

1. REVISÃO DA LITERATURA

2.1 Monitorização Ambulatorial de Pressão Arterial de 24 horas (MAPA 24h)

A MAPA-24h tornou-se um tema de interesse científico considerável, com mais de 11.624 artigos listados no PubMed em 2016.[9] Em reconhecimento da sua importância na prática clínica e pesquisa da hipertensão, este método tem se tornado importante ferramenta para o estabelecimento do prognóstico cardiovascular e de lesão em órgão alvo.[20] [21] Também tem demonstrado ser útil para definir os efeitos da terapia anti-hipertensiva.[22]

Estudos transversais e longitudinais têm demonstrado valor prognóstico superior para os valores médios das 24 h, durante o dia, e os valores médios noturnos em comparação com valores de consultório. Nesses estudos, em comparação com valores de consultório, os valores ambulatoriais de PA foram mais associados com lesão subclínica em órgão alvo. [23] O ensaio

clínico multicêntrico japonês HOMED-BP demonstrou que PA residencial fornece uma estimativa mais confiável da real PA do paciente do que medidas convencionais de PA.[24]

Estudo da coorte japonesa de Ohasama avaliou a significância prognóstica da MAPA 24h para o desenvolvimento de doença renal crônica (DRC). Foram seguidos 843 participantes durante 8,3 anos e DRC foi definida como proteinúria positiva ou taxa de filtração glomerular estimada (eTFG) $\leq$ 60 ml/min/1,73 m^2. PA noturna foi o melhor preditor de desenvolvimento de DRC (Risco Relativo (RR) ajustado 1,21; IC 95% 1,04-1,39), permanecendo significativo mesmo após realizado ajuste mútuo no modelo para PA noturna e diurna.[25]

Kang e colaboradores realizaram um estudo prospectivo observacional que envolveu 573 pacientes não tratados com objetivo de investigar a acurácia entre MRPA no diagnóstico de hipertensão mascarada (PA de consultório normal e ambulatorial elevada) e do jaleco branco (PA de consultório elevada e ambulatorial normal) em comparação a MAPA 24h. MRPA teve baixa sensibilidade (amplitude 47-74%) e alta especificidade (86–94%), sugerindo que MRPA funciona com um complemento, mas não substitui a MAPA 24h.[26]

Entre os estudos que avaliaram a importância da MAPA-24h em hipertensos, o ensaio clínico Syst-Eur (*Systolic Hypertension in Europe Trial*), demonstrou que a média de pressão arterial sistólica noturna foi o melhor preditor de eventos cardiovasculares. 808 pacientes com idade ≥ 60 anos e hipertensão arterial sistólica isolada foram acompanhados por um média 4,4 anos. O aumento de 10 mmHg na média noturna aferida por MAPA 24h

associou-se de forma independente com mortalidade cardiovascular (RR 1,34; IC 95% 1,03-1,75). [27]

Ohkubo e colaboradores demonstraram que risco para mortalidade cardiovascular foi significativamente relacionado aos quintis mais elevados de PAS 24h, PAD 24h, PAS diurna, PAD diurna e PAD noturna. O risco de mortalidade cardiovascular tende a aumentar para o quintil mais alto da PAS noturna (>132 mmHg) embora a diferença não foi estatisticamente significativa.[28]

O estudo de Dublin foi o primeiro estudo de grande escala na população de hipertensos (n= 5292) que avaliou a significância prognóstica da MAPA 24h. O mesmo confirmou os dados reportados no estudo japonês anterioriormente descrito. Vários componentes da MAPA 24h demonstraram ser superiores a PA de consultório em predizer risco de morte cardiovascular em 5 anos. Os RR (após ajuste para sexo, IMC, presença de diabetes, história de eventos cardiovasculares, tabagismo e PA consultório) para cada 10 mm Hg de aumento na PAS foram: 1,12 (IC 95% 1,06–1,18; p< 0,001) para PAS diurna e 1,21 (IC 95% 1,15–1,27; p< 0,001) para PAS noturna.[29] O mesmo grupo publicou em 2008 um subanálise da mesma coorte avaliando pacientes hipertensos idosos (> 65 anos) reiterando os achados prévios que MAPA 24h é o preditor mais acurado para mortalidade cardiovascular.[30]

O estudo PAMELA verificou a PA de consultório, MAPA-24h e Monitorização Residencial de Pressão Arterial (MRPA) numa amostra representativa da população de Monza/Itália (2051 indivíduos com idade entre 25-74 anos). Nesta coorte italiana, após 131 meses de seguimento, houve

maior consistência na associação entre o risco de morte e o aumento da PA aferida por MAPA-24h e MRPA comparando-se com aferição pressórica de consultório Entretanto, não foi demonstrada diferença na capacidade total de predizer mortalidade, indicando que a presença de hipertensão, independente do método utilizado, confere aumento de risco cardiovascular.[31]

Metanálise publicada em 2008 que avaliou a associação da PAS 24h e incidência de eventos cardiovasculares incluiu 20 estudos de coorte. Mesmo após ajuste para PA de consultório, 4 estudos totalizando 4975 participantes e 499 desfechos forneceram estimativas similares para 10 mmHg de aumento na PAS 24h, (RR 1,21: IC 95% 1,10–1,33; p< 0,001). Houve associação consistente entre PAS 24h e acidente vascular encefálico (AVC), mortalidade cardiovascular, mortalidade total e eventos cardíacos para 10 mmHg de aumento da PAS 24-h.[32] A PA noturna demonstrou ser um preditor mais consistente para mortalidade cardiovascular e total.

O conjunto de evidências que demonstram a capacidade da MAPA 24h em aferir de forma mais precisa o risco cardiovascular associado ao aumento pressórico fez com que as Diretrizes de 2011 do “National Institute for for Clinical Excellence (NICE)” apoiassem a ampla utilização deste método para confirmação de hipertensão em indivíduos com PA de consultório >140/90 mmHg. Adicionalmente, recomendam o uso sistemático da MAPA 24h, sendo que esta poderia potencialmente aumentar sua habilidade preditiva a partir da análise da VPA nas 24h. [33]

Para que este método de aferição da PA possa ser amplamente utilizável e reprodutível e que o resultados apresentados pela literatura forneça

dados mais confiáveis, a Sociedade Europeia de Cardiologia publicou em 2013 suas Diretrizes sugerindo que para registros satisfatórios da MAPA 24h as medidas de PA devem ser feitas em intervalos de pelo menos de 30 minutos e os registros necessitam de pelo menos 20 medidas válidas durante a vigilia e de 7 medidas válidas durante o sono.[34]

Além disso, outros fatores relacionados a PA, não restritos somente aos valores pressóricos absolutos podem estar associados à progressão das doenças cardiovasculares. A MAPA 24h permite que outros parâmetros ligados à pressão arterial possam ser estudados, como por exemplo, as relações pressóricas de sono e vigília e parâmetros de variabilidade durante o período de 24 horas.

2.2 Variabilidade da Pressão Arterial (VPA)

Os valores de PA variam consideravelmente dentro das 24 horas: de batimento a batimento, minuto a minuto, hora a hora, e de dia para noite (denominada variabilidade PA de curto prazo). Uma variação substancial também é observada entre as medidas da PA realizadas entre visitas clínicas realizadas ao longo de semanas, meses e até anos (variabilidade da pressão arterial de longa prazo). A VPA é o resultado de interações complexas entre fatores extrínsecos ambientais e comportamentais com mecanismos regulatórios cardiovasculares (hormonais e neural central ou influências reflexas) ainda não completamente conhecidas, que por sua vez, também podem afetar o prognóstico cardiovascular.[35]

O comportamento dinâmico dos valores da PA durante o período de 24h foi demonstrado pela primeira vez com monitoramento da PA intra-arterial em pacientes ambulatoriais[36] [37] [38] e a MAPA 24h fornece uma avaliação robusta de variabilidade de curto prazo, desde que o intervalo entre as medições não seja mais do que 15 minutos.[12] [13] [14] [39] Além disso, as dificuldades técnicas dos registros contínuos da PA (instabilidade do manguito do dedo fora do ambiente laboratorial e implementação de registros invasivos num ambiente de vida diária) tem limitado sua utilização na prática clínica. Uma abordagem alternativa para a estimativa da VPA de curto prazo dentro das 24 horas consiste em realizar a MAPA 24h com aferições realizadas em intervalos de 15 a 20 minutos.[9]

A MAPA 24h permite a realização de estimativas simples de VPA de curto prazo através do cálculo do DP da PA 24 horas[10] e também pelo cálculo do Coeficiente de variação (DP×100/média PA),[39] ambos dependentes dos níveis médios de PA. Devido a simplicidade dos seus cálculos, estes índices são influenciados não somente pelas variações de curto prazo mas também pelo grau de redução dia-noite e são sensíveis a instabilidade da PA em resposta a estressores específicos (postura, emocional, estresse e dor). A fim de evitar a interferência das flutuações dia-noite da PA nas medidas de variabilidade de curto prazo, índices alternativos têm sido propostos para estimar mudanças mais rápidas da PA.[35]

2.2.1 Valor preditivo da VPA para lesão subclínica em órgão alvo

Parati e colaboradores[37] demonstrou que VPA diurna aumentada mensurada pelo DP 24 h associou-se com um aumento do risco para hipertrofia do ventrículo esquerdo (HVE) determinado pelo ECG em 108 pacientes hipertensos independentemente dos valores pressóricos médios.

Outros estudos, no entanto, não encontraram os mesmos resultados. Veerman e colaboradores.[40] relataram uma correlação não significativa entre DP diurno e dano em órgão alvo. Os autores se justificam que o pequeno tamanho da amostra poderia ser a razão potencial para a discrepância com os achados prévios da literatura. Bilo e colaboradores[14] também não observaram correlação significativa entre índice de massa do ventrículo esquerdo (VE) e DP 24h. No entanto, encontraram que tanto o DP diurno como DP ponderado foram correlacionados significativamente com índice de massa do VE mesmo após ajuste para viéses de confusão. Estes achados demonstram que os resultados são sensíveis ao índice escolhido e talvez estas discrepâncias encontradas entre DP dia e DP 24 h possam ser explicadas pela queda da PA à noite (“dipping”).

A maioria dos estudos tem utilizado DP como uma medida de VPA e a adequação de tal índice tem sido contestada, pois ele reflete somente a dispersão das medidas em torno de um único valor (média) não representando a ordem em que foram obtidas medidas da PA.[12] [41] O DP ponderado tenta remover o efeito do “dipping” e ,contrariamente ao DP 24h, demonstrou estar associado de forma independente à dano em órgão alvo.

Alguns estudos tem utilizado outro índice como medida da VPA denominado Variabilidade Real Média (“Average Real Variability-ARV”) que consiste na diferença média absoluta entre leituras sucessivas de PA. Foi descrito inicialmente por Mena e colaboradores[12] e após por Pierdomenico e colaboradores.[41] No estudo de Zhang[42] realizado com hipertensos idosos, a análise de regressão multivariada demonstrou que a Variabilidade Real Média correlacionou-se independentemente com a espessura da camada íntima-média da artéria carótida, índice de massa do VE e microalbuminúria 24h. Os pacientes com maior VPA tiveram maior incidência de placas e disfunção cardiovascular (P< 0,001).

Já o trabalho de Leoncini e colaboradores publicado em 2013 que avaliou 169 hipertensos não tratados comparou diferentes índices de variabilidade, incluindo a Variabilidade Real Média. Este foi o melhor preditor independente de lesão em órgão alvo considerando-se que a maioria dos indivíduos apresentou hipertrofia do ventrículo esquerdo (31%).

Mulè e colaboradores analisaram a relação entre dano renal subclínico (definido por presença de microalbuminuria ou eTFG entre 30 mL/min/1,73 m^2 e 60 mL/min/ 1,73 m^2) e VPA de curto prazo em 328 indivíduos hipertensos. Os autores utilizaram vários índices de variabilidade obtidos a partir da MAPA 24h. A Variabilidade Real Média da PAS 24h foi significativamente mais elevada em pacientes com dano renal subclínico e mesmo após ajuste, esta associação manteve-se significativa (p=0,04). Além disso, a Variabilidade Real Média da PAS 24h, DP ponderado da PAS 24h, e DP PAS diurna associaram-se independentemente e inversamente à eTFG.[43]

Outros estudos que avaliaram a relação entre VPA e lesão em órgão alvo encontraram resultados variados. Como já mencionado, o trabalho de Parati e colaboradores[37] encontrou associação entre VPA e gravidade de lesão em órgão alvo (escore baseado na presença de hipertrofia do VE, anormalidade no raio-x de tórax, anormalidades de fundo de olho mais evento clínico e/ou anormalidade renal). O mesmo grupo conduziu outro estudo com um período de acompanhamento de 7 anos para avaliar relevância prognóstica da VPA de curto prazo em 73 pacientes hipertensos.[38] VPA 24h no início da pesquisa associou-se independentemente à lesão em órgão alvo no seguimento. Da mesma forma, outro estudo com 700 pacientes hipertensos e normotensos, DP PAS diurna associou-se com o grau de lesão em órgão alvo. Entretanto após a realização de ajuste para PA média não foi encontrada associação forte entre VPA e hipertrofia do VE.[44]

Evidências de recente meta-análise publicada sugerem que existe uma fraca correlação positiva entre VPA de curto prazo e índice de massa ventricular esquerda. O trabalho incluiu ao final 12 artigos que poderiam utilizar qualquer medida sumária de VPA de curto prazo obtidos através da MAPA 24h. Variabilidade Média Real; DP; DP ponderado e coeficiente de variação através dos períodos das 24h/diurno/noturno foram identificados como medidas de variabilidade. A meta-análise do estudo demonstrou que os coeficientes de correlação do índice de massa ventricular esquerda com DP da PAS 24h foi 0,22 (IC 95% 0,12–0,31); com DP PAS diurna foi 0,19 (IC 95% 0,15–0,25); com DP ponderado da PAS foi de 0,23 (IC 95% 0,13–0,33); e com a Média real da variabilidade PAS 24h foi 0,37 (IC 95% 0,01–0,65).[45]

Os resultados do estudo prospectivo de Sander e colaboradores com seguimento de 3 anos demonstram que o padrão de PA circadiana, particularmente, VPA sistólica diurna, está positivamente associado com o desenvolvimento precoce de ateromatose nas carótidas de pacientes. Na análise multivariada a VPA sistólica foi o melhor preditor da progressão do espessamento da íntima nas carótidas além de aumentar a chance de eventos cardiovasculares (RR 1,87: IC 95% 1,08 - 3,2; p< 0,01). [46]

Estudos clínicos que realizaram registros ambulatoriais intermitentes de PA demonstram que valores aumentados de VPA de curto prazo estão associados com aumento da prevalência e progressão de lesão em órgão alvo cardíaco, vascular e renal.[47] [48] [49] [50] Em recente trabalho publicado em uma população de pacientes hipertensos não tratados, recém-diagnosticados e com fração de ejeção ventricular esquerda normal, valores aumentados de DP da PA diurna e da PAS 24h ponderada foram associados com comprometimento precoce da função sistólica ventricular esquerda.[51]

“The Jackson Heart Study” é um estudo de base populacional desenvolvido na cidade de Jackson, Mississippi em adultos afro-americanos. O trabalho publicado em 2015 avaliou 1022 indivíduos que realizaram MAPA 24h no início do estudo. O objetivo era avaliar a associação entre VPA 24h e doença renal crônica. Doença renal crônica (DRC) foi definida como relação albumina/creatinina ≥30 mg/g ou eTFG <60 mL/min/1,73 m^2 e VPA foi definida por 2 métricas: DP dia-noite e Variabilidade Real Média. Os dados do estudo sugerem uma associação entre DRC e valores levados de DP dia-noite e Variabilidade Real Média. Entretanto estas associações foram explicadas

primariamente pelos valores elevados da média PA 24h.[52] Já no trabalho de Ryu e colaboradores não se encontrou associação entre Variabilidade Real Média e dano renal (definido com eTFG<30 mL/min/1,73 m^2 e proteinuria) numa ampla amostra coreana de pacientes hipertensos com DRC.[53]

Doença dos pequenos vasos cerebrais (DPV) pode ser subclínica por um longo tempo.Além disso, hipertensão é o principal fator de risco para DPV, a qual é um importante contribuinte para AVC e declínio cognitivo em idosos. Neste contexto, um estudo de coorte avaliou se DPV relaciona-se com VPA de curto prazo independentemente dos níveis pressóricos da PA. Foram incluídos 487 hipertensos assintomáticos que se submeteram a exame de ressonância magnética e MAPA 24h. Entre as métricas de VPA calculadas, somente a Variabilidade Real Média da PAS associou-se independentemente com a presença de DPV, mesmo após ajuste para níveis ambulatoriais de PA e outras covariáveis.[54]

2.2.2 Valor preditivo da VPA para eventos cardiovasculares e mortalidade

Estudos que tem utilizado a MAPA 24h tem mostrado que um aumento da VPA nas 24 h pode ser preditivo para eventos cardiovasculares[13 19 55 56 57] e mortalidade cardiovascular[13 19 58] independentemente dos níveis pressóricos médios. Entretanto em alguns trabalhos, VPA apresentou uma predição moderada para eventos cardiovasculares, confirmando o papel predominante dos valores médios da PA 24h na predição de risco cardiovascular.[59]

O valor preditivo para risco cardiovascular da VPA de curto prazo não é tão bem estabelecido quanto o da variabilidade visita-a-visita. Hansen e colaboradores[19] realizaram uma ampla coorte populacional (8938 indivíduos) e investigaram a relação entre VPA registrada no início do estudo com eventos cardiovasculares. A VPA foi mensurada através do DP e da Variabilidade Real Média nas 24h. O tempo mediano de seguimento foi de 11,3 anos e os autores concluíram que embora a VPA de curto prazo tenha sido um preditor de desfechos fatais e não-fatais sua contribuição para estratificação de risco foi pequena pois adicionou apenas 0,1% para explicar risco para ocorrência do evento (RR 1,07: IC 95% 1,01- 1,13; p< 0,05).

Evidências do ensaio clínico randomizado ASCOTBPLA que avaliou variabilidade de curto prazo e longo prazo sugerem que embora não seja um forte preditor como a variabilidade visita a vista, VPA de curto prazo medida pelo coeficiente de variação prevê risco de eventos vasculares independentemente da media diurna da PAS media.[15]

O Ohasama Study, com desenho prospectivo, acompanhou 1542 pacientes com mais de 40 anos da zona rural japonesa e com seguimento médio de 8,5 anos, identificou uma associação direta e independente entre VPA e mortalidade cardiovascular.[58]

Outros trabalhos com achados similares corroboram para o entendimento de que a VPA tenha um papel importante na doença cardiovascular.[60] [61] Verdecchia e colaboradores acompanharam 2649 indivíduos com hipertensão recentemente diagnosticada e sem tratamento por 16 anos (média de 6 anos) e observaram maior número de eventos

cardiovasculares e cerebrovasculares em pacientes com variabilidade da PA elevada, avaliada pelo desvio padrão. Após análise multivariada a variabilidade da pressão sistólica elevada no período da noite esteve associada a um excesso de risco de 51% para eventos cardiovasculares, mas perdeu sua significância estatística para eventos cerebrovasculares após ajuste para viéses de confusão.[55]

As análises preliminares do estudo PIUMA realizado na Itália demostrou associação entre o aumento da VPA (medida pelo desvio padrão da PA diruna e noturna) e desfecho composto de eventos cardiovasculares, cerebrovasculares e vasculares periféricos, mas a significância prognóstica deste aumento da VPA não foi detectável na análise multivariada.[61]

O estudo multicêntrico “ABP-International study” investigou a relação entre MAPA 24h e morbimortalidade cardiovascular. A base de dados foi construída com os registros de dados de 8 estudos: 3 europeus, 3 japoneses, 1 norte americano e 1 australiano.[62] Foram analisados 7112 participantes hipertensos não tratados com idade média 52±15 anos e com tempo de seguimento mediano de 5,5 anos. No modelo multivariado, a VPA noturna foi preditor independente de mortalidade por todas as causas (DP PAS noturna p=0,0003; DP PAD noturna p<0,0001); mortalidade cardiovascular (DP PAS noturna p=0,0082; DP PAD noturna p<0,0001); e eventos cardiovasculares (DP PAS noturna p=0,0003; DP PAD noturna p<0,0001). No modelo ajustado completo, DP PAS noturna de ≥12,2 mmHg foi associado a 41%, 55% e 59% de aumento de risco para eventos cardiovasculares, morte cardiovascular e mortalidade por todas as causas, respectivamente.

O estudo INTERACT2 avaliou o efeito da VPA nos desfechos em 90 dias em pacientes com hemorragia intracerebral espontânea e PA elevada. Manning e colaboradores demonstraram associações lineares e significativas entre DP PAS na fase hiperaguda (primeiras 24 horas) e na fase aguda (dia 2 a dia 7) e desfecho primário (morte ou deficiência grave em 90 dias). As associações foram similares para o desfecho secundário (mudança na pontuação ordinal da escala Rankin modificada em 90 dias) tanto na fase hiperaguda como na aguda.[63] Mais recentemente, Tanaka e colaboradores relataram associação significativa entre DP PAS dentro das 24h da deterioração neurológica e desfecho desfavorável (OR 2,75; IC 95% 1,45-6,12 por quartil).[64]

Recente metanálise avaliou a significância prognostica da VPA de curto prazo em AVC agudo. Foram incluídos 7 estudos para avaliar o efeito da VPA (aferida pelo DP da PA sistólica ou coeficiente de variação da PA sistólica) nos desfechos funcionais (morte ou incapacidade). Para incrementos de 10 mmHg, na VPA da PAS houve associação significativa com desfecho funcional ruim (OR 1,2: IC 95% 1,1-1,3). Os autores afirmam que a revisão dos estudos incluídos suporta este achado principal e, além disso, sugerem que a VPA sistólica pode estar associada com um risco aumentado de hemorragia intracraniana no grupo tratado com a terapia trombolítica. [65]

Outra revisão sistemática com metanálise avaliou o valor prognóstico da VPA dentro das 24h. O trabalho avaliou estudos publicados até abril de 2013 com pelo menos 1 ano de seguimento e que avaliassem medida da VPA nas 24h, dia ou noite. Além disso, deveriam avaliar os seguintes desfechos: mortalidade por todas as causas, mortalidade cardiovascular,

eventos cardiovasculares totais, AVC e doença arterial coronariana. O estudo incluiu 24 estudos e as análises de predições incluiu 16 trabalhos. Os autores identificaram 36 medidas diferentes de VPA e 13 definições de período diurno e noturno. Várias medidas de VPA dependem das diferenças entre o tempo diurno e noturno da PA, e não existem até o momento uma universalidade de definições das horas que constituem o dia e a noite. A revisão sistemática também encontrou incoerências nos trabalhos referentes as definições dos resultados de desfechos cardiovasculares e na expressão dos riscos relativos. Descenso noturno com base em variação percentual foi a medida mais pesquisada e a única medida para a qual os dados puderam ser significativamente agrupados. A presença de descenso noturno ou menor PA noturna foram associados a menor risco de eventos cardiovasculares. Os autores concluem enfatizando que a interpretação e aplicação na prática clínica da VPA das 24 horas é dificultada pela evidências insuficientes e metodologias divergentes e recomendam uma maior padronização de métodos.[66]

2.3 Variação da pressão arterial no tempo (Índice “time rate”)

Utilizando as medidas da MAPA de 24h Zakopoulos e colaboradores propuseram o Índice “time rate” (Time Rate of Blood Presure Variation) que consiste de uma medida de variabilidade da PA derivada da taxa de variação da PA ambulatorial no tempo a qual, de certa forma, reflete melhor a real variação pressórica ao longo das 24h quando comparada a parâmetros baseados no desvio padrão das médias. No trabalho pioneiro utilizando este índice, os autores avaliaram 539 indivíduos e demonstraram uma associação

independente entre o índice “time rate” e a espessura da carótida aferida por ecografia. No entanto, não são definidos pontos de corte como referência de normalidade, mas é apresentando uma nova perspectiva de parâmetro para análise da VPA. [11]

O mesmo grupo também demonstrou associação do índice “time rate” 24h com aumento da massa ventricular esquerda. Os autores avaliaram 998 pacientes, dos quais 365 eram normotensos, 448 hipertensos e 185 com hipertensão do avental branco, observando que os maiores determinantes relacionados à hipertrofia do ventrículo esquerdo (HVE) foram o índice de massa corporal (IMC), a variabilidade da PAS aferida pelo índice “time rate” 24h, além do gênero masculino e idade. [67]

A extensão do dano em órgão alvo tem sido associada tanto com hemodinâmica central como rigidez arterial. Com o objetivo de avaliar estes parâmetros Stamatelopoulos e colaboradores recrutaram 232 pacientes hipertensos e 241 normotensos controles. A VPA foi calculada através do índice “time rate” 24h. As PAS e PAD centrais aórticas foram avaliadas não invasivamente pela análise de onda de pulso. Já o espessamento da íntima-média das artérias carótidas foi mensurado por ultrassonografia. Dentre todos os tradicionais fatores de risco e parâmetros de monitoramento ambulatorial da PA e PAS de consultório, somente índice “time rate” 24h associou-se significativamente com espessamento da íntima-media das artérias carótidas, e esta associação manteve-se significativa mesmo após ajuste para fatores de confusão.[68]

A relação deste mesmo índice e a perda de função renal, estimada pela taxa de filtração glomerular (TFG), foi analisada em 803 pacientes com hipertensão não tratada. O grupo com TFG ≤ 60ml/min/1,73 m^2 apresentou maior variabilidade da pressão arterial sistólica (PAS) nas 24 horas mesmo após ajuste para os parâmetros basais e valores da MAPA. No modelo de regressão logística a idade, sexo masculino, PAS de consultório e o "time rate" da PAS de 24h foram fatores independentes relacionados à perda de função renal.[50]

Em outro trabalho, este grupo avaliou o índice "time rate" 24h e a gravidade e topografia das lesões coronarianas. A topografia e a gravidade das lesões arteriais coronarianas foram avaliadas através do Escore Gensini e o índice "time rate" através da MAPA 24h. Os pacientes com doença arterial coronariana (n=123) apresentaram a taxa de variação PAS diurna significativamente mais elevada em relação ao grupo controle (n=139). Um aumento de 0,1 mmHg na taxa de variação PAS diurna correlacionou-se com incremento de 4,935 no escore Gensini.[69]

Acidentes vasculares cerebrais de diferentes etiologias estão associados com diferentes padrões de alteração da PA. Neste contexto, Zis e colaboradores publicaram 2 trabalhos em que avaliaram o índice "time rate" 24h entre diferentes subtipos de AVC na fase aguda do evento. No primeiro,de 2011[70] foram descritos dados preliminares e no de 2013 os do seguimento de 1 ano. No estudo, 109 pacientes com AVC (94 isquêmicos e 15 hemorrágicos) realizaram MAPA 24h dentro de 24 horas após o começo dos sintomas. Pacientes com taxas mais elevadas de variação da PAS foram mais propensos

a ter desfecho negativo em 1 ano (OR 1,96; IC 95% 1,16–3,32). Além disso, para cada aumento de 0,1 mmHg/min na taxa de variação da PAS 24h (índice “time rate”) houve um aumento de 1,96 vezes na probabilidade de desfecho negativo. Desta forma, o índice “time rate” 24h mostrou-se prognóstico entre os subtipos de AVC na fase aguda do evento, e está associado com desfecho em 1 ano. Ainda com esta amostra de pacientes o grupo grego avaliou a possível associação entre formação de edema cerebral pós AVC agudo e índice “time rate” 24h. Os autores encontraram associação do índice “time rate” 24h com a formação de edema subsequente em pacientes com AVC agudo.[72]. Diante de tais resultados é sugerido que a redução do índice “time rate”, na fase aguda, poderia levar a melhores desfechos em pacientes que tiveram acidente vascular cerebral.[71]

Em 2014 o grupo de Zakopoulos e colaboradores publicou novo estudo desta vez avaliando a associação com desenvolvimento em órgão alvo em pacientes hipertensos não tratados. Um total de 85 indivíduos realizaram MAPA 24h e medidas ultrassonográficas da artéria carótida, e foram divididos em grupos de acordo com os valores de PA (130/80 mmHg). Pacientes hipertensos (n=45) apresentaram valores do índice “time rate” 24h significativamente mais elevados (P<0,05). Nas análises de regressão linear múltipla pacientes hipertensos demonstraram associações independentes de espessura médio-intimal da artéria carótida com os seguintes fatores: PAS 24h (p=0,033) e índice “time rate” PAS 24h (p=0,002).[73]

Com o intuito de avaliar a associação entre lesão macrovascular avaliada através do índice tornozelo braquial (ITB) e VPA através do índice

“time rate” 24h pesquisadores do Hospital de Clínicas de Porto Alegre realizaram estudo transversal avaliando 425 hipertensos. Os indivíduos foram agrupados de acordo com a presença ou ausência de ITB alterado (valores ≤ 0,9 ou ≥ 1,4). No modelo de regressão logística o índice “time rate” 24h associou-se com ITB, independentemente da idade (RR= 6,9; IC 95% 1,1- 42,1; p=0,04). No modelo de regressão linear múltipla, após ajuste para idade, PAS e diabetes, o índice “time rate” 24h manteve-se associado ao ITB (p < 0,01).[74]

Em outro estudo mais recente do mesmo grupo avaliou-se associação entre VPA de curto prazo (avaliado através do índice “time rate” 24h) e função diastólica e hipertrofia do VE em pacientes hipertensos controlados e não controlados. Após o ajuste para fatores de confusão, o índice “time rate” 24h não diferiu entre os pacientes controlados e não controlados. Variabilidade PA não se associou com HVE ou função diastólica após ajustes para PAS 24 h e idade. Os pacientes com PA controlada e não controlada apresentaram similar variabilidade PAS avaliada pelo índice time rate, o qual não se associou com HVE ou função diastólica. [75]

Tem sido sugerido que o tratamento anti-hipertensivo possa ser direcionado para a redução da VPA além de reduzir os níveis absolutos da PA 24h, mas as evidências neste sentido ainda são limitadas. Além disso, permanecem lacunas a respeito da real associação, independente das médias pressóricas ou outros fatores de confusão, entre os diferentes índices de VPA obtidos pela MAPA 24h e dano cardiovascular. Além disso, inexistem critérios de normalidade dos diferentes índices de VPA propostos e a sua aplicabilidade

clínica ainda não está totalmente definida na avaliação de indivíduos de alto risco (hipertensos e diabéticos, por exemplo).

3. JUSTIFICATIVA

Estudos prévios com objetivo de avaliar a associação entre a variabilidade da PA, avaliada pelos índices MAPA 24h, e danos em órgãos-alvo demostram resultados contraditórios e não apresentam comparações de desempenho entre os índices. Além disso, são escassos os estudos que avaliaram esta associação em indivíduos de alto risco, especialmente em hipertensos diabéticos. Desta forma a ampliação de estudos nesta área faz-se necessário.

Além disso, a significância prognóstica da variabilidade da PA para desfechos cardiovasculares ainda é debatida. Falta padronização dos métodos para avaliação da variabilidade da PA e a dificuldade em transpor os resultados dos estudos diretamente para a prática clínica diária demonstra que talvez, neste momento, a melhor maneira de se avaliar criticamente a informação disponível na literatura é através da realização de uma revisão sistemática, selecionando-se as evidências disponíveis sobre a variabilidade da PA por diferentes métodos e sua relação com o desenvolvimento de eventos cardiovasculares em estudos observacionais.

Ademais, estudo original realizado em nosso meio avaliando a associação entre a VPA e desfechos ecocardiográficos desenvolvido em amostra de alto risco cardiovascular como hipertensos diabéticos poderia acrescentar evidências nesta área.

Considerando-se estes aspectos, desenvolvemos 2 estudos: revisão sistemática e estudo transversal e com os seguintes objetivos:

4. OBJETIVOS

4.1 Objetivo geral:

Revisão Sistemática

Avaliar a associação entre a variabilidade da PA aferida por diferentes métodos de monitorização da PA e ocorrência de desfechos cardiovasculares em revisão sistemática de estudos observacionais em indivíduos hipertensos.

Estudo transversal

Analisar a associação entre diferentes parâmetros de variabilidade pressórica incluindo índice “time rate” aferido por MAPA-24h e parâmetros ecocardiográficos em indivíduos com hipertensão e diabetes mellitus.

4.2 Objetivos específicos:

Revisão Sistemática

1 Avaliar se a variabilidade da PA aferida por medidas de PA intermitente através da MAPA se associam a desfechos cardiovasculares maiores (morte total, morte cardiovascular, e desfecho compostos de infarto agudo do miocárdio (IAM) fatal e não-fatal, AVE (AVE) fatal e não-fatal, insuficiência cardíaca, revascularização miocárdica ou angina pectoris) em indivíduos hipertensos;

2 Avaliar se a variabilidade da PA aferida por medidas de PA intermitente através da MAPA se associa a desfechos substitutivos tais como hipertrofia de ventrículo esquerdo, disfunção vascular periférica, microalbuminúria e perda de função renal em indivíduos hipertensos;

3 Avaliar se a variabilidade da PA aferida por medidas de PA consecutivas através do Finapres e Portpres se associam a desfechos cardiovasculares maiores (morte total, morte cardiovascular, e desfecho compostos de infarto agudo do miocárdio (IAM) fatal e não-fatal, AVE fatal e não-fatal, insuficiência cardíaca, revascularização miocárdica ou angina pectoris) em indivíduos hipertensos;

4 Avaliar se a variabilidade da PA aferida por medidas de PA consecutivas através do Finapres e Portpres se associam a desfechos substitutivos (hipertrofia de ventrículo esquerdo, disfunção vascular periférica, microalbuminúria e perda de função renal) em indivíduos hipertensos;

Estudo transversal

1 Descrever a associação entre os diferentes parâmetros de VPA fornecidos pela MAPA 24h (índice “time rate”, coeficiente de variação, desvio padrão das médias) com dano em órgão-alvo (hipertrofia de ventrículo esquerdo) em pacientes com hipertensão e DM tipo 2.

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association with left ventricular hypertrophy and diastolic function. J Hum Hypertens 2015.

6 ARTIGO 1- SYSTEMATIC REVIEW

Blood pressure variability measured by different methods and its association with cardiovascular outcomes: a systematic review and meta-analysis

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ACKNOWLEDGMENTS

Supported by *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq) and *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES).

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Conflict of interest statement: The authors declared no conflict of interest.

ABSTRACT

Objective: Blood pressure (BP) variability is hypothesized to have important prognostic value in evaluating cardiovascular risk, but the prognostic significance of short-term BP variability and very short-term remains uncertain, including in evaluating cardiovascular risk and its influence in predicting target organ damage. The aim of the current study was examine the association between BP variability and cardiovascular risk including its influence on the presence of target-organ damage.

Methods: We conducted a systematic review and meta-analysis of prospective studies and randomly selected population samples that related any summary measure of short-term (over 24 h) and very short-term (beat to beat) of BP variability obtained from ambulatory blood pressure monitoring (ABPM) and continuous BP recordings was included. We searched PubMed, EMBASE, and the Cochrane Library to February 2015. Primary outcomes were all-cause mortality, cardiovascular mortality and cardiovascular events. Substitutive cardiovascular events: nonfatal stroke; transient ischemic attack, peripheral vascular disease, left-ventricular hypertrophy, impaired renal function.

Results: Of the 6.871 identified articles, 21 articles were included, amounting to 18.056 patients. The studies are very heterogeneous, especially regarding the use of BP variability and sample of each study. Although all subjects had hypertension, they were classified according to organ damage, treatment

status, high and low variability Index, and presence of other medical conditions. Due to this diversity among the studies, only one meta-analysis of a secondary outcome was possible. Using the random effects model, no association was observed between these groups and creatinine levels (0.10 mg/dl; IC 95% -0.01 – 0.22; I^2 = 98%).

Conclusion: There is large diversity among the available studies in the BP variability protocols, the indices selected to quantify BP variability and the end points used for evaluation. Short-term BP variability within 24h might be considered for risk stratification in population and cohort studies but key questions remain unanswered. These are: the choice of a optimal variability index that could represent the impact of BP variability on the cardiovascular system; the normal values or targets of BP variability to be achieved with antihypertensive treatment; and whether treatment-induced changes in short-term BP variability might also improve or affect target organ damage and cardiovascular event risk.

Keywords: Blood pressure variability- ambulatory blood pressure- cardiovascular outcomes

INTRODUCTION

Hypertension determines an increased risk of cardiovascular events[1] and mortality.[2] Lowering of office blood pressure (BP) with treatment is effective in reducing morbidity and mortality.[3] Additional information can be provided by 24-h ambulatory blood pressure monitoring (ABPM) concerning these risks. Average BP measured in usual life conditions through ABPM may be a better predictor of cardiovascular outcomes than office BP.[4] Moreover, fluctuations of BP over time may also provide prognostic information not usually obtained with average office or ambulatory BP.[5] Some studies have indicated that increasing BP variability is associated with development, progression, and severity of cardiac, vascular, and renal organ damage and with an increased incidence of cardiovascular morbimortality[6 7 8 9 10 11 12]

Blood pressure characteristically presents fluctuations within the day (providing data of very short and short-term BP variability) and over more prolonged periods of time (between days, months, seasons and even years, providing data of long term BP variability). This BP variability results from the interplay of extrinsic environmental and behavioral factors and cardiovascular regulatory mechanisms (humoral and neural influences).[5] Continuous beat-to-beat BP recordings, repeated office BP measures, 24-h ABPM, or home BP monitoring (HBPM) have been used for the assessment of BP variability. Although the precise quantification of very short and short-term BP variability

requires beat to beat BP recording,[13] its assessment is also possible, even less accurately, through the use of noninvasive ABPM. Several indices have been used to estimate the short-term BP variability and these have been related to the presence of subclinical damage in one or multiple organs, including the heart, kidney, and vessels, independently of BP levels.[9 14 15] However, studies in which short-term BP variability was estimated by ABPM yielded conflicting results,[16 17 8 18] , thus current guidelines do not recommend their use in clinical practice.[19 20] Moreover, depending on the method and the time interval considered for analysis, the clinical significance and prognostic implications of a given measure of the BP variability may in fact differ substantially.[5]

Furthermore the predictive value of short-term BP variability is less well established than the visit-to-visit and day-to-day BP variability.[21] Studies have demonstrated that visit-to-visit systolic BP variability assessed by repeated measurements in office visits is a strong predictor of stroke (independent of the average BP)[22] and mortality.[23] Evidence from randomized the controlled trial ASCOTBPLA which evaluated short-term and long-term BP variability suggest that although not as strong a predictor as visit-to-visit variability, short-term BP variability measured by the coefficient of variation predicts risk of vascular events regardless of average daytime mean systolic BP.[24] In addition, the lack of standardization of the different indices of BP variability obtained by ABPM and standards of normality hinder their clinical applicability in evaluating high-risk patients.[26]

The aim of this study was to conduct an updated systematic review of the literature and to investigate which methods and indices of assessment of BP

variability have been used, as well as their prognostic value as predictors of cardiovascular outcomes and target-organ damage.

METHODS

Data sources and searches

We included prospective observational studies (cohort, cross-sectional or case–control) and randomly selected population samples (randomized clinical trials) that explored the relationship between short-term (over 24h) and very short-term (beat to beat) BP variability and primary outcomes (all-cause mortality, cardiovascular mortality, cerebrovascular and cardiovascular events) or intermediate endpoints of BP-related target organ damage (carotid intima media thickness, carotid thickness, left ventricular hypertrophy, heart failure, hospitalization for cardiovascular diseases, renal impairment, urinary albumin excretion, peripheral vascular disease, renal insufficiency, myocardial infarction, stroke, revascularization, creatinine). Blood pressure variability was measured through any type of variability measure and obtained by non-invasive ABPM and/or continuous BP recordings.

The following databases were searched: PUBMED (1980-February 2015), EMBASE (1980-February 2015), and Cochrane Library (1980-february 2015), using MESH terms and/or a combination of text words related to BP variability and our outcomes. Our full search strategy is given in the supplementary information (appendix 1) which includes different spellings and combinations of words.

Original papers that included representative samples of subjects with arterial hypertension were eligible for inclusion in the present analysis. Exclusion criteria were: studies in pregnant women, children, experimental studies or retrospective studies, narrative reviews, letters, congress abstracts, and studies evaluating circadian rhythm. There were no language restrictions. Non-English papers were translated by expert translators or with online translation software. Reference lists of all obtained original papers were hand searched to identify further relevant studies.

Data extraction

Relevant data were extracted by two independent investigators (D.M. and A.S.O.S.) that reviewed the titles and abstracts of all articles and extracted data from the final articles selected, and controversies were solved by a third investigator (J.N.). Additional data have been obtained by personal contact with authors of the selected papers. When the same research group had published more than one paper, we investigated possible overlapping of the study sample and only the most recent work was considered. Several groups of papers with duplicate or overlapping patient populations were included because they reported different measures, outcomes or methods of analysis. Each group was counted as a single study.

The full texts of relevant articles were obtained and the independent evaluators reviewed the selected papers taking into account the inclusion criteria. They also performed the assessment of describing and presenting findings of studies through the Strobe checklist[27] combined version for observational studies by individual paper. Disagreements were solved by

discussion and revision with a third author (J.N.). This evaluation was performed for all studies included except for the Pringle et al's study,[28] which consists of a randomized clinical trial. We conducted our systematic review and meta-analysis according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (PRISMA).[29]

Statistical Analysis

The summary effects and 95% confidence intervals were calculated using random effects model. A summary using fixed effects model was calculated as exploratory analysis. The heterogeneity of the studies was evaluated through I^2 inconsistency test. All analyzes were conducted using Review Manager 5.1 software (Cochrane Collaboration).

RESULTS

The initial search identified 6.871 articles, of which 614 were duplicates and 6.206 were excluded after the analysis of titles and abstracts. After reviewing the remaining 51 full-text articles, 21 articles met the eligibility criteria and were included in the review (Figure 1).

Characteristics of the studies

In terms of design, most of the studies were cross-sectional (n=12), [10] [15] [30] [31] [32] [33] [34] [35] [36] [37] [38] [39] six were prospective cohorts,[40] [41] [42] [43] [44] [45] two were case-control studys[46] [47] and one was a randomized clinical trial.[28] Table 1 lists the characteristics of the studies that evaluated the short-term BP variability through the ABPM and very short-term by continuous measurements (finapres,

portapres and finometer) totalizing 18.056 subjects. The very short-term BP variability was also assessed in 121 individuals (3 studys) by portapress,[30] finometer[38] or finapress.[37]

The study samples ranged from 33 to 7112 individuals and included hypertensive subjects, but patients differed between studies regarding the use or not of antihypertensive treatment: three studies[34 41 44] included hypertensive patients using antihypertensive medication, two articles evaluated treated and untreated hypertensive individuals, [31 45] and the great majority of papers included untreated hypertensive subjects (n=15). Only one study (Pringle et al)[28] did not describe whether individuals were using antihypertensive medication or not.

Concerning the methodology to assess and quantify the BP variability, there was great diversity among the studies in the parameters and indices used. Ten studies used standard deviation (SD) of 24h/daytime/nightime; two articles utilized SD of daytime/nightime;[34 35] four studies measured only the SD of 24h; [10 31 38 46] and one study used the SD of 24h/nightime.[30] In addition to SD, three studies also included the coefficient of variation (CV)[36 40 44] and one study[32] only reported CV, but data was not shown in the paper. Eto et al[44] besides evaluating the SD and CV also explored average real variability (ARV), and others two papers assessed in addition to the ARV the SD.[15 45] Furthermore Leoncini et al[15] evaluated BP variability by the crude and weighted standard deviation (w.SD).

The mean values of systolic BP SD 24h, daytime SD, nighttime SD were 17.2 mm Hg, 15.8 mm Hg, 12.7 mm Hg, with an average of ranges: 12.7–22.9, 12.7–22.1 and 10.0–15.8 mm Hg, respectively.

There were few studies reporting other indices. Zakopoulos et al[39] described by the first time a new index proposed by his group defined as the first derivative of the systolic BP values against time ("time rate of systolic BP variation" or "time rate index") of 24h/daytime/nighttime. After one year the same group published a paper evaluating this new index on daytime and nighttime.[35] Another study reported the time rate index only of 24 hours.[10]

One study[37] reported the variation of the BP by the SD supine beat-to-beat, other article used the SD of "beat-to-beat" of BP and the time rate of "beat-to-beat" BP.[38] Angelats et al.[30] used two measures: BP variability by long and short term, which were not described in any other article.

In relation to the outcomes, most studies reported primary endpoints as cardiovascular events and mortality[28 40 41 42 43 44 45] and one study evaluated cerebrovascular events.[44] Among the intermediate outcomes, the most cited by the studies was the left ventricular hypertrophy[30 34 35 37 43 47] followed by left ventricular mass idex.[15 32 36 46] Three articles[43 44 28] demonstrated the number of subjects presenting stroke, heart failure and acute myocardial infarction. Other three studies[33 38 39] described the carotid thickness. Laboratory analyzes, such as urinary excretion was evaluated in 805 patients, and described by three articles[33 36 37] and albuminuria was analyzed by three other studies[31 43 44] totaling 3457 hypertensive subjects. Just one study showed the outcome hospitalization in 33 patients.[43]

In order to explore the clinical significance of BP variability, six papers stratified the sample into groups (low and high variability).[31 36 41 42 44 45] These studies used a cut-off point baseado on the median SD value of 24h systolic BP or diastolic BP. Eto et al. was the only one that used the median CV value of 24h systolic BP as a cut-off point. (Table 2)

Figure 2 presents the mean values of creatinine with subgroup meta-analysis reported for groups of low and high BP variability. Three articles stratifyed the population studied in low and high of BP variability.[31 44 45] Using the random effects model, no association was observed between these groups and creatinine levels (0.10 mg/dl; IC 95% -0.01 – 0.22; I^2 = 98%). Among the three articles included in the meta-analysis, none of them is the specific source of heterogeneity, even excluding Pierdomenico's article[45] the result is I^2 = 93%.

Table 3 shows the descriptive evaluation of the studies. Considering the item "title and summary", 52.5% of the articles were poorly described, 40% described satisfactorily and few were classified as partially satisfactory (12.5%). Considering the introduction, most of the articles (95%) were satisfactorily described, filling in detail the recommended requirements of the STROBE, whereas only 2.5% were partially satisfactory and unsatisfactory described. The methods contained 13 items to be covered by the studies, so the descriptions were better in some items and worse in others. 24.3% of the studies described satisfactory their results, while the majority of (52.5%) described unsatisfactorily and 23.2% partially satisfactory. In the description of the results, 17.7% of the studies were classified as satisfactory, 62.3% as poor, and 20% as partially satisfactory. In the discussion, 57.5% of the papers were described

satisfactorily, 23.7% were not satisfactory and 18.8% were partially satisfactory. Considering all the items mentioned above, 48% had unsatisfactory description (48%), 32% satisfactory and 20% partially satisfactory.

DISCUSSION

There is an increasing interest and accumulating evidence on BP variability, especially on its impact in clinical outcomes, with the majority of the studies evaluating short-term variability using the ABPM. The present systematic review underlines that the available information could not be fully compiled because of the great heterogeneity of the terms used to refer to BP variability, the many different measurement protocols used, and the multiple BP variability indices used, as well as several different outcomes evaluated in these studies. Moreover, inconsistencies exist in the definitions of cardiovascular and target organ damage outcomes. All these issues precluded meta-analyses to be performed. In short, our review demonstrates the absence of good epidemiological studies exploring the relationship between BP variability and primary cardiovascular and target organ damage endpoints.

In our systematic review we showed by meta-analysis no association between BP variability groups and creatinine levels, even excluding Pierdomenico's article[45] the result was I^2 = 93%, demonstrating that none of the articles included in the meta-analysis were the source of heterogeneity. The changes in diurnal pattern of BP has also been investigated and its association with kidney organ damage. Certain diseases that are characterized by increased sympathetic activation drive,[49] important reductions in day/night BP

difference have been reported, suggesting that elevated sympathetic activity is associated with reduced nocturnal BP dipping. And this reduction have been shown to be influenced also by salt sensitivity,[50] sleep breathing disorders (i.e., obstructive sleep apnea), leptin and insulin resistance,[51] endothelial dysfunction,[52] and others. However, in this paper the authors used only as variability marker the means of day and night systolic BP.

The evidence in regard to the association of BP variability with target organ damage is mainly based on cross-sectional analyses. Overall, the studies investigating the association between BP variability and LVH have mostly examined short-term BP variability, and suggest an independent association of short-term BP variability with target organ damage (assessing the left ventricular mass by left ventricular mass index-LVMI). Few data was found evaluating the association between BP variability and other cardiac outcomes (renal, arterial and vascular consequences).[9 10 28] In particular, Zakopoulos et al.[35] 2006 examining the relation of the rate of BP variation (short-term BP variability) with left ventricular mass (determined by echocardiography) demonstrated that daytime rate of systolic BP variation is positively and continuously associated with the left ventricular mass independent of baseline characteristics, BP levels, BP variability and nocturnal BP dipping. On the contrary, Veerman et al.[37] reported a non-significant correlation of left ventricular mass with day SD. A potential reason for the discrepancy in results between the two studies cited is the reduced sample size (n=33) in the Veerman's study. These findings suggest that the results are sensitive to the index of BP variability chosen and leads to the question of which variability measurement is in fact accurate for the purpose of predicting outcomes.

Other explanation for these seemingly contradictory results may be the more appropriate index of short-term BP variability because it only reflects the dispersion of measures around a single value, the average BP, regardless of the order in which the measurements were obtained.[53] The CV is also another index usually used, but this index also has a dependency on mean BP levels.[54] In order to avoid the interference of day/night BP fluctuations on short-term BP variability measures, alternative indices have been proposed for estimating faster BP changes: average real variability (ARV); the residual BP variability; "weighted" 24 h BP SD; variance independent of the mean (VIM), and others[15] However, in this review, only the ARV[15 44 45] and weighted 24 h BP SD[15] were reported in studies where cardiovascular or target organ damage outcomes were also shown.

Studies using ABPM have shown an initial increase in BP variability within the 24 h to be predictive for cardiovascular events and cardiovascular mortality.[40] Pringle et al.[28] demonstrated that increased night-time systolic BP variability was a risk factor for stroke, even after adjusting for BP levels and other confounding variables. Night-time systolic BP variability is also an independent risk factor for cardiac events in untreated hypertensive patients.[43] However, in a large population cohort (11 populations, n=8938, 11-yr follow-up), BP variability assessed from ABPM did not contribute much to risk stratification over and beyond average 24-hour BP,[11] confirming the prevailing role of 24 h mean BP values in cardiovascular risk prediction.[26]

A recent systematic review searched for similar information as this present review, but also included studies that evaluated long-term BP variability.

In accordance with our review, multiple methods and outcomes reported precluded the authors to perform meta-analyses of very short and short-term BP variability studies. Night dipping based on percentage change was the most researched measure and the only measure for which data could be pooled. Night dipping or lower night-time BP was associated with lower risk of cardiovascular events.[55] However, whether it is the reduction in nocturnal BP dipping or the increase in absolute level of average BP at night that really matters is an issue still under investigation.[56]

Our results are consistent with other studies where variations in the methods and definitions of variability measures and indices were described. [21] [55] [56] [57] We perform a systematic review of the methods of analysis and prognostic value of 24-hour BP variability, considering other measures of BP variability and exploring the cardiovascular risk and the influence on the target-organ damage.

One of the eligibility criteria of the review was that the studies evaluate hypertensive subjects. Some studies included subjects from the general population, [36] [43] [40] promoting a possible selection bias.

Some limitations of this review should be pointed out. The most important is the high clinical heterogeneity of the study samples and the diversity of definitions of BP variability. There was no standardization of studies regarding the time interval between BP measurements (every 30 min or every 20 min); as this measurement represents a low frequency sampling, then accuracy of BP variability estimates assessed by ABPM may be reduced. Moreover, it has been reported that some antihypertensive drugs reduce BP variability[58], then, studies

that included treated and untreated patients might generated biased results. Finally, the majority of the studies included (12 of the 21 studies) were cross-sectional, limiting the assessment of cause–effect relationships. Although the vast majority of articles presented the correlation coefficients, each paper had different outcomes and mostly stratified the population in different ways. Furthermore, some studies did not do adequate adjustment for covariates or additional analysis.

According to the guidelines for ABPM published in 2014 by the European Society of Hypertension,[20] on the basis of the available evidence, short-term BP variability within 24h might be considered for risk stratification in population and cohort studies. However, at present it does not represent a parameter for routine use in clinical practice.

In conclusion, this systematic review emphasizes that before deciding that short-term BP variability is a useful method that could be used in daily practice, future studies are needed to answer several fundamental research questions. Studies must determine: (i) which index represents more accurately the impact of BP variability on the cardiovascular system; (ii) which measure of BP variability has the best performance as a risk marker/factor; (iii) which are the normal values or targets of BP variability to be achieved with antihypertensive treatment; (iv) whether treatment-induced changes in short-term BP variability and might also improve affect target organ damage and cardiovascular event risk.

CONFLICT OF INTEREST

There are no conflicts of interest.

ACKNOWLEDGEMENTS

This research was funded by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

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Figure 1. Flowchart of the studies included in the Systematic Review

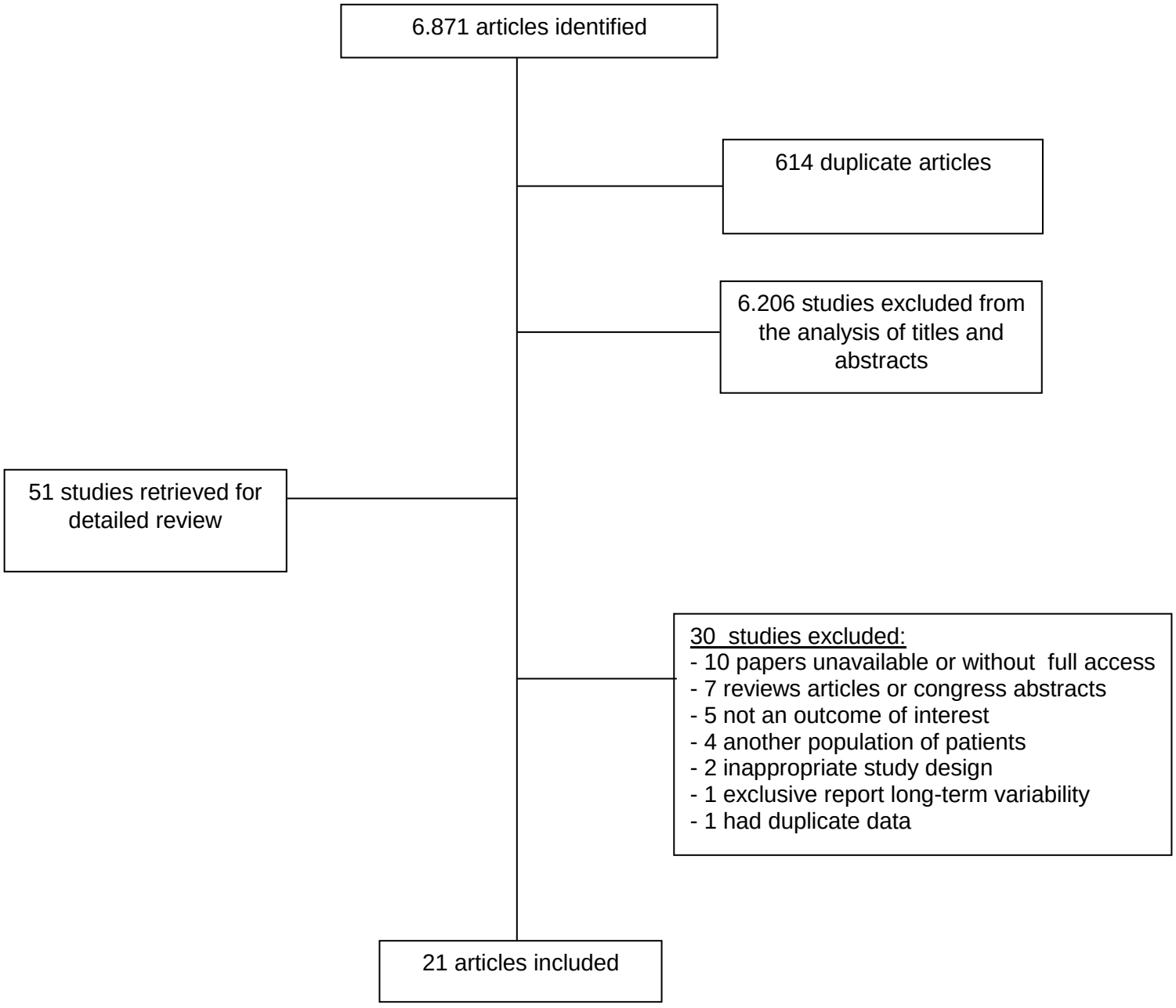


Table 1. *Study characteristics using 24h ABPM*					
Author, year	Design	Patients	Variability Measure	Outcomes	n
Schulte KL, 1993	Case-control	Untreated hypertensive and normotensive	SD (SBP, DBP) -24h	LVM; LVMI	97
Veerman DP, 1996	Cross-sectional	Hypertensive patients	SD (SBP, DBP)- day, night SD supine beat-to-beat (SBP, DBP)	LVH; LVMI; urinary albumin excretion; albumin/creatinine ratio	33
Kristensen KS, 2001	Cross-sectional	Untreated hypertensive from general practice and normal subjects drawn at random from Danish national register	SD (SBP, DBP) -24h, day, night CV (SBP, DBP)- 24h, day, night	LVMI; albuminuria	566
Pringle E, 2003	Randomized Clinical Trial	Hypertensive (International database on ambulatory BP monitoring in relation to cardiovascular outcomes-IDACO)	SD (SBP, DBP)- 24h, day, night	Cardiovascular death; cardiac event; myocardial infarction; stroke, heart failure	744
Angelats EG, 2004	Cross-Sectional	Untreated hypertensive	SD (SBP, DBP)- 24h, night	LVH	43
Pierdomenico SD, 2005	Cohort	Untreated hypertensive (Chieti University)	SD (SBP, DBP)- 24h, day, night	CV outcomes (fatal and nonfatal cardiovascular events)	1088
Eto M. 2005	Cohort	Hypertensive	SD (SBP, DBP)- 24h, day, night ARV (SBP, DBP)- 24h CV (SBP)- day, night, 24h	Cardiovascular death, cerebrovascular event; myocardial infarction; stroke; heart failure; creatinine	106
Zakopoulos NA, 2005	Cross-sectional	Uncomplicated hypertensive, normotensive	Rate of SBP variation- 24-h, daytime, night-time	Common carotid artery intima-media thickness	234
Ichihara A, 2006	Cross-sectional	Untreated hypertensive attending the outpatient hypertension clinic	SD (SBP, DBP)- 24h, day, night	Arterial wall stiffness; carotid intima–media thickness; urinary albumin excretion	203
Pierdomenico	Cohort	Treated hypertensive, (Chieti	SD (SBP, DBP)- 24h, day, night	CV outcome (fatal and	1472

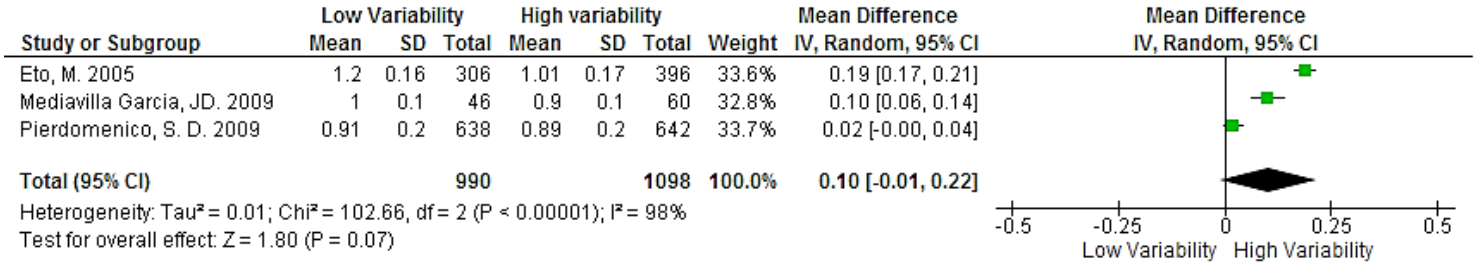
SD, 2006		University)		nonfatal cardiovascular events)	
Zakopoulos NA, 2006	Cross-sectional	Normotensive; white-coat hypertensive and uncomplicated hypertensive	SD (SBP, DBP)- day, night; Rate of variation (SBP, DBP)- daytime, night-time	LVM	448
Verdecchia P, 2007	Cohort	Hypertensive (progetto PIUMA)	SD (SBP, DBP)- 24h, day, night	Cardiovascular death; cardiac event; cerebrovascular event; myocardial infarction; stroke; LVH; heart failure; hospitalization, creatinine	2649
Mediavilla Garcia JD, 2009	Cross-Sectional	Treated and untreated hypertensive	SD (SBP)- 24h	Glomerular filtration (creatinine)	702
Ozawa M, 2009	Cross-sectional	Hypertensive patients hospitalized for the educational program	SD (SBP, DBP)- daytime, nighttime	LVH and brachial–ankle pulse wave velocity	92
Pierdomenico SD, 2009	Cohort	Hypertensive (Chieti University)	SD (SBP, DBP)- 24h, day, night ARV (SBP, DBP)- 24h	CV events	1280
Manios E, 2009	Cross-sectional	Untreated hypertensive	SD (SBP, DBP)- 24h Rate of variation (SBP, DBP)- 24h	Impaired renal function (estimated glomerularfiltration rate)	803
Ajayi OE, 2011	Cross-sectional	Nigerian hypertensive	CV (SBP, DBP)- 24h (data not shown)	LVMI	130
Leoncini G, 2013	Cross-sectional	Untreated hypertensive attending outpatient clinic	SD (SBP, DBP)- 24h, awake, asleep ARV (SBP, DBP)- 24h, awake, asleep wSD (SBP, DBP)- 24h, awake, asleep	LVMI	169
Palatini P, 2014	Cohort	Untreated hypertensive patient (ABP-International study)	SD (SBP, DBP)- 24h, day, night CV (SBP, DBP)- night (data not shown)	CV events and mortality	7112

Shin SM, 2014	Case-control	Young adults hypertensive (never treated hypertension); healthy controls	SD (SBP, DBP)- 24h	Changes of LV function	40
Manios E, 2014	Cross-sectional	Hypertensive	SD (SBP, DBP)- 24h Time rate 24h (SBP, DBP) SD of "beat-to-beat" (SBP, DBP) Time Rate of "beat-to-beat" (SBP, DBP)	Common carotid artery intima-media thickness	45
Characteristics studies using Portapress/Finapres/Finometer					
Angelats EG, 2004	Cross-sectional	Untreated hypertensive	Long-term variability and short-term (intersemihoraria) (SBP)	LVH	43
Veerman DP, 1996	Cross-sectional	Referred to hypertension clinic because of suspected hypertension	SD- day	LVMI	33
Manios E, 2014	Cross-sectional	Hypertensive	SD (SBP, DBP)- 24h Rate of variation (SBP, DBP)- 24h SD of "beat-to-beat" (SBP, DBP) Time Rate of "beat-to-beat" (SBP, DBP)	CCA-IMT	45
Abbreviations: SD, standard deviation; ARV, average real variability; CV, coefficient of variation; wSD, weighted standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVM, left ventricular mass; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; CV, cardiovascular event.					

Table 2: *Studies Comparing High and Low BP Variability*			
Author, year	n	Definition Low and high variability	Results
Kristensen KS, 2001	420 (High Variability: 210; Low Variability: 210)	Magnitude of the deviation of the mean daytime SBP (cut off = 12.14)	GF<60 ml/m2 (n(%))= 7.2 (Low variability group); GF<60 ml/m2 (n((%))= 25,5 (High variability group). Variables were independently associated with high BP variability- OR 5.44 (1.830–16.184); p= 0.002 (GF). Creatinine (mg/dl), mean (DE)= 1,01 (0,17) (Low variability) ; Creatinien (mg/dl), mean (DE)= 1,2 (0,16) (High variability)
Pierdomenico SD, 2005	1088 (High Variability: 462; Low Variability: 626)	Subjects with the SD of daytime or night-time systolic BP < or > the median of the population	119 events. Cardiovascular Event n(%)= 119(8); MI- n(%)=31 (2,1) (7 fatal); Stroke- n(%)= 49 (3.3) (10 fatal); Revascularization- n(%)= 19 (1.3); HF- n(%)=9 (0.6); Renal Failure- n(%)=3 (0.2); The event rates per 100 patient-years (according to daytime BP)=> (LOW VARIABILITY)= 1.18; (HIGH VARIABILITY)= 2.01; according to night-time BP=> (LOW VARIABILITY)= 1.2 (HIGH VARIABILITY)= 2.05
Eto M. 2005	106 (High Variability: 46; Low Variability: 60)	Patients with SD of daytime systolic and diastolic BP below or above the group mean (12.3 and 9.3mmHg, respectively)	119 events. Cardiovascular Event n(%)= 55(5); MI- n (%)=15 (1.4) (1 fatal); Stroke- n(%)= 29 (2.7) (3 fatal); Revascularization- n(%)= 5 (0,4); HF- n(%)=3 (0.3) (REQUIRING HOSPITALIZATION); Renal Failure- n(%)=1 (0.09) (REQUIRING DIALISIS); The event rates per 100 patient-years=> (LOW VARIABILITY)= 0.72; (HIGH

			VARIABILITY)= 1.5;
Pierdomenico SD, 2006	1472 (High Variability: 734; Low Variability: 738)	Patients showed a mean CV value of 10.6%	All: Cardiovascular Death: 3 (3.18%), Cerebrovascular Event: 39 (41.34%), MI: 7 (7.42%), Stroke: 15 (14.15%), IC: 3 (3,18%), Creatinine: 1.0±0.1(SEM), high CV: Creatinine: 1.0±0.1(SEM), low CV: Creatinine: 0.90±0.1(SEM)
Mediavilla Garcia JD, 2009	702 (High Variability: 306; Low Variability:396)	Hypertensives classified according to their CV and SD of systolic and diastolic daytime BP; SD below or above median	Mean (SD) LVMI(gm−2)=102.7 (28.3); r=0.24 (p<0.01)
Pierdomenico SD, 2009	1280 (High Variability: 638; Low Variability: 642)	Patients with the SD or ARV of daytime and night time systolic/diastolic BP below or above the group median (10.9/8.4 or 8.7/6.6, and 9.1/7.8 or 7.9/6.7, respectively, for initially untreated subjects, and 11.7/8.4 or 8.9/6.5, and 10.0/8.1 or 8.4/6.8, respectively, for initially treated subjects)	RR SBP= 2.07 (1.31-328). RR DBP= 1.36 (0.92-2.02)
Abbreviations: SD, standard deviation; ARV, average real variability; CV, coefficient of variation; wSD, weighted standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVM, left ventricular mass; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; CV, cardiovascular event.			

Figure 2: Comparison between high and low blood pressure variability on mean values of creatinine



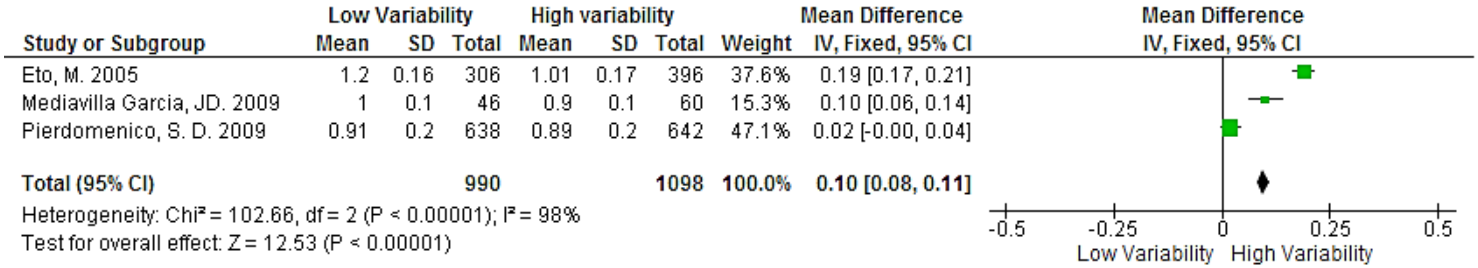


	Table 3. Descriptive evaluation of the studies recommended requirements of the STROBE																																
		Appraisal Criterion																															
Study	**Title and abstract**		**Introduction**		**Methods**														**Results**										**Discussion**				**Other information**
			Background/rationale	Objective	Study design	Setting	Participants		Variables	Data sources/measurement	Bias	Study size	Quantitative variables	Statistical methods					Participants			Descriptive data			Outcome data	Main results			Other analyses	Key results	Limitations	Interpretation	Generalisability	Funding
	1a	1b	2	3	4	5	6a	6b	7	8	9	10	11	12a	12b	12c	12d	12e	13a	13b	13c	14a	14b	14c	15	16a	16b	16c	17	18	19	20	21	22
Angelats EG. 2004	X	√	√	√	X	X	SP	N/A	SP	√	X	X	X	SP	X	X	X	X	X	X	X	SP	X	N/A	√	X	X	X	X	√	SP	√	X	X
Mediavilla Garcia, JD. 2009	X	SP	√	SP	√	√	√	N/A	SP	√	X	X	X	SP	√	X	X	X	SP	X	X	SP	X	N/A	√	SP	√	X	X	√	SP	√	SP	X
Palatini, P. 2014	X	SP	√	√	√	SP	SP	X	SP	SP	X	X	SP	√	√	X	X	√	SP	X	√	SP	X	√	√	SP	√	X	√	√	√	√	X	X
Ajayi, O. E. 2011	X	√	√	√	SP	SP	√	N/A	SP	SP	X	X	X	SP	√	X	X	X	X	X	X	SP	X	N/A	√	X	X	X	√	√	SP	SP	X	X
Ichihara A. 2006	X	√	√	√	SP	SP	√	N/A	SP	√	X	X	X	√	X	X	X	X	X	X	X	SP	X	N/A	√	SP	X	X	X	√	SP	√	X	√
Pierdomenico, SD. 2006	X	√	√	√	X	SP	X	X	SP	√	X	X	SP	√	√	X	X	X	X	X	X	SP	X	√	√	SP	√	√	X	√	SP	√	√	X
Leoncini, G. 2013	X	√	√	√	SP	SP	SP	N/A	SP	√	X	X	√	√	X	X	X	X	√	√	√	√	√	N/A	SP	SP	X	√	X	√	SP	√	√	X
Pierdomenico, SD. 2005	X	SP	√	√	X	SP	SP	X	SP	√	X	X	√	√	√	X	X	X	X	X	X	SP	X	√	√	SP	X	√	X	√	SP	√	√	X
Ozawa, M. 2009	X	SP	√	√	√	√	SP	N/A	SP	√	X	X	√	√	X	X	X	X	X	X	X	SP	X	N/A	X	SP	X	X	X	√	X	SP	X	√
Shin, S. M. 2014	X	√	SP	√	SP	SP	SP	√	SP	√	X	X	√	SP	X	X	X	X	SP	X	X	SP	√	N/A	SP	X	SP	X	√	√	√	√	X	√
Verdecchia, P. 2007	X	√	√	√	√	SP	√	X	SP	SP	X	X	X	√	X	X	X	X	X	X	X	SP	X	√	√	SP	√	√	X	√	SP	√	X	√
Eto, M. 2005	X	√	√	√	X	SP	SP	X	SP	SP	X	X	X	√	X	X	X	X	X	X	X	SP	X	√	√	SP	X	√	X	√	√	√	SP	√
Zakopoulos, N. A., 2006	X	√	√	√	√	√	√	N/A	SP	SP	X	X	X	√	X	X	X	X	X	X	X	SP	X	N/A	SP	SP	X	X	√	√	√	√	X	X
Kristensen, K. S. 2001	√	√	√	√	SP	SP	SP	N/A	SP	SP	X	X	X	√	X	X	X	X	X	X	X	SP	X	N/A	SP	SP	X	X	X	√	X	√	X	X
Pierdomenico, S. D. 2009	X	SP	√	√	√	√	SP	X	SP	√	X	X	√	√	X	X	X	X	X	X	√	SP	X	√	√	SP	X	√	√	√	SP	√	X	X
Veerman, D. P. 1996	X	√	√	√	SP	SP	SP	N/A	SP	√	X	X	X	√	X	X	X	X	X	X	X	X	X	N/A	X	SP	X	X	X	√	X	SP	X	X
Schulte, KL. 1993	X	√	√	X	X	SP	SP	SP	SP	SP	X	X	X	SP	X	X	X	X	X	X	X	SP	X	N/A	X	SP	X	X	X	√	X	SP	X	X
Manios, E. 2014	X	√	√	√	√	√	√	N/A	SP	√	X	X	√	√	√	X	X	X	X	X	X	SP	X	N/A	X	SP	X	X	X	√	√	√	X	X
Pringle, E. 2003	√	√	√	√	√	SP	SP	N/A	SP	SP	X	X	X	SP	X	X	X	X	X	X	X	SP	X	√	SP	SP	X	X	X	√	X	SP	X	√
Manios, E. 2009	X	√	√	√	X	√	SP	N/A	SP	√	X	X	√	√	√	X	X	X	X	X	X	SP	X	N/A	SP	SP	X	X	X	√	√	√	X	X
Zakopoulos, N. A. 2005	X	√	√	√	√	√	√	N/A	SP	√	X	X	√	√	√	X	X	X	X	X	X	SP	X	N/A	X	SP	X	X	X	√	√	√	X	X
	√ - satisfied;																																	
	X – not satisfied;																																	
	N/A – not applicable																																	
	SP - satisfied partially																																	
	No description given																																	

Appendix 1. Search strategy

- Pubmed

OUTCOMES

"death"[MeSH] OR “death” OR “Determination of Death” OR “Near-death Experience” OR “Cardiac Death” OR “Death, Cardiac” OR “cardiovascular diseases”[MeSH] OR “Cardiovascular Disease” OR “Disease, Cardiovascular” OR “Diseases, Cardiovascular” OR "Mortality"[Mesh] OR “Mortalities” OR “Case Fatality Rate” OR “Case Fatality Rates” OR “Rate, Case Fatality” OR “Rates, Case Fatality” OR “Mortality, Excess” OR “Excess Mortalities” OR “Mortalities, Excess” OR “Excess Mortality” OR “Decline, Mortality” OR “Declines, Mortality” OR “Mortality Declines” OR “Mortality Decline” OR “Mortality Determinants” OR “Determinant, Mortality” OR “Mortality Determinant” OR “Determinants, Mortality” OR “Mortality, Differential” OR “Differential Mortalities” OR “Mortalities, Differential” OR “Differential Mortality” OR “Age-Specific Death Rate” OR “Age-Specific Death Rates” OR “Death Rate, Age-Specific” OR “Death Rates, Age-Specific” OR “Rate, Age-Specific Death” OR “Rates, Age-Specific Death” OR “Age Specific Death Rate” OR “Death Rate” OR “Death Rates” OR “Rate, Death” OR “Rates, Death” OR “Mortality Rate” OR “Mortality Rates” OR “Rate, Mortality” OR “Rates, Mortality” OR "myocardial infarction"[MeSH] OR “Infarction, Myocardial” OR “Infarctions, Myocardial” OR “Myocardial Infarctions” OR “Cardiovascular Stroke” OR “Cardiovascular Strokes” OR “Stroke, Cardiovascular” OR “Strokes, Cardiovascular” OR “Myocardial Infarct” OR “Infarct, Myocardial” OR “Infarcts, Myocardial” OR “Myocardial Infarcts” OR "ventricular dysfunction, left"[MeSH] OR “Left Ventricular Dysfunction” OR “Dysfunction, Left Ventricular” OR “Dysfunctions, Left Ventricular” OR “Left Ventricular Dysfunctions” OR “Ventricular Dysfunctions, Left” OR "Hypertrophy, Left Ventricular"[MeSH] OR “Left Ventricular Hypertrophy” OR “Hypertrophies, Left Ventricular” OR “Left Ventricular Hypertrophies” OR “Ventricular Hypertrophies, Left” OR “Ventricular Hypertrophy, Left” OR "Stroke"[MeSH] OR “Strokes” OR “Apoplexy” OR “CVA (Cerebrovascular Accident)” OR “CVAs (Cerebrovascular Accident)” OR “Cerebrovascular Accident” OR “Cerebrovascular Accidents” OR “Cerebrovascular Apoplexy” OR “Apoplexy, Cerebrovascular” OR “Cerebrovascular Stroke” OR “Cerebrovascular Strokes” OR “Stroke, Cerebrovascular” OR “Strokes, Cerebrovascular” OR “Vascular Accident, Brain” OR “Brain Vascular Accident” OR “Brain Vascular Accidents” OR “Vascular Accidents, Brain” OR “Cerebral Stroke” OR “Cerebral Strokes” OR “Stroke, Cerebral” OR “Strokes, Cerebral” OR “Stroke, Acute” OR “Acute Stroke” OR “Acute Strokes” OR “Strokes, Acute” OR “Cerebrovascular Accident, Acute” OR “Acute Cerebrovascular Accident” OR “Acute Cerebrovascular Accidents” OR “Cerebrovascular Accidents, Acute” OR “Heart Failure”[MeSH] OR “Cardiac Failure” OR “Heart Decompensation” OR “Decompensation, Heart” OR “Heart Failure, Right-Sided” OR “Heart Failure, Right Sided” OR “Right-Sided Heart Failure” OR “Right Sided Heart Failure” OR “Myocardial Failure” OR

“Congestive Heart Failure” OR “Heart Failure, Congestive” OR “Heart Failure, Left-Sided” OR “Heart Failure, Left Sided” OR “Left-Sided Heart Failure” OR “Left Sided Heart Failure” OR "Myocardial Revascularization"[MeSH] OR “Myocardial Revascularizations” OR “Revascularization, Myocardial” OR “Revascularizations, Myocardial” OR “Internal Mammary Artery Implantation” OR "angina pectoris"[MeSH] OR “Stenocardia” OR “Stenocardias” OR “Angor Pectoris” OR "Peripheral Vascular Diseases"[MeSH] OR “Disease, Peripheral Vascular” OR “Peripheral Vascular Disease” OR “Vascular Disease, Peripheral” OR “Peripheral Angiopathies” OR “Angiopathies, Peripheral” OR “Angiopathy, Peripheral” OR “Peripheral Angiopathy” OR “Vascular Diseases, Peripheral” OR “Diseases, Peripheral Vascular” OR "Renal Insufficiency"[MeSH] OR “Renal Insufficiencies” OR “Kidney Insufficiency” OR “Insufficiency, Kidney” OR “Kidney Insufficiencies” OR “Kidney Failure” OR “Failure, Kidney” OR “Failures, Kidney” OR “Kidney Failures” OR “Renal Failure” OR “Failure, Renal” OR “Failures, Renal” OR “Renal Failures” OR “Renal Insufficiency, Chronic”[MeSH] OR “Chronic Renal Insufficiencies” OR “Renal Insufficiencies, Chronic” OR “Chronic Renal Insufficiency” OR “Kidney Insufficiency, Chronic” OR “Chronic Kidney Insufficiency” OR “Chronic Kidney Insufficiencies” OR “Kidney Insufficiencies, Chronic” OR “Chronic Kidney Diseases” OR “Chronic Kidney Disease” R “Disease, Chronic Kidney” OR “Diseases, Chronic Kidney” OR “Kidney Disease, Chronic” OR “Kidney Diseases, Chronic” OR “Chronic Renal Diseases” OR “Chronic Renal Disease” OR “Disease, Chronic Renal” OR “Diseases, Chronic Renal” OR “Renal Disease, Chronic” OR “Renal Diseases, Chronic” OR “Renal Dialysis”[MeSH] OR “Dialyses, Renal” OR “Renal Dialyses” OR “Dialysis, Renal” OR “Hemodialysis” OR “Hemodialyses” OR “Dialysis, Extracorporeal” OR “Dialyses, Extracorporeal” OR “Extracorporeal Dialyses” OR “Extracorporeal Dialysis” OR “Kidney Transplantation"[MeSH] OR “Renal Transplantation” OR “Renal Transplantations” OR “Transplantations, Renal” OR “Grafting, Kidney” OR “Kidney Grafting” OR “Transplantation, Kidney” OR “Kidney Transplantations” OR “Transplantations, Kidney” OR “creatinine”[MeSH] OR “Krebiozen” OR “Creatinine Sulfate Salt” OR “Salt, Creatinine Sulfate” OR “Sulfate Salt, Creatinine” OR “Carotid Intima-Media Thickness”[MeSH] OR “Carotid Intima Media Thickness” OR “Intima-Media Thickness, Carotid” OR “carotid arteries”[MeSH] OR “Arteries, Carotid” OR “Artery, Carotid” OR “Carotid Artery” OR “glomerular filtration rate”[MeSH] OR “Filtration Rate, Glomerular” OR “Filtration Rates, Glomerular” OR “Glomerular Filtration Rates” OR “Rate, Glomerular Filtration” OR “Rates, Glomerular Filtration” OR “prognosis”[MeSH] OR “Prognoses” OR “hospitalization”[MeSH] OR “Hospitalizations” OR “urinary albumin excretion” OR “prognostic significance”

AND **VARIABILITY**

“blood pressure variability” OR “blood pressure variation” OR “short-term blood pressure variability” OR “short-term variability of blood pressure” OR “rate of blood pressure variation” OR “variability index” OR “time rate” OR “time rate of blood pressure variation” OR “blood pressure variabilities” OR “ambulatory blood pressure variability”

- Embase

OUTCOMES

death OR 'cardiac death' OR 'cardiovascular disease' OR 'disease cardiovascular' OR 'mortality' OR 'case fatality rate' OR 'mortality decline' OR 'mortality determinants' OR 'age specific death rate' OR 'death rate' OR 'mortality rate' OR 'myocardial infarction' OR 'myocardial infarct' OR 'ventricular dysfunction left' OR 'left ventricular dysfunction' OR 'hypertrophy left ventricular' OR 'left ventricular hypertrophy' OR 'stroke' OR 'apoplexy' OR 'brain vascular accident' OR 'cerebral stroke' OR 'acute stroke' OR 'heart failure' OR 'cardiac failure' OR 'heart decompensation' OR 'myocardial failure' OR 'congestive heart failure' OR 'heart failure congestive' OR 'myocardial revascularization' OR 'internal mammary artery implantation' OR 'angina pectoris' OR 'stenocardia' OR 'peripheral vascular diseases' OR 'peripheral vascular disease' OR 'vascular diseases peripheral' OR 'renal insufficiency' OR 'kidney insufficiency' OR 'kidney failure' OR 'renal failure' OR 'renal insufficiency chronic' OR 'chronic kidney insufficiency' OR 'cardiovascular diseases' OR 'renal dialysis' OR 'hemodialysis' OR 'kidney transplantation' OR 'renal transplantation' OR 'kidney grafting' OR 'transplantation kidney' OR 'creatinine' OR 'krebiozen' OR 'carotid intima media thickness' OR 'carotid arteries' OR 'carotid artery' OR 'glomerular filtration rate' OR 'prognosis' OR 'hospitalization' OR 'urinary albumin excretion' OR 'urinary albumin excretion rate'

AND **VARIABILITY**
'blood pressure variability' OR 'blood pressure variability'/exp OR 'short-term variability of blood pressure'/exp OR 'rate of blood pressure variation'/exp OR 'variability index'/exp OR 'time rate' OR 'time rate of blood pressure variation'/exp OR 'blood pressure variabilities'/exp

- Cochrane

OUTCOMES

All the MESH terms including OR “urinary albumin excretion” OR “prognostic significance”

AND **VARIABILITY**
“Blood pressure determination”[MeSH] OR 'blood pressure variability' OR 'blood pressure variability' OR 'short-term variability of blood pressure' OR 'rate of blood pressure variation' OR 'variability index' OR 'time rate' OR 'time rate of blood pressure variation' OR 'blood pressure variabilities'

7 ARTIGO 2- CROSS-SECTIONAL STUDY

Blood pressure variability and its association with echocardiographic parameters in hypertensive diabetic patients

Running head: BP variability and echocardiographic variables

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ACKNOWLEDGMENTS

Supported by Fundo de Incentivo à Pesquisa e Eventos (FIPE) of the Hospital de Clínicas de Porto Alegre; Grant 11-0059, Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq); Grant 472792/2009-1, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and by Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS).

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Conflict of interest statement: The authors declared no conflict of interest.

ABSTRACT

Background: Blood pressure (BP) variability is associated with target organ damage in hypertension and diabetes. The 24h ambulatory blood pressure monitoring (24h-ABPM) has been proposed as an evaluation for BP variability using several indexes [standard deviation (SD) of mean BP, coefficient of variation (CV), BP variation over time (time-rate index)]. **Methods:** We evaluated the association between BP variability measured by 24h-ABPM indexes and echocardiographic variables in a cross-sectional study in 305 diabetic-hypertsnsive patients. **Results:** Two groups were defined by the median (0.55 mmHg/min) of time-rate systolic BP (SBP) index and classified as low or high variability. Age was 57.3±6.2 years, 196 (64.3%) were female. Diabetes duration was 10 (5.0-16.2) years, HbA1c was 8.2±1.9%. Baseline clinical characteristics were similar between low (n=148) and high (n=157) variability groups. Office SBP and systolic 24h-ABPM were higher in the high variability group (139.9 mmHg *vs* 146.0 mmHg, P=0.006; 128.3 mmHg *vs* 132.9 mmHg, P=0.019, respectively). Time-rate index, SD and CV of SBP, were higher in high variability group (P<0.001; P<0.001 and P=0.003, respectively). Time-rate index was not independently associated with the echocardiographic's variables in multiple linear model when adjusting for age, 24h-ABPM, diabetes duration and HbA1c. The multiple linear regression model revealed that the significant and independent determinants for septum thickness, relative wall thickness and posterior wall thickness (parameters of left ventricular hypertrophy) were: age (p=0.025; p=0.010; p=0.032, respectively) and 24h-SBP (p<0.001 in the three parameters). **Conclusion:** BP variability estimated by

24h-ABPM is not independently associated with echocardiographic parameters in diabetic-hypertensive patients.

Keywords: diabetes mellitus tipe 2, echocardiography, hypertension.

BACKGROUND

Observational studies had consistently shown the continuous relationship between office systolic and diastolic blood pressure (BP) and cardiovascular events.[1] Indeed, the causal role of high BP for cardiovascular disease was fully confirmed by clinical trials.[2] The evidence that high BP increases the risk for cardiovascular events, and the consistent reduction of these events by clinical trials of BP-lowering agents are robust proofs of the concept that high BP is a major cardiovascular determinant.[3]

Methods of out-of-office BP measurement such as 24h ambulatory BP monitoring (24h-ABPM) evaluated in general population or in hypertensive-based longitudinal studies also showed a close relationship between BP elevation and cardiovascular risk.[4 5] Other parameters assessed by 24h-ABPM, beyond the average of BP, such as BP variability, may provide additional information regarding the cardiovascular risk.[6 7] Blood pressure fluctuations are a result of the interplay between external environmental stimuli, vascular environment and biological autonomic circulatory regulation.[8] Measures of BP variability can be obtained through different methods or indexes[9] and short-term BP variability over a 24h period estimated from 24h-ABPM can be measured by a more refined estimation such as the time-rate index. This index is calculated as the mean of the absolute ratios of the differences between successive BP measures and the time (in minutes) between them. It quantifies how fast and in which direction systolic BP (SBP) values change and, thereby, is claimed to offer an insight into how steep these changes are. Cross-sectional and longitudinal studies showed an independent relationship between the time-rate

index and target-organ damage or cerebrovascular events.[10] [11] [12] [13] Echocardiographic evaluation is recommended to assess asymptomatic organ damage in hypertensive patients since left ventricular hypertrophy and diastolic dysfunction are independently associated with cardiovascular outcomes.[14] These variables could be used as surrogates to assess the possible association between BP variability and cardiovascular risk in high-risk patients.

Considering the high cardiovascular risk profile[15] and the frequent occurrence of autonomic dysfunction in diabetic patients,[16] the relationship between the short-term variability over a 24h period and target-organ damage should be estimated. This relationship has not been well evaluated in observational studies.[17] The present cross-sectional study aims to address this issue by evaluating the potential association between variables of BP variability including the time-rate index of 24h-SBP and echocardiographic parameters of cardiac chambers, left ventricular hypertrophy and diastolic function.

METHODS

This is a cross-sectional study conducted in the outpatient clinic of a tertiary hospital (Hospital de Clínicas de Porto Alegre/Brazil), from April 2010 to December 2011. The data came from a larger study that aimed to assess cardiovascular risk in diabetic hypertensive patients through non-invasive methods.[18] [19] [20]The study was approved by the Ethics Committee of Porto Alegre Clinics Hospital (Hospital de Clínicas de Porto Alegre- GPPG 09-636) which is accredited by the Office of Human Research Protections as an Institutional Review Board. All participants signed an informed consent form before entering the study.

The study population was selected from a consecutive sample of 2342 screened patients. Patients were included in this analysis if they had a previous diagnosis of type 2 diabetes mellitus and hypertension, as ascertained by their personal history of the diseases or because they were using antidiabetic and/or antihypertensives for treatment, and were less than 65 years of age. Exclusion criteria were body mass index (BMI) ≥ 35 kg/m,2 cancer, arrhythmias (e.g., atrial fibrillation) that could interfere with BP measurement and 24h-ABPM recordings. According to these criteria, 351 patients were included (Figure 1).

Patients who met the inclusion criteria and agreed to participate underwent a demographic and clinical baseline data collection, including the assessment of duration of diabetes and hypertension and its known chronic complications, smoking habits, previous cardiovascular diseases, medication in use, BMI, and office BP levels.

Blood pressure was measured after 15 minutes of rest with an automatic sphygmomanometer (ONROM Comfort III Visomat Incoterm, Germany). High office BP levels were defined as office BP higher than 140/90 mmHg.

Among the 351 selected individuals, 93.1% (n=327) underwent 24h-ABPM (Spacelabs 90207, Redmond, WA) on an usual working day, performed at up to four months after the initial evaluation (approximately 75% of patients had full evaluation within 30 days). Readings were obtained automatically at 15-minute intervals during the day and at 20-min intervals during the night for the duration of the 24h ABPM period. Cuff size was chosen according to arm circumference. Daytime was defined as the interval between 06:00-22:00 h and nighttime was the interval between 22:00-06:00 h. Individuals with less than 6 and 18 measures during the night and the day periods, respectively (n=24) were

excluded from further analysis. All individuals were instructed to rest or sleep during the nighttime and to maintain their usual activities during daytime. Based on the results of the 24h-ABPM, the mean 24h-SBP and diastolic BP (DBP) were calculated for each patient. We calculated three different parameters of SBP variability: the standard deviation of mean (SD), coefficient of variability (CV= SD/mean pressure X100%) and rate of change in SBP over time (mmHg/min), defined as the first derivative values of SBP by time (time-rate index). This index allows the calculation of the sum of angular coefficients and aims to measure how fast or how slow and which direction SBP values change. The measure was calculated using the following formula:[9]

$$R = |\bar{r}| = \frac{\sum_{i=1}^{N-1} |r_i|}{N-1}$$

In the formula, *r* is the rate of BP variability over time (considering the differences between BP measurements in each time intervals) and *N* is the number of recordings.

Echocardiography was performed in 98.3% (n=345) patients by a single investigator, usually on the same day of the 24h-ABPM. Images were obtained using a commercially available instrument (GE Healthcare VIVID 7, Buckinghamshire, UK) equipped with a 4 MHz transducer, according to the recommendations of the American Society of Echocardiography,[21] using three consecutive cardiac cycles. Standard parasternal and apical views were performed with subjects in the partial left decubitus position. Left ventricular volumes and ejection fraction were calculated by the Simpson formula; ventricular mass was calculated based on wall thickness adjusted in two ways: to the body surface area and indexed to body height to the power of 2.7.

Relative wall thickness (RWT) was defined as “septum + posterior wall (PW) thickness” divided by “left ventricular diastolic diameter” Diastolic function was evaluated based upon mitral inflow doppler measurements (maximum early flow velocity in diastole- E wave- and maximum late velocity flow in diastole- A wave). Peak early (E’) and peak late (A’) tissue Doppler velocities were assessed at the mitral annulus, determining values as the average of septal and lateral wall measurements. The variables septum and PW thickness, RWT and left ventricular mass índex were used for categorical analyzes on the prevalence of left ventricular hypertrophy, adopting the reference values proposed by the American Society of Echocardiography.[21] Hypertrophy was defined considering the normal range of 1.0 cm to septum obtained in a representative sample of adults in the city of Porto Alegre, as previously described.[22]

Fasting blood samples were collected for laboratory analysis using commercial kits. Plasma glucose was evaluated by a glucose oxidase method, serum creatinine by Jaffé’s reaction, and glycated hemoglobin (HbA1c) by ion-exchange HPLC (Merck-Hitachi L-9100 HbA_{1c} analyzer; reference range 4.8–6.0%; Merck, Darmstadt, Germany). Serum total cholesterol and triglycerides were measured by enzymatic-colorimetric methods (Merck Diagnostica, Germany; Boehringer Mannheim, Argentina), and High-density lipoprotein (HDL) cholesterol by a homogeneous direct method (autoanalyzer, ADVIA 1650). Low-density lipoprotein (LDL) cholesterol was calculated using Friedewald’s formula.[23] Glomerular filtration rate was calculated using the MDRD (Modification of diet in renal disease) equation.[24] C-Reactive Protein was measured using an ultrasensitive assay by nephelometry (Bayer nephelometer,

Leverkusen, Germany), capable of evaluating values in the range of 1-4 mg/l. Urinary albumin excretion was evaluated by immunoturbidimetry (MICROALB-AMES Kit, CA, USA). Abnormal albuminuria was defined as albuminuria of 17 mg/dl or more.[25]

Statistical analyses

The comparison groups were defined by the median of time-rate index of 24h-SBP and classified as low and high variability of time-rate index: values ≤ 0.54 mmHg/min or ≥ 0.55 mmHg/min, respectively. Comparisons were tested by Pearson's chi-square test, Student's *t* test, and Mann-Whitney test. Logistic regression models and multiple linear regression were used to evaluate the association between echocardiographic's variables and parameters of variability of 24h-SBP. Age, 24h-SBP, diabetes duration (years) and HbA1c were included in models. Continuous variables are expressed as mean ± SD or median and interquartile range. Categorical variables are expressed as number (%).

Sample size calculation was based upon the mean differences in two echocardiographic variables of septum and E/E', between low and high variability. Considering the 1:1 proportion in low and high variability groups, a SD of 0.17 cm, an alpha error of 5%, and power of 90% to detect a 10% increase in the septum, the sample size estimation was 124 patients (62 in each group). For the E/E' ratio we considered a SD of 3.6, considering the same proportion, alpha error and power to detect a 15% of difference between groups, the sample size estimation was 162 patients (81 in each group).

Logarithmic transformation was applied to microalbuminuria before parametric tests were applied. *P* values < 0.05 (two-tailed) were considered to

be statistically significant. Statistical Package for Social Science (SPSS, Chicago, IL.) version 18.0 was used for the analyses.

RESULTS

A total of 305 patients was evaluated. The characteristics of the subjects studied, grouped as low and high variability (time-rate index of 24h-SBP) are presented in Table 1. Patients were 57.3 ± 6.2 years, 196 (64.3%) were women, and 207 (68.3%) were caucasian. Body mass index, previous history of stroke, use of statins were higher in low variability group; insulin use was higher in the high variability group. Previous history of any cardiovascular disease was present in 88 patients (29.4%), but was similar between groups. The other characteristics were similar in both groups.

Office BP recordings and 24h-ABPM parameters are presented in Table 2. Systolic BP was 6.1 mmHg (P=0.006) higher in the high variability as compared to the low variability group, as well as mean and daytime SBP of 24h-ABPM (P=0.019 and P<0.001, respectively). The time-rate index of 24h-SBP was higher in the high variability group as compared to the low variability group (0.648 mmHg/min *vs* 0.459 mmHg/min, respectively; P<0.001), such as the other parameters of variability, SD SBP (13.76 mmHg *vs* 11.37 mmHg, respectively) and CV of SBP (10.99% *vs* 8.89%, respectively) were higher in the group of high variability when compared to the group of low variability.

Echocardiographic measurements are presented in Table 3. From the total sample, 178 patients (58.4%) had ventricular hypertrophy considering a cut-off point of 1 cm. When stratified by gender and considering the threshold values for the population of Porto Alegre[22] the proportions were 93.6% and

95.9% for men and women, respectively. Considering de diastolic function and the cut-off point >8 for the E/E' ratio, 234 patients (76.8%) showed abnormal values.[22]

The time-rate index of SBP was not associated with the echocardiographic's variables in multiple linear model when adjusting for age, 24h-SBP, duration of diabetes (years) and HbA1c (Table 4). The multiple linear regression model revealed that the significant and independent determinants for septum thickness, RWT and PW thickness (parameters of left ventricular hypertrophy) were: age (p=0.025; p=0.010; p=0.032, respectively) and 24h-SBP (p<0.001 in the three parameters). Considering the parameters of diastolic function, age was the only variable that was significantly associated with isovolumetric relaxation time (IVRT) and E/E' ratio.

The other variability parameters were also analyzed, but also showed no significant differences between low and high variability groups.

DISCUSSION

The results of this cross-sectional study in a sample of hypertensive-diabetic patients did not show associations between BP variability assessed through 24h-ABPM with echocardiographic variables related to diastolic function, left ventricular hypertrophy and cardiac chamber diameters. The variables significantly associated with parameters of left ventricular hypertrophy (septum thickness, RWT and PW thickness) and diastolic function (IVRT and E/E') were age and 24h-SBP, and the only parameter associated with diastolic function (IVRT and E/E') was age.

Cross-sectional and longitudinal studies showed a positive association between BP variability and cardiovascular risk in pure hypertensive patients. The identification of higher risk patients through variables beyond the absolute values of BP could have practical applications. High risk patients with high BP variability could be chosen to have lower BP targets. Moreover, there is some evidence of a class difference effect between antihypertensive drugs in the within-individual visit-to-visit variability of BP. This potential effect on BP variability could be the guide to an optimal antihypertensive treatment in higher risk patients.[26] In a prospective study, Zis P et al.[13] reported that patients with higher 24h rates of SBP variation assessed by the time-rate index were more likely to have a negative neurologic outcome at one year after stroke. Moreover, a cross-sectional study with 539 subjects showed an independent association between time-rate index of 24h-SBP and intima-media thickness of the carotid measured by ultrasound[9] However, the authors did not define the cutoff points of BP variability normality. In another cross-sectional study 24h-BP variability of SBP was independently associated with impaired renal function.[12]

The association of time-rate index of SBP with echocardiographic parameters was previously studied by Zakopoulos et al in a cross-sectional study. They demonstrated that a 0.1 mmHg/min increase in the daytime rate of SBP variation was associated with an increment of 7.087 g (95% confidence interval 4.775–9.399) in the left ventricular mass.[27] Short-term BP variability can be estimated through different indexes derived from 24h-ABPM. Mena et. al in a longitudinal study with 312 hypertensive patients identified an independent relationship between the “average real variability index”, an index that also averages the absolute differences of consecutive measurements, and

cardiovascular events. This positive relationship was not identified with the SD of the mean SBP.[28] Despite these evidences, guidelines do not recommend the use of BP variability parameters for routine clinical use in hypertensive patients, mainly because the lack of threshold values of BP variability and the absence of evidences of any intervention effect.[7] [29]

Diabetes is associated with higher values of short-term BP variability.[30] Ozawa *et al* in a prospective study with diabetic hypertensive patients demonstrated higher values of 24h-SBP and DBP variability than the non-diabetic hypertensive group (SD of mean SBP, 18.2 mmHg *vs* 14.5 mmHg; p=0.041 and SD of mean DBP, 11.5 mmHg *vs* 9.6 mmHg; p=0.042). A prospective study in patients with type 2 diabetes has shown that nighttime BP variability estimated by SD of the nighttime SBP and DBP was an independent predictor of future incidence of cardiovascular events.[31] However in other reports in diabetic patients, especially with nephropathy and sympathovagal imbalance, there was an absence of nighttime BP falling because of functional impairment of the autonomic nervous system.[32] [33]

Unfortunately, information on diabetic neuropathy, which could have influenced the BP variability, was not available in our study.

In the present study we analyzed the relationship of short-term BP variability and echocardiographic parameters in a high risk sample. Diabetic hypertensive patients have approximately twice the risk of developing cardiovascular events when compared to purely hypertensive patients. Moreover, 56% of our sample had history of previous cardiovascular disease, the median duration of diabetes was 10 years, the mean HbA1c was 8.2 ± 1.9% and almost 60% had left ventricular hypertrophy. This high-risk profile of the subjects evaluated can

explain our negative results, as parameters of BP variability may not add cardiovascular risk information beyond age or BP values in such a high-risk sample.

Certain limitations of the present study should be acknowledged. Firstly, we quantified the rate of BP changes using discontinuous 24h-ABPM techniques, which cannot adequately assess short-lasting BP fluctuations and can only provide some insight into slow and relatively 'long-term' BP oscillations. Secondly, the echocardiographic phenotypes assessed are not in fact endpoints. However, in longitudinal studies, these echocardiographic abnormalities have been associated with primary outcomes. Several studies have also confirmed the prognostic significance of left ventricular hypertrophy and diastolic dysfunction.[34] [35] Therefore, the detection and quantification of these echocardiographic variables seems to be relevant in the monitoring of target-organ damage in diabetic-hypertensive patients.

CONCLUSION

In conclusion, in a diabetic hypertensive high risk sample, BP variability estimated by time-rate índex of SBP was not independently associated with echocardiographic parameters of left ventricular hypertrophy or diastolic function. The use of BP variability for risk stratification beyond the absolute level of BP in this clinical setting should be questioned. Prospective studies in diabetic hypertensive patients with hard outcomes could better confirm our findings.

ACKNOWLEDGMENTS

Supported by Fundo de Incentivo à Pesquisa e Eventos (FIPE) of the Hospital de Clínicas de Porto Alegre; Grant 11-0059, Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq); Grant 472792/2009-1, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and by Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS).

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

DM collected, analyzed data and wrote manuscript. LL, MS, PL, AB, FA, EL, VF and DM performed the experiments and gathered the data. MG and BDS conceived the study, arranged the collaboration, initiated the manuscript, edited and compiled the final version for submission. All authors read, approved the final manuscript and agree for the publication.

LIST OF ABBREVIATIONS

BP= blood pressure

24h-ABPM= 24h ambulatory BP monitoring

SBP= Systolic BP

DBP= Diastolic BP

BMI= body mass index

SD= standard deviation

CV= coefficient of variability

RWT= Relative wall thickness

PW= posterior wall

HbA1c= glycated hemoglobina

HDL= High-density lipoprotein

LDL= Low-density lipoprotein

IVRT= Isovolumetric relaxation time

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Table 1 – Clinical characteristics of the participants according to blood pressure variability

Characteristics	Total sample (n=305)	Low variability (n = 148)	High variability (n = 157)	*P*
Age	57.3 ± 6.2	57.9 ± 6.4	57.5 ± 6.0	0.565
Female gender	196 (64.3)	99 (66.9)	97 (61.8)	0.354
Caucasian	207 (68.3)	99 (66.9)	110 (70.1)	0.334
Duration of diabetes (years)	10 (5 – 16)	10 (5 – 16)	10 (5 – 17)	0.466
Weight	78.3 ± 12.8	79.6 ± 13.6	77.3 ± 12.1	0.116
BMI (kg/m^2)	30.1 ± 3.8	30.7 ± 3.9	29.6 ± 3.7	0.013
Waist circumference	102 ± 9	103 ± 10	101 ± 91	0.203
Neck circumference	38.5 ± 3.5	38.5 ± 3.3	38.6 ± 3.7	0.874
Smoking				0.803
No	163 (33.4)	81 (55.9)	82 (52.2)	
Yes	38 (12.6)	18 (12.4)	20 (12.7)	
Former	101 (54)	46 (31.7)	55 (35.0)	
Abnormal albuminuria[a]	70 (23)	31 (20.9)	39 (24.8)	0.404
With any previous cardiovascular comorbidity[b]	88 (28.9)	43 (29.0)	45 (28.7)	0.520
Myocardial infarction	38 (12.6)	16 (11.0)	22 (14.1)	0.410
Coronary artery bypass grafting	13 (4.3)	4 (2.8)	9 (5.8)	0.199
PCI	25 (8.3)	9 (6.3)	16 (10.3)	0.210
Heart failure	26 (8.7)	15 (10.3)	11 (7.1)	0.318
Stroke	28 (9.5)	19 (13.5)	9 (5.8)	0.024
Medications				
Insulin	143 (47.2)	58 (39.5)	85 (54.5)	0.009
1 Antihypertensive drug	50 (16.4)	22 (14.9)	28 (17.8)	0.537

2 Antihypertensive drug	87 (28.5)	38 (25.7)	49 (31.2)	0.311
≥ 3 Antihypertensive drug	168 (55.1)	88 (59.5)	80 (51)	0.167
Antiplatelet	199 (65.9)	101 (68.7)	98 (63.2)	0.315
Statins	210 (69.8)	113 (76.9)	97 (63)	0.009
Laboratory characteristics				
HbA1c (%)	8.2 ± 1.9	8.2 ± 1.9	8.3 ± 1.9	0.743
Fasting plasma glucose (mg/dL)	159.3 ± 72.4	162.2 ± 74.8	156.7 ± 70.4	0.533
Total cholesterol (mg/dL)	178.8 ± 42.4	176.6 ± 38.7	180.7 ± 45.6	0.426
HDL cholesterol (mg/dL)	41.9 ± 11.8	42.1 ± 12.3	41.8 ± 11.4	0.793
Triglycerides (mg/dL)	155 (103.8 – 234)	152 (103 – 216)	163 (104 – 248)	0.534
GFR (mL/min/1.73m^2)	90.4 ± 26.8	89.1 ± 26.4	91.7 ± 27.2	0.401

The comparison groups were defined by the median of time-rate index of 24h systolic BP and classified as low and high variability of time-rate index: values ≤ 0.54 or ≥ 0.55, respectively.

BMI: body mass index; PCI: Percutaneous coronary intervention; GFR: estimated glomerular filtration rate calculated by the MDRD equation; BP: blood pressure.

[a] Abnormal albuminuria, defined by albuminuria >17 mg/L.

[b] With previous cardiovascular comorbidity= when reported at least one previous cardiovascular disease (Myocardial infarction; Coronary artery bypass grafting; PCI; Heart failure; Stroke).

Continuous variables are expressed as mean ± standard deviation or median (interquartile range (p_{25}-p_{75})). Categorical variables are expressed as number (%). Comparisons (low variability *vs.* high variability) were tested by Pearson's χ^2 test, Student t test and Mann-Whitney test.

Table 2. Office blood pressure recordings and ambulatory blood pressure monitoring parameters of the participants according to blood pressure variability

	Total sample (n=305)	Low variability (n = 148)	High variability (n = 157)	P
Office SBP (mmHg)	143.0 ± 19.3	139.9 ± 17.5	146.0 ± 20.6	0.006
Office DBP (mmHg)	82.0 ± 10.6	81.4 ± 10.6	82.6 ± 10.7	0.355
24h-ABPM SBP (mmHg)	130.6 ± 16.9	128.3 ± 14.7	132.9 ± 18.6	0.019
24h-ABPM DBP (mmHg)	76.5 ± 9.3	75.7 ± 10.0	77.3 ± 8.6	0.144
Daytime 24-ABPM SBP (mmHg)	133.7 ± 15.9	130.5 ± 14.5	136.9 ± 16.7	< 0.001
Daytime 24-ABPM DBP (mmHg)	78.9 ± 10.0	77.9 ± 10.4	79.9 ± 9.7	0.080
Nighttime 24-ABPM SBP (mmHg)	124.0 ± 18.3	122.6 ± 18.4	125.5 ± 18.2	0.169
Nighttime 24-ABPM DBP (mmHg)	69.6 ± 10.7	69.8 ± 11.2	69.5 ± 10.4	0.817
Time-rate index SBP (mmHg/min)	0.557 ± 0.116	0.459 ± 0.058	0.648 ± 0.075	< 0.001
SD SBP (mmHg)	12.60 ± 4.40	11.37 ± 4.24	13.76 ± 4.25	< 0.001
CV SBP (%)	9.97 ± 6.29	8.89 ± 3.16	10.99 ± 8.10	0.003

The comparison groups were defined by the median of time-rate index of 24h systolic BP and classified as low and high variability of time-rate index: values ≤ 0.54 or ≥ 0.55, respectively.

BP: blood pressure; ABPM: ambulatory blood pressure monitoring; SBP: systolic blood pressure; DBP: diastolic blood pressure; SD SBP: Standard deviation of mean SBP; CV SBP: Coefficient of variability SBP.

Data are expressed as mean ± standard deviation. Comparisons (low variability *vs.* high variability) were tested by Student t test.

Table 3. Echocardiographic parameters of the participants according to blood pressure variability

	Total sample (n=305)	Low variability (n = 148)	High variability (n = 157)	P
Cardiac chamber diameters				
Aorta (cm)	3.16 ± 0.36	3.17 ± 0.37	3.14 ± 0.34	0.383
Left atrium (cm)	3.80 ± 0.45	3.83 ± 0.46	3.77 ± 0.42	0.238
LVSD (cm)	2.99 ± 0.40	2.99 ± 0.42	2.99 ± 0.39	0.898
LVDD (cm)	4.58 ± 0.47	4.61 ± 0.47	4.55 ± 0.46	0.291
Right ventricle (cm)	2.15 ± 0.28	2.16 ± 0.27	2.13 ± 0.28	0.470
LVEF (%)	64.66 ± 5.27	64.90 ± 5.09	64.42 ± 5.44	0.856
Left ventricular hypertrophy				
RWT	0.43 ± 0.08	0.43 ± 0.09	0.43 ± 0.07	0.780
Septum thickness (cm)	1.00 ± 0.17	1.00 ± 0.18	0.99 ± 0.16	0.676
PW Thickness (cm)	0.95 ± 0.15	0.95 ± 0.15	0.95 ± 0.15	0.683
LVMI (g/m^2)	99.19 ± 30.24	100.38 ± 32.24	98.08 ± 28.33	0.513
LAVI (mL/m^2)	29.14 ± 9.98	29.32 ± 10.64	28.97 ± 9.34	0.497
Diastolic function				
E wave velocity (m/s)	0.98 ± 0.18	0.97 ± 0.20	0.99 ± 0.16	0.494
A wave velocity (m/s)	0.82 ± 0.23	0.82 ± 0.24	0.82 ± 0.23	0.976
E wave DT (m/s)	235.28 ± 44.16	233.07 ± 45.26	237.37 ± 43.13	0.397
A wave length (cm/s)	179.15 ± 42.30	176.44 ± 42.15	181.71 ± 42.41	0.292
E/A ratio (m)	0.95 ± 0.30	0.94 ±0.28	0.95 ± 0.33	0.795
E’ wave velocity (m/s)	0.07 ± 0.03	0.07 ± 0.01	0.08 ± 0.04	0.387

E/E' ratio	11.10 ± 3.66	11.22 ± 4.08	10.99 ± 3.22	0.586
IVRT (m/s)	109.22 ± 18.15	109.42 ± 19.11	109.04 ± 17.24	0.855

The comparison groups were defined by the median of time-rate index of 24h systolic BP and classified as low and high variability of time-rate index: values ≤ 0.54 or ≥ 0.55, respectively.

LVSD: left ventricular systolic diameter; LVDD: Left ventricular diastolic diameter; LVEF: Left ventricular ejection fraction; RWT: relative wall thickness; PW: posterior wall; LVMI: left ventricular mass index; LAVI: Left atrial volume index; IVTR: Isovolumetric relaxation time; DT: E wave deceleration time; BP: blood pressure.

Data are expressed as mean ± standard deviation. Comparisons (low *vs.* high variability) were tested by Student t test.

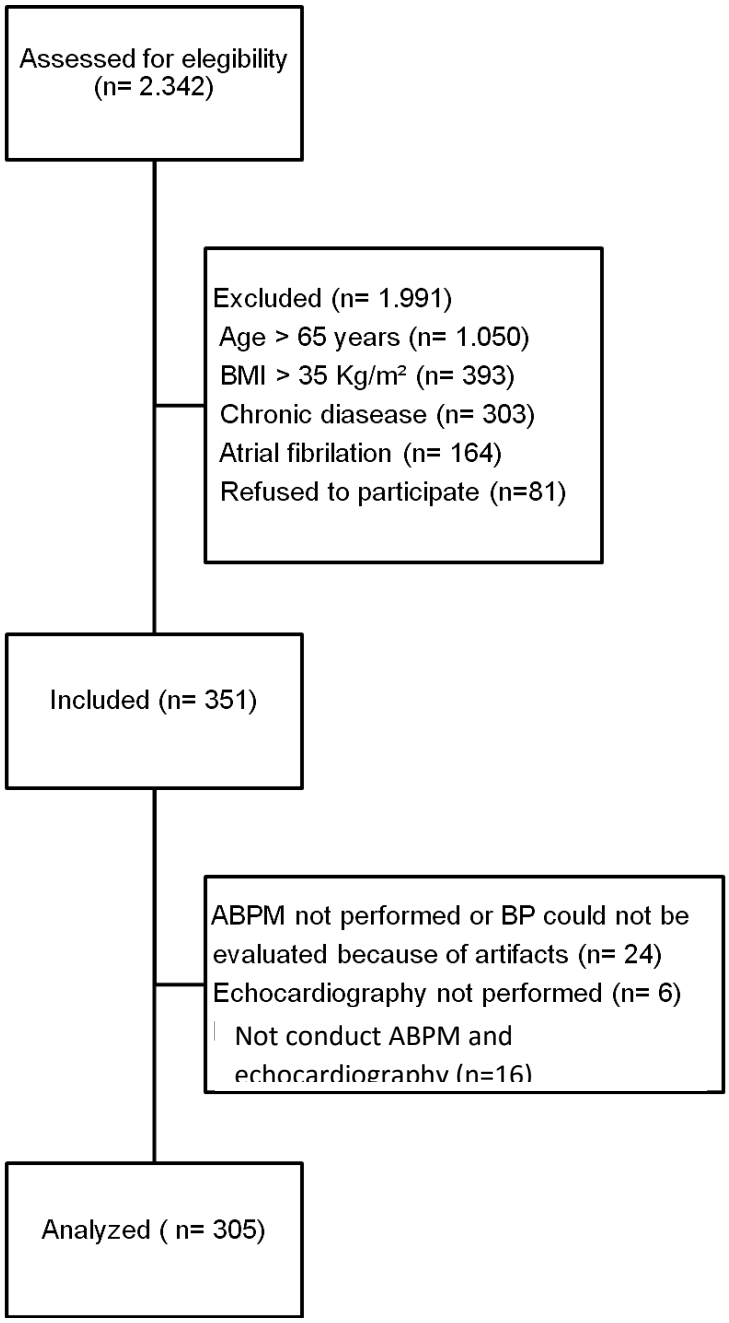
Table 4. Association between time-rate index and echocardiographic's variables in multiple linear model

	Beta	S.E.	*P*
Left ventricular hypertrophy			
- Septum thickness (cm)			
Time-rate SBP (mmHg/min)	-0.029	0.086	0.739
Age (years)	0.004	0.002	0.025
24h-ABPM SBP (mmHg)	0.002	0.001	< 0.001
Diabetes duration (years)	< 0.001	0.001	0.510
HbA1c (%)	0.003	0.005	0.635
- RWT			
Time-rate index SBP (mmHg/min)	-0.044	0.041	0.277
Age (years)	0.002	0.001	0.010
24h-ABPM SBP (mmHg)	0.001	<0.001	<0.001
Diabetes duration (years)	0.001	0.001	0.134
HbA1c (%)	0.001	0.003	0.583
- PW Thickness			
Time-rate SBP (mmHg/min)	0.006	0.075	0.937
Age (years)	0.003	0.001	0.032
24h-ABPM SBP (mmHg)	0.002	<0.001	<0.001
Diabetes duration (years)	<0.001	0.001	0.591
HbA1c (%)	<0.001	0.005	0.977
Diastolic function			
- IVRT (m/s)			
Time-rate SBP (mmHg/min)	-5.243	9.248	0.571
Age (years)	0.889	0.174	<0.001

24h-ABPM SBP (mmHg)	0.041	0.054	0.443
Diabetes duration (years)	-0.139	0.130	0.284
HbA1c (%)	0.644	0.581	0.269
- E/E' ratio			
Time-rate SBP (mmHg/min)	0.419	1.911	0.826
Age (years)	0.128	0.036	<0.001
24h-ABPM SBP (mmHg)	0.004	0.011	0.744
Diabetes duration (years)	0.003	0.027	0.899
HbA1c (%)	-0.042	0.120	0.727

BP: blood pressure; SBP: systolic blood pressure; ABPM: Ambulatory Blood Pressure Monitoring; HbA1c: glycated hemoglobina; RWT: Relative wall thickness; PW: posterior wall; IVRT: isovolumetric relaxation time. Adjusted for age, 24h-ABPM-hour ABPM SBP, duration of diabetes (years) and HbA1c.

Figure 1. Flowchart of patient's selection. BMI, body mass index; ABPM, ambulatory blood pressure monitoring; BP, blood pressure.



8 CONCLUSÕES E CONSIDERAÇÕES FINAIS

Fatores relacionados a PA, não restritos somente aos valores pressóricos absolutos podem estar associados à progressão das doenças cardiovasculares. A MAPA 24h permite que outros parâmetros ligados à pressão arterial possam ser estudados, como por exemplo, as relações pressóricas de sono e vigília e parâmetros de variabilidade durante o período de 24 horas. Neste sentido, estudos foram desenvolvidos focando também estas outras abordagens da MAPA 24h

A significância prognóstica da variabilidade da PA para desfechos cardiovasculares ainda é debatida. Falta padronização dos métodos para avaliação da variabilidade da PA e a dificuldade em transpor os resultados dos estudos diretamente para a prática clínica diária demonstra que talvez a melhor maneira de se avaliar criticamente a informação disponível na literatura é através da realização de uma revisão sistemática, selecionando-se as evidências disponíveis sobre a variabilidade da PA por diferentes métodos e sua relação com o desenvolvimento de eventos cardiovasculares em estudos observacionais.

Observamos que existe na literatura grande diversidade entre os estudos disponíveis nos protocolos variabilidade da PA, nos índices selecionados para quantificar a variabilidade da PA e nos desfechos utilizados para a avaliação. Nossa revisão sistemática reforça a posição da Sociedade Europeia de Hipertensão a qual indica que a variabilidade da PA a curto prazo dentro de 24 h pode ser considerada para a estratificação de risco em estudos

populacionais e de coorte mas não indica seu uso no contexto clínico. Questões fundamentais permanecem sem resposta, incluindo o índice de variabilidade ideal que representa o impacto da variabilidade PA sobre o sistema cardiovascular; valores normais ou alvo de variabilidade PA a serem alcançados com o tratamento anti-hipertensivo; e se as alterações induzidas pelo tratamento da variabilidade da PA a curto prazo podem também promover efeito nas lesões de órgão alvo e risco de evento cardiovascular.

Além disso, conforme demonstramos em nossos resultados, a variabilidade da PA estimada pelo índice time rate da PA sistólica não se associou independentemente aos parâmetros ecocardiográficos de hipertrofia ventricular ou função diastólica mesmo em pacientes de alto risco cardiovascular como hipertensos diabéticos. O uso da variabilidade da PA para estratificação de risco além dos níveis absolutos da PA neste cenário clínico de pacientes hipertensos e diabéticos deve ser questionada.