UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS:

ENDOCRINOLOGIA

MONITORIZAÇÃO AMBULATORIAL DA PRESSÃO ARTERIAL, EXCREÇÃO URINÁRIA DE ALBUMINA E ALTERAÇÕES ESTRUTURAIS CARDÍACAS EM PACIENTES COM DIABETES MELITO TIPO 2

TESE DE DOUTORADO

CRISTIANE BAUERMANN LEITÃO

Porto Alegre, fevereiro de 2007

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Tese de Doutorado apresentada ao Programa de Pós-Graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul (UFRGS) como requisito parcial para obtenção do título de Doutor em Endocrinologia.

Porto Alegre, fevereiro de 2007

L533e Leitão, Cristiane Bauermann

Monitorização ambulatorial da pressão arterial, excreção urinária de albumina e alterações estruturais cardíacas em pacientes com diabetes melito tipo 2/ Cristiane Bauermann Leitão; orient. Jorge Luiz Gross; co-orient. Luís Henrique Canani. – 2007.

74 f. : il.

Tese (doutorado) – Universidade Federal do Rio Grande do Sul. Faculdade de Medicina. Programa de Pós-Graduação em Ciências Médicas: Endocrinologia. Porto Alegre, BR-RS, 2007.

1. Diabetes mellitus tipo II 2. Albuminúria 3. Pressão arterial I. Gross, Jorge Luiz II. Canani, Luís Henrique III.Título.

NLM: WK 810

Catalogação Biblioteca FAMED/HCPA

DEDICATÓRIA

Aos meus pais e avós.

AGRADECIMENTOS

Aos melhores orientadores que um aluno de doutorado poderia desejar: Prof. Dr. Jorge Luiz Gross, pela disponibilidade durante a redação desta tese, pela confiança depositada na minha capacidade de trabalho e pelas oportunidades de crescimento acadêmico e profissional que me foram oferecidas e Prof. Dr. Luís Henrique Canani, pelos ensinamentos diários nas áreas de clínica e de pesquisa, pela paciência para responder minhas dúvidas, pela disponibilidade para resolver as dificuldades apresentadas ao longo do meu doutorado e pela amizade. A convivência com estes dois professores determinou a qualidade da minha formação como médica e pesquisadora e aumentou a responsabilidade em não desapontá-los nas minhas realizações futuras.

À Profa. Dra. Sandra Pinho Silveiro, por compartilhar seus conhecimentos médicos, incentivar a minha busca pela informação mais atualizada e pela amizade desde a época da residência.

À colega e amiga Caroline Kaercher Kramer, pela fundamental ajuda na coleta dos dados e atendimento dos pacientes, além de estar disponível para uma “terapia de apoio” nos momentos mais críticos.

Aos alunos de iniciação científica Patrícia B. Bolson, Juliana C. Boza, Milene Moehelecke e Lana C.F. Pinto, pela indispensável colaboração no atendimento dos pacientes e realização dos procedimentos do estudo com responsabilidade e dedicação.

Aos residentes da UBS Santa Cecília/HCPA, pela agradável convivência e pela oportunidade de troca de ensinamentos, em especial à Camila Furtado de Souza, pela amizade.

À Raquel Scherer de Fraga, Tatiana Rech e Paula Blasco Gross, amigas com as quais sei que poderei contar em todas as situações da minha vida e à Letícia Weiss Ribeiro por ser mais do que uma irmã.

À minha família, por manter-se unida nas adversidades, por não julgar as minhas falhas e fraquezas e pelo incentivo contínuo que possibilita o meu crescimento acadêmico, profissional e pessoal. Aos meus avós, Otto Affonso Bauermann e Dorvalina Maria Bauermann, por terem construído esta família.

À minha mãe, meu pai e meu irmão, que são os verdadeiros responsáveis pelas minhas vitórias.

Ao Rafael, pelo carinho, companheirismo, cumplicidade e compreensão. Por valorizar e incentivar a minha dedicação ao trabalho como médica e pesquisadora. Pelos momentos de alegria e tranqüilidade e principalmente pelo suporte emocional nestes três últimos mais difíceis anos.

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LISTA DE ABREVIATURAS

AAMI	*Association for the Advancement of Medical Instrumentation*
ABPM	*Ambulatory blood pressure monitoring*
ACE	*Angiotensin converting enzyme*
ADA	*American Diabetes Association*
A1c	Teste A1c
BHS	*British Hypertension Society*
BMI	*Body mass index*
BP	*Blood pressure*
CI	*Confidence interval*
DM	Diabetes melito ou *Diabetes Mellitus*
DN	*Diabetic Nephropathy*
DR	*Diabetic Retinopathy*
EUA	Excreção urinária de albumina
GFR	*Glomerular filtration rate*
HAS	Hipertensão arterial sistêmica
HPLC	*High performance liquid chromatography*
MAPA	Monitorização ambulatorial da pressão arterial
MDRD	*Modification of Diet in Renal Disease*
MH	*Masked hypertension*
Micro-HOPE	*Micro- Heart Outcomes Prevention Evaluation*
NAC	Neuropatia autonômica cardiovascular
ND	Nefropatia diabética
N/D	Noite/dia ou *nighttime/daytime*
OR	*Odds ratio*
PA	Pressão arterial
PAMELA	*Pressioni Arteriose Monitorate e Loro Associazioni*
RD	Retinopatia diabética
SD	*Standard deviation*
UAER	*Urinary albumin excretion rate*
UKPDS	*United Kingdom Prospective Diabetes Study*

Todos os Pacientes com Diabetes Melito tipo 2 Devem Realizar Monitorização Ambulatorial da Pressão Arterial?

Should all Patients with type 2 Diabetes Mellitus Undergo Ambulatory Blood Pressure Monitoring?

Título abreviado: Diabetes melito e pressão arterial ambulatorial

Short title: Diabetes mellitus and ambulatory blood pressure

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Unitermos: diabetes melito, pressão arterial, monitorização ambulatorial da pressão arterial, complicações crônicas

Keywords: diabetes mellitus, blood pressure, ambulatory blood pressure monitoring, chronic complications

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Artigo aceito para publicação no periódico Arquivos Brasileiros de Cardiologia

Resumo

A hipertensão arterial sistêmica (HAS) é um dos principais fatores de risco para a instalação e progressão das complicações crônicas do diabetes melito (DM) tipo 2.

A medida da pressão arterial (PA) através da monitorização ambulatorial da PA (MAPA) apresenta melhor correlação com o desenvolvimento de lesões em órgãos-alvo do que a medida no consultório. Além disso, permite a avaliação de parâmetros pressóricos distintos como as médias das PAs sistólica e diastólica das 24 h, do dia e da noite, cargas pressóricas e ausência do descenso noturno, além da identificação de pacientes com HAS do avental branco e mascarada.

Os pacientes com DM apresentam maiores médias de PA diurna e noturna do que os sem DM. Além disso, um terço do pacientes normotensos com DM tipo 2 apresentam HAS mascarada, que está associada a um aumento da albuminúria e da espessura das paredes do ventrículo esquerdo. Por outro lado, a prevalência e o efeito da HAS do avental branco nos pacientes com DM ainda não foram adequadamente avaliados. A determinação da ausência do descenso noturno da PA não acrescenta informação às medidas da PA nas 24 h, no dia ou na noite, mas a medida da PA noturna parece ser relevante na retinopatia do DM.

Em conclusão, a determinação da PA através da MAPA é capaz de estratificar de forma mais adequada os pacientes em risco para o desenvolvimento das complicações crônicas do DM e tornou-se um instrumento indispensável para o controle efetivo da PA nestes pacientes.

Abstract

Hypertension is one of the main risk factors for the onset and progression of chronic complications in type 2 diabetes mellitus (DM).

Ambulatory blood pressure (BP) monitoring (ABPM) provides a better correlation with target organ lesions than BP obtained in the office. Furthermore, it allows the evaluation of distinct BP parameters such as the 24-h, daytime and nighttime systolic and diastolic BP means, BP loads and the absence of nocturnal drop of BP, as well as the identification of white-coat and masked hypertension.

DM patients have higher daytime and nighttime BP means than non-DM patients. In addition, one third of normotensive type 2 DM patients have masked hypertension, which is associated with an increase in albuminuria and in left ventricle wall thickness. On the other hand, the prevalence and effect of white-coat hypertension in type 2 DM patients have not yet been properly evaluated. The absence of nocturnal drop of BP does not add information to the 24 h, daytime or nighttime BP measurements, but the nighttime BP means seem to be relevant in DM retinopathy.

In conclusion, BP determination by ABPM allows better patient risk stratification for the development of DM chronic complications and is an essential instrument for effective BP control in these patients.

Pressão Arterial e Diabetes Melito

O diabetes melito (DM) tipo 2 está associado ao desenvolvimento de complicações crônicas microvasculares e macrovasculares de elevada morbi-mortalidade[1,2]. Os fatores de risco clássicos e melhor estudados para o desenvolvimento e progressão das complicações crônicas do DM são o tempo de doença, a hiperglicemia, a hipertensão arterial sistêmica (HAS), a dislipidemia e o tabagismo, além de fatores genéticos[3-8]. O tratamento da hiperglicemia e da HAS resulta em prevenção primária e redução da progressão da retinopatia diabética (RD) e nefropatia diabética (ND)[9,10]. A HAS parece ter particular importância, pois a redução da pressão arterial (PA) de 154/87 mm Hg para 144/82 mm Hg no estudo *United Kingdom Prospective Diabetes Study* (UKPDS) resultou em redução de 37% no desenvolvimento de complicações microvasculares enquanto que a redução observada para o tratamento intensivo da hiperglicemia foi apenas de 25%[9,10].

A HAS é prevalente nos pacientes com DM tipo 2, estando presente em 30% no momento do diagnóstico do DM e em até 73% durante o seu curso clínico[1,11]. No entanto, alterações da homeostase pressórica podem ocorrer em pacientes com DM sem qualquer evidência de doença renal[12,13].

O objetivo do presente trabalho é revisar as alterações pressóricas presentes em pacientes com DM e determinar o papel da monitorização ambulatorial da PA (MAPA) na identificação destas alterações e a sua indicação na prática clínica.

Monitorização Ambulatorial da Pressão Arterial

A MAPA começou a ser realizada na década de 60, quando foram desenvolvidos equipamentos não invasivos capazes de medir a PA durante as 24 h, enquanto o paciente estivesse desenvolvendo as suas atividades diárias habituais. O primeiro aparelho de MAPA era volumoso, utilizava o método auscultatório de medida da PA e necessitava de insuflação

manual[14]. Somente na década de 70 foi desenvolvido um sistema portátil de MAPA que possibilitou a sua utilização em pesquisa e na prática clínica. Todavia, estes aparelhos ainda eram pesados e utilizavam o método auscultatório, que dependia da presença de um pulso braquial palpável e amplo, mas não necessitavam de insuflação manual.

Atualmente, a MAPA realiza a medida da PA nas 24 h através de um aparelho portátil totalmente automático constituído de um monitor de aproximadamente 350 g que é acoplado na cintura do paciente e é ligado a um manguito de borracha convencional (como os utilizados para a medida da PA no consultório) através de uma cânula de borracha flexível. O manguito é colocado no braço não dominante do paciente e realiza medidas de PA com intervalos de tempo que são ajustados no *software* do monitor utilizado. Tipicamente, são realizadas medidas a cada 15-30 minutos durante o dia e noite. A medida da PA é realizada pelo método oscilométrico, que capta as oscilações causadas pelo fluxo de sangue que se inicia após a desinsuflação do manguito. As oscilações iniciam antes do primeiro som de Korotkoff (PA sistólica) utilizado pelo método auscultatório e termina após o quinto som de Korotkoff (PA diastólica). A maior oscilação captada pelo aparelho é a PA média. Os valores de PA sistólica e diastólica registrados no aparelho são derivados através de fórmulas matemáticas estabelecidas para cada marca de monitor.

Para que um monitor possa ser utilizado em pesquisa ou na prática clínica, deve-se realizar a validação contra medidas obtidas pelo manômetro de mercúrio, que continua sendo o método padrão de medida de PA[15]. Os monitores validados conforme protocolos da *British Hypertension Society (BHS)* ou da *Association for the Advancement of Medical Instrumentation (AAMI)* podem ser identificados no site: http://www.dableducational.org/sphygmomanometers/devices_3_abpm.htm.

A maioria dos estudos que relacionam a medida da PA e o desenvolvimento de lesão em órgãos-alvo, em pacientes com HAS essencial com ou sem DM, foram realizados utilizando como referência a medida da PA no consultório[9,16,17]. No entanto, estudos recentes têm demonstrado que a medida de PA através da MAPA apresenta melhor correlação com os desfechos de interesse do que a medida da PA no consultório[18,19]. Além disso, a adoção das medidas da MAPA como parâmetro para acompanhamento de pacientes em tratamento da HAS foi superior na predição de desfechos cardiovasculares em comparação com a simples medida da PA no consultório[20].

A utilização da MAPA permite a análise de parâmetros até então impossíveis de serem registrados através da medida de PA no consultório, como as médias de PA sistólica e diastólica de 24-h, do dia e da noite; as cargas pressóricas e a ausência de descenso noturno da PA[21]. Além disso, permite a identificação de duas novas categorias de pacientes: com HAS do avental branco e com HAS mascarada. Cada um destes parâmetros será detalhado a seguir.

Valores Pressóricos Médios

Os valores pressóricos médios são determinados através de cálculo de médias das medidas realizadas no período das 24 h. As médias das PAs diurnas e noturnas são definidas com base no período de vigília e sono relatado pelo paciente no dia do exame. Os valores obtidos em cada uma destas medidas se correlacionam com aumento da massa do ventrículo esquerdo e maior mortalidade cardiovascular e geral na população em geral[22,23]. A partir dos valores pressóricos médios é possível calcular a pressão de pulso (PA sistólica – PA diastólica), que é um marcador de maior rigidez arterial.

Cargas Pressóricas

As cargas pressóricas são definidas pela porcentagem de medidas de PA acima de valores previamente definidos: 24-h e dia ≥140/90 mm Hg e noite ≥120/80 mm Hg. Cargas

pressóricas <20% são consideradas normais, entre 20-50% intermediárias e ≥50% elevadas. A elevação na carga pressórica está associada com desenvolvimento de lesão em órgão-alvo[24,25].

Ausência de Descenso Noturno da Pressão Arterial

Existe uma variação circadiana fisiológica da PA que é caracterizada por valores mais baixos de PA durante o sono. Ocorre, tipicamente, uma queda da PA noturna maior que 10% em relação à média da PA diurna. Desta maneira, a ausência de descenso noturno da PA é definida pela queda de PA noturna <10% ou índice noite/dia (N/D) (PA noturna/PA diurna) >0,9[21]. Este cálculo é realizado para os valores sistólicos e diastólicos. A ausência de descenso noturno da PA está associada ao desenvolvimento de lesões em órgãos-alvo e aumento de mortalidade em diversos contextos[26,27].

Hipertensão do Avental Branco

A HAS do avental branco é definida como presença de HAS nas medidas de PA de consultório (PA ≥140/90 mm Hg) em pacientes com valores normais de PA na MAPA (PA <135/85 mm Hg nas medidas diurnas). Estes pacientes representam de 20-30% da população dos indivíduos hipertensos[28]. Os pacientes com este diagnóstico são tradicionalmente considerados como normotensos e sem necessidade de tratamento. Esta conduta é baseada nos estudos iniciais que demonstraram que estes indivíduos não apresentavam eventos desfavoráveis durante o curso clínico da doença[29-31]. No entanto, a análise criteriosa destes relatos demonstra que os pacientes apresentaram menor lesão em órgãos-alvo em relação aos pacientes com HAS, mas ambos em vigência de tratamento anti-hipertensivo, pois na logística dos estudos os pacientes eram acompanhados e tratados pelo seu médico assistente, que não tinha conhecimento dos resultados do MAPA e definia a conduta terapêutica com base nos resultados da PA do consultório.

Estudos mais recentes demonstraram que os pacientes com HAS do avental branco apresentam maior hipertrofia de ventrículo esquerdo[22] e maior mortalidade cardiovascular[32] em comparação com os indivíduos normotensos. Estes achados apontam para um grupo de pacientes com HAS de gravidade intermediária em relação aos normotensos e hipertensos, isto é, apresentam maior lesão em órgãos-alvo do que os normotensos, mas quando tratados da mesma maneira que os hipertensos apresentam melhores desfechos clínicos do que os últimos.

Hipertensão Mascarada

A mais recente categoria de pacientes definida pelas medidas da MAPA é a de pacientes com HAS mascarada ou pseudonormotensão. São indivíduos com PA normal no consultório (<140/90 mm Hg), mas classificados como hipertensos na medida da PA diurna da MAPA (≥135/85 mm Hg) e representam 10-20% dos indivíduos com PA normal no consultório[28]. Estes pacientes apresentaram risco para eventos cardiovasculares semelhantes aos indivíduos hipertensos[22,32,33], reforçando a superioridade da medida da MAPA na definição do risco cardiovascular.

Monitorização de Pressão Arterial em Pacientes com Diabetes Melito

A maioria dos estudos a respeito de padrões pressóricos em pacientes com DM relata alterações nos valores da PA nas 24 h, mesmo antes do diagnóstico de HAS[34,35]. A análise de cada um dos parâmetros da MAPA em pacientes com DM será discutida, de forma detalhada, a seguir.

Valores Pressóricos Médios e Diabetes Melito

Os pacientes com DM tipo 1 apresentam maiores médias de PA de 24-h, tanto sistólica quando diastólica, em comparação com os controles sem DM[36,37].

A associação entre ND e aumento dos valores absolutos de PA na MAPA foram demonstrados até mesmo em estágios precoces da lesão renal[12]. Um estudo realizado pelo nosso grupo em pacientes com DM tipo 1 demonstrou que indivíduos normoalbuminúricos e hiperfiltrantes (filtração glomerular >134 ml/min/1,73 m^2) apresentaram maior PA diastólica noturna quando comparados com pacientes normofiltrantes[12]. Da mesma forma, a análise de 117 pacientes normoalbuminúricos com DM tipo 1 da Dinamarca, agrupados a partir da mediana da excreção urinária de albumina (EUA) (EUA = 4,2 μg/min), demonstrou que os paciente com albuminúria mais elevada apresentavam maiores níveis de PA sistólica nas 24 h, diurna e noturna além de maiores médias de PA diastólica nas 24 h e durante a noite[38]. Estes dados foram confirmados em um estudo prospectivo realizado em pacientes com DM tipo 1 normoalbuminúricos, no qual os pacientes que progrediram para microalbuminúria apresentavam maiores níveis de PA diastólica durante o dia na avaliação inicial[39]. Resultados semelhantes foram identificados em um estudo transversal realizado em pacientes com DM tipo 2 normoalbuminúricos[13]. As médias das PAs nas 24 horas e as pressões de pulso apresentaram correlações positivas e significantes com a medida da EUA em uma amostra de 90 pacientes brasileiros[13]. Da mesma maneira, maiores médias da PA nas 24 h, diurna e noturna, maiores PAs de pulso e cargas pressóricas foram descritas conforme a progressão para graus mais avançados da ND (microalbuminúria e macroalbuminúria) em pacientes com DM tipo 2[40]. Em um estudo transversal realizado no nosso centro, com 270 pacientes com DM tipo 2, os valores médios da PA nas 24 h, no dia e na noite apresentaram correlações positivas e significantes com a EUA e com a massa do ventrículo esquerdo[41]. Os resultados das PAs sistólicas foram os mais consistentes e com maior magnitude de associação e permaneceram relacionados após ajustes para possíveis fatores de confusão.

Resultados semelhantes foram descritos para a associação entre as médias da PA na MAPA e a RD. O aumento da PA diastólica noturna foi associado com a presença de RD em um estudo transversal em pacientes com DM tipo 1 dinamarqueses[42]. Da mesma maneira, em uma coorte de pacientes com DM tipo 1 brasileiros, a PA diastólica do dia e das 24 h previu o desenvolvimento e a progressão da RD[43]. Nos pacientes com DM tipo 2, um levantamento transversal estabeleceu um aumento progressivo dos valores de PA sistólica e diastólica das 24 h, do dia e da noite conforme a gravidade da RD[40].

A avaliação da associação dos valores médios da PA na MAPA e a presença de doença macrovascular somente foi analisado de forma transversal e em pacientes com DM tipo 2. As médias de PA sistólica e diastólica do dia, da noite e a PA de pulso foi maior nos pacientes com diagnóstico de doença macrovascular[40].

Cargas Pressóricas e Diabetes Melito

A existência de associação entre maiores cargas pressóricas e aumento da EUA foi demonstrada em pacientes com DM tipo 1[44,45] e tipo 2[13]. Recentemente, correlações entre as cargas pressóricas e a EUA, massa do ventrículo esquerdo, espessura interventricular e parede posterior do ventrículo esquerdo em pacientes com DM tipo 2[41] foram demonstradas pelo nosso grupo. Da mesma maneira, a presença de RD estava associada com maiores valores de carga pressórica diastólica noturna nesta mesma amostra de pacientes[41].

Ausência do Descenso Noturno da Pressão Arterial e Diabetes Melito

Uma elevada prevalência de ausência de descenso noturno da PA foi observada nos pacientes com DM tipo 1[36,37], podendo atingir até mesmo 78% dos pacientes em comparação com 39% dos controles sem DM[37]. Estas alterações nas medidas da MAPA se correlacionam com a presença de neuropatia autonômica cardiovascular (NAC)[46-48]. Os estudos realizados em pacientes com DM tipo 2 apresentam resultados semelhantes[34]. Fogari et al. analisaram

199 indivíduos (96 com DM tipo 2 e 103 sem DM) e demonstraram que os pacientes com DM apresentavam uma maior prevalência de anormalidades do descenso noturno (sem descenso ou aumento paradoxal da PA durante a noite) em relação aos controles[34]. Esta diferença foi semelhante na presença ou não de HAS (30% vs. 31% nos com DM normotensos e hipertensos e 6,0% vs. 6,4% nos controles sem DM normotensos e hipertensos, respectivamente)[34].

A maior prevalência de ausência de descenso noturno nos estudos realizados em pacientes com DM tipo 1 em comparação aos com DM tipo 2 (78 vs. 30%)[34,37] pode estar relacionada à maior descompensação do DM nos primeiros. A hiperglicemia altera o volume plasmático circulante, podendo interferir na hemodinâmica renal e distribuição do fluxo sangüíneo, alterando o descenso noturno normal da PA. Além disso, a insulina apresenta um papel importante na regulação do sistema nervoso autônomo. A melhora do controle glicêmico por uma semana em pacientes com DM do tipo 1 diminuiu as médias pressóricas da MAPA e aumentou a queda da PA durante a noite[49], reforçando a teoria exposta.

A ausência do descenso da PA durante o sono foi estudada em filhos de pacientes com DM tipo 2, não sendo encontradas diferenças em relação aos controles, isto é, indivíduos sem história familiar de DM[50]. No entanto, em um subgrupo de não-diabéticos com história familiar de DM tipo 2, mas que já apresentavam NAC, foi demonstrada menor queda da PA durante a noite[50], confirmando a impressão de que a ausência de descenso noturno é uma característica relacionada ao DM, presente até mesmo em indivíduos suscetíveis mas sem a expressão clínica do DM, e determinada pela presença de NAC. Posteriormente, foi demonstrado que pacientes com DM tipo 1 normotensos e normoalbuminúricos sem descenso noturno apresentavam maior prevalência de testes para NAC alterados[51]. Nestes, a ausência

de descenso noturno se correlacionou com a EUA na análise de regressão linear múltipla[51], sugerindo uma associação entre ausência de descenso noturno e maiores níveis de EUA.

No entanto, a contribuição da ausência de descenso noturno para o desenvolvimento e progressão das complicações crônicas do DM permanece controversa. A maioria dos estudos que analisaram este parâmetro da MAPA enfocaram o desenvolvimento e progressão da ND. Alguns autores encontraram resultados positivos[35,40,52-56] enquanto outros não foram capazes de estabelecer esta relação[44,57,58]. A maioria dos estudos foi realizada com delineamento transversal ou de casos e de controles, sugerindo apenas associação entre o fator em estudo (descenso noturno) e o desfecho (ND), e alguns apresentam análise estatística e interpretação de dados suscetíveis a críticas[54,55]. Apenas 2 estudos foram prospectivos, ambos em coortes de pacientes com DM tipo 1 normoalbuminúricos, e acompanharam os pacientes até o desenvolvimento de microalbuminúria[39,59]. No primeiro deles, a associação entre ausência de descenso e desenvolvimento de microalbuminúria desapareceu após controle para duração do DM[59]. No segundo estudo, esta associação só foi evidente na MAPA realizada no seguimento dos pacientes (e não na avaliação basal) sugerindo que o surgimento da microalbuminúria e aumento da PA noturna sejam concomitantes[39,60].

Um aspecto até o momento não levado em consideração na interpretação dos dados destes estudos é o valor médio da PA dos pacientes sem descenso noturno da PA. A maioria dos resultados aponta para maiores valores de PAs sistólicas e diastólicas nos grupos de pacientes que progridem para microalbuminúria ou estágios mais avançados de lesão renal[39,40] e, desta maneira, a elevação das médias de PA seria responsável pelos piores desfechos e não a ausência do descenso. Por este motivo, realizamos um estudo a fim de determinar a importância relativa de diversos parâmetros pressóricos em relação a desfechos microvasculares (ND e RD) e alterações estruturais cardíacas (massa do ventrículo esquerdo,

espessura do septo interventricular e da parede posterior do ventrículo esquerdo) em 270 pacientes com DM tipo 2[41]. Os valores médios de PA, principalmente as medidas sistólicas na MAPA, apresentaram correlações mais consistentes e de maior magnitude com os desfechos do que os índices N/D da PA. Em relação à EUA e espessuras das paredes do ventrículo esquerdo, os índices N/D perderam a associação após os ajustes para potenciais fatores de confusão. A PA noturna e o índice N/D da PA diastólica foram mais relevantes e agregaram informação aos demais valores da PA somente quando o desfecho analisado foi a RD.

Hipertensão do Avental Branco e Diabetes Melito

A prevalência de hipertensão do avental branco foi inicialmente descrita como sendo maior nos pacientes com DM, podendo chegar a 74% nos pacientes com DM tipo 1[61] e 51% nos com DM tipo 2[62]. Posteriormente, estes achados foram contestados em pacientes com DM tipo 2. Nielsen et al. encontraram uma prevalência de avental branco de 23% nos normoalbuminúricos, 8% nos microalbuminúricos e 9% nos macroalbuminúricos[63]. Desta maneira, os pacientes normoalbuminúricos não diferiram da prevalência esperada para pacientes hipertensos essenciais (20-30%)[37]. A pequena prevalência de HAS do avental branco nos pacientes com microalbuminúria e macroalbuminúria é devido à alta incidência de HAS estabelecida nestes grupos. Estes dados não foram replicados e a repercussão do diagnóstico da HAS do avental branco nas complicações crônicas do DM não foram adequadamente avaliadas até o momento.

Hipertensão Mascarada e Diabetes Melito

A prevalência da HAS mascarada em pacientes com DM tipo 2 é de 30%[64], maior do que a relatada na literatura para indivíduos sem DM (10-20%)[28]. O efeito da HAS mascarada sobre as complicações crônicas do DM somente foi avaliado em um estudo em pacientes com DM tipo 2 brasileiros[64]. Foi observada maior EUA, maior prevalência de albuminúria normal-

alta, microalbuminúria e macroalbuminuria (Figura 1) e maiores espessuras das paredes do ventrículo esquerdo. Estas associações foram independentes das medidas da PA no consultório.

Indicações de Monitorização Ambulatorial da Pressão Arterial em Pacientes com Diabetes Melito

As indicações clássicas para a realização da MAPA em pacientes com DM tipo 1 e 2, presentes nos consensos nacionais e internacionais são as mesmas dos pacientes sem DM[21,65]: (1) suspeita de HAS do avental branco, (2) avaliação de HAS resistente (PA não controlada no consultório apesar do uso de 3 ou mais anti-hipertensivos com mecanismos de ação diferentes), (3) HAS episódica (medidas da PA no consultório normais ou elevadas com história de medidas casuais maiores detectadas em momentos episódicos), (4) suspeita de episódios de hipotensão, (5) avaliação da eficácia terapêutica anti-hipertensiva.

Diante dos dados expostos nesta revisão, propõe-se uma ampliação nas indicações clássicas de realização da MAPA em pacientes com DM. Visto que 30% dos pacientes normotensos com DM tipo 2 apresentam HAS mascarada, associada com aumento da EUA e da espessura das cavidades cardíacas, e que a PA noturna está associada com a presença da RD, recomenda-se a realização da MAPA em todos os pacientes com DM, a fim de que seja possível a realização do diagnóstico da HAS mascarada e avaliação da PA noturna.

Considerações Finais

O estudo da homeostase pressórica, através da MAPA, tem possibilitado o esclarecimento do papel da HAS no desenvolvimento de lesões em órgãos-alvo em pacientes com HAS essencial. Além disso, permite a análise de novas classes de hipertensos (ex: HAS do avental branco e HAS mascarada) e de variáveis associadas à PA até então não estudadas

(ex: cargas pressóricas e ausência do descenso noturno da PA) e que alteram o prognóstico dos pacientes em risco.

A transposição destes resultados para os indivíduos com DM tem confirmado a maioria dos achados e assim agregado dados novos aos conceitos já estabelecidos. Os pacientes com DM apresentam uma elevada prevalência da HAS mascarada que está associada com lesão renal e cardíaca. A prevalência a o efeito da HAS do avental branco nos pacientes com DM ainda necessita de avaliação mais criteriosa. Os piores desfechos renais atribuídos à ausência de descenso noturno da PA parecem ser, na verdade, decorrentes de maiores valores das médias de PA na MAPA. A PA noturna e os índices N/D da PA parecem ser importantes apenas para o desenvolvimento da RD.

Em conclusão, a determinação da PA através da MAPA é capaz de estratificar de forma mais adequada os pacientes em risco para o desenvolvimento das complicações crônicas do DM e tornou-se um instrumento indispensável para a avaliação da PA nestes pacientes. Ensaios clínicos com o tratamento da PA baseado no controle de cada um dos parâmetros da MAPA são necessários a fim de estabelecer o real benefício renal, ocular e cardiovascular desta estratégia no tratamento de pacientes com DM.

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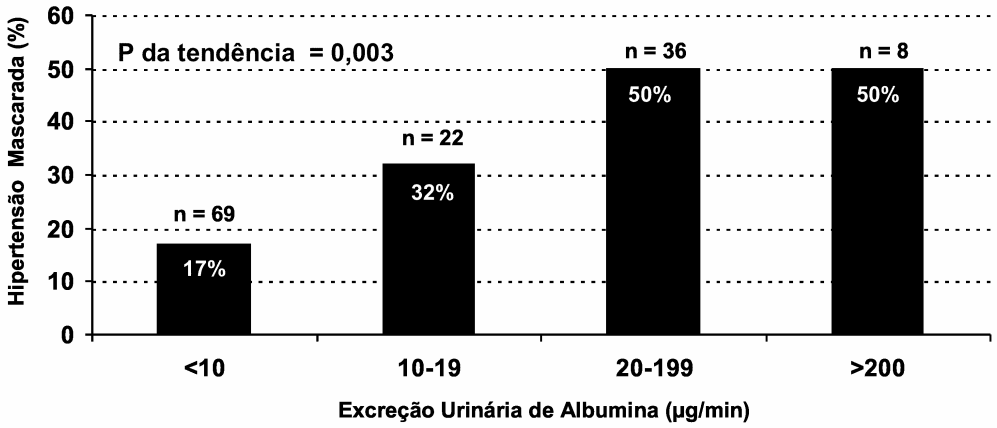

Figura 1. Prevalência de hipertensão mascarada conforme a excreção urinária de albumina

Masked Hypertension, Urinary Albumin Excretion Rate and Echocardiographic Parameters in Putatively Normotensive Type 2 Diabetes Mellitus Patients

Short running title: Masked hypertension and type 2 diabetes

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Artigo publicado no periódico Diabetes Care em maio de 2007.

Abstract

OBJECTIVE: To evaluate the impact of masked hypertension (MH) in normotensive type 2 diabetes mellitus (DM) patients on microvascular complications and echocardiographic parameters.

RESEARCH DESIGN AND METHODS: A cross-sectional study was conducted in 135 normotensive patients with type 2 DM. Patients underwent urinary albumin excretion rate (UAER) measurement, echocardiography and 24-h ambulatory blood pressure (BP) monitoring (AMBP). Patients with increased daytime BP levels (≥135/85 mm Hg) were classified as MH.

RESULTS: The prevalence of MH was 30% (n = 41). Normotensives and MH, based on AMBP, were not different in terms of age, DM duration, smoking habit, BMI, waist circumference, serum creatinine, glycemic or lipid profiles. The office systolic BP was higher in the MH (127.8 ± 7.5 vs. 122.9 ± 10.2 mm Hg, P = 0.003) than normotensive group. UAER was also increased in the MH group [21.3 (2.5 - 1223.5) vs. 8.1 (1.0 - 1143.0) μg/min, P = 0.001], as well as the interventricular septum (1.01 ± 0.15 vs. 0.94 ± 0.13 cm, P = 0.015) and posterior wall thickness (0.96 ± 0.12 vs. 0.90 ± 0.10 cm, P = 0.006). After adjustments for DM duration, sex, smoking, LDL-cholesterol and A1c values, all associations were sustained for daytime systolic BP but not for office systolic BP.

CONCLUSIONS: Type 2 DM patients with MH have higher UAER and enlargement of ventricular walls compared with the normotensive patients according to ABPM. Therefore, ABPM monitoring is important to identify this high-risk group so as to be able to take interventionist measures.

Keywords: masked hypertension, type 2 diabetes, nephropathy, left ventricular hypertrophy.

Hypertension is a major risk factor for the development and progression of chronic complications in type 2 diabetes mellitus (DM) (1; 2). Blood pressure (BP) evaluation over a 24 h ambulatory BP monitoring (ABPM) period correlates better with outcomes than ordinary office BP measurements in both hypertensives (3) and the general population (4). In addition, systolic ambulatory BP is associated with the urinary albumin excretion rate (UAER) even in normoalbuminuric type 2 DM patients (5). The ABPM also allows the analysis of other BP parameters, otherwise not documented by the office BP evaluation, such as nocturnal dipping patterns, presence of white-coat hypertension, BP loads and a novel subgroup of patients with masked hypertension (6).

Masked hypertension is defined by elevated mean daytime BP levels at 24-h ABPM (BP ≥135/85 mm Hg) in office normotensive individuals (BP <140/90 mm Hg). In a population based study it was detected in 9% of the individuals tested (7). Before the ABPM became available, these patients were not detected and were believed to have the same risk for cardiovascular events as the normotensive population. However, emerging evidence shows that masked hypertension is associated with higher left ventricle wall thickness (7) and increased cardiovascular mortality (8) in comparison to normotensive individuals.

This issue has yet to be examined in patients with DM and the aim of this study is to analyze the impact of masked hypertension in type 2 DM patients concerning microvascular complications and echocardiographic parameters.

Research Design and Methods

Patients

A cross-sectional study was performed in 135 patients with type 2 DM selected from a cohort of 270 patients followed since 1994 at the outpatient clinic of the Hospital de

Clínicas de Porto Alegre. The inclusion criteria were a diagnosis of type 2 DM (>30 years of age at onset of DM, no previous episode of ketoacidosis or documented ketonuria, and treatment with insulin only after 5 years of diagnosis) and BP levels at office evaluation <140/90 mm Hg on at least 2 occasions during a 6-month period and in the day of office and ABPM examination. Patients with creatinine >1.5 mg/dl, other renal diseases, cardiac arrhythmia or postural hypotension were excluded. The Ethics Committee of the hospital approved this study, and informed consent was obtained from all patients.

Patient evaluation

Patients underwent an interview and clinical examination to record demographic and anthropometrical data, as previously described (9). Indirect ophthalmoscopy was performed through dilated pupils by an ophthalmologist and for the purpose of this study patients were classified only according to the presence or absence of any degree of diabetic retinopathy.

BP evaluations were performed one week after withdrawal from all medications with antihypertensive effect. The mean of two office BP examinations, measured with a mercury sphygmomanometer using the left arm and with the patient in a sitting position, after a 5-minute rest, on the same day of ABPM, was considered for the analyses. ABPM was performed by oscillometry (Spacelabs 90207, serial numbers 207/024751 and 207/038016, with calibration certification), with a 15-minute interval in the daytime and 20-minute interval in the nighttime periods. Patients were advised to maintain their usual daily activities. Sleep time was recorded as the period between the time when the patient went to bed and the time when the patient woke up in the next morning. All ABPM evaluations were performed on a normal workday. The means of 24-h, daytime and nighttime systolic and diastolic BP were recorded, as well as BP loads (percentage of 24-h

and daytime BP measurements ≥140/90 mm Hg and nighttime ≥120/80 mm Hg). The patients BP status was classified according to ABPM into: normotension (daytime ambulatory BP mean <135/85 mm Hg) and masked hypertension (daytime ambulatory BP mean ≥135/85 mm Hg) (10; 11).

Echocardiograms (n = 101) were obtained according to the recommendations of the American Society of Echocardiography (12) using standard parasternal and apical views with subjects in the partial left decubitus position using a commercially available instrument (Hewellet Packard sonus 1000). Left ventricular mass was calculated based on wall thickness and was adjusted to the body surface area. The cardiologist who performed the echocardiograms was unaware of the subjects' clinical or laboratorial characteristics.

The glomerular filtration rate (GFR) was estimated using the formula of the Modification of Diet in Renal Disease (MDRD) Study: 186*[serum creatinine$^{-1.154}$*age$^{-0.203}$*(0.742 if female)*(1.210 if African-Descendant)] (13).

Patients were classified according to UAER into 4 groups: low-normoalbuminuric (UAER <10 μg/min, n = 69), high-normoalbuminuric (UAER 10 – 19 μg/min, n = 22), microalbuminuric (UAER 20-199 μg/min, n = 36) and macroalbuminuric (UAER ≥200 μg/min, n = 8), based on 24-h sterile and timed urine collections, 2 of 3 samples, 6 months apart. Those patients using ACE inhibitors or angiotensin receptor blockers had these medications stopped one week prior to urine collection.

Laboratory methods

UAER was measured by immunoturbidimetry (Microlab, Ames- Bayer, Tarrytown, NY, USA; intra- and interassay coefficient variations of 4.5% and 11.0%, respectively). A1c was measured by a HPLC system [high performance liquid chromatography- Merck-Hitachi 9100 (normal range 4-6%)]. Fasting plasma glucose was measured by the glucose-

peroxidase colorimetric enzymatic method (Biodiagnóstica). Creatinine was measured by the Jaffé method and the lipid profile by a colorimetric method.

Statistical analysis

Student t test or chi-square test were used to compare clinical and laboratorial data. Quantitative variables without a normal distribution were submitted to logarithmic transformation. Data are expressed as the mean ± SD except for UAER, triglycerides, serum creatinine and BP loads [median (range)]. Sequential models of multiple linear regressions were performed with the following dependent variables: log-UAER, interventricular septum, posterior wall thickness and left ventricular mass. P values <0.05 (2-tailed) in the univariate analysis were considered to be significant.

Results

Masked hypertension was found in 41 (30%) normotensive type 2 DM patients. Both groups (normotension and masked hypertension, based on ABPM) were not different regarding age, DM duration, smoking habit, BMI and waist circumference (Table 1). There was an excess of male prevalence in the masked hypertension group (71 vs. 45%, P = 0.005). Concerning laboratorial characteristics, there was no difference between the groups for the glycemic and lipid profiles, as well as for serum creatinine and estimated GFR. The office systolic BP was higher in patients with masked hypertension (127.8 ± 7.5 vs. 122.9 ± 10.2 mm Hg, P = 0.003) (Table 2). The office diastolic BP was comparable in the two groups. The daytime BP measurements were higher in the masked hypertension group, as expected, since it was part of the definition of the group. The same was true for most of 24-h and nighttime BP measurements.

UAER was increased in the masked hypertension [21.3 (2.5 - 1223.5) vs. 8.1 (1.0 - 1143.0) μg/min, P = 0.001] in comparison to the normotension group (Figure 1). Likewise, the prevalence of masked hypertension increased with the progression of UAER starting from the high-normoalbuminuric group (low-normoalbuminuric: 17.6%, high-normoalbuminuric: 33.3%, microalbuminuric: 51% and macroalbuminuric: 50%; P for trend = 0.003), reflecting increased kidney damage in these patients.

Patients with masked hypertension had also higher interventricular septum (1.01 ± 0.15 vs. 0.94 ± 0.13 cm, P = 0.015) and posterior wall thickness (0.96 ± 0.12 vs. 0.90 ± 0.10 cm, P = 0.006) than the normotension group. The left ventricular mass tends to be enlarged in patients with masked hypertension (150.2 ± 32.90 vs. 140.5 ± 26.5 g/1.73 cm^2), but did not reach conventional statistic significance (P = 0.111).

Sub-analyzes were performed with patients not on ACE inhibitors/angiotensin receptor blockers (88% of the sample, n = 119) or not on medications with antihypertensive effect (77% of the sample, n = 104) and similar results were found (data not shown).

The prevalence of any degree of diabetic retinopathy was similar in both groups (masked hypertension: 30% vs. normotension: 34%, P = 0.678).

Since patients with masked hypertension had higher office systolic BP levels (+ 4.9 mm Hg), the present findings could be attributed to this difference. In order to elucidate the real association of masked hypertension with UAER and the echocardiographic parameters, and to evaluate the possible confounding effect of a higher office systolic BP, two approaches were applied and are presented subsequently.

The first approach was to perform multiple linear regression analysis with the potential outcomes of increased BP (UAER and echocardiographic parameters: interventricular septum thickness, posterior wall thickness and left ventricular mass) as the

dependent variables. Therefore, 4 models were constructed with DM duration, sex, smoking habit, LDL-cholesterol, A1c test and one of the BP measurements (office systolic or daytime systolic BP) as independent variables. The daytime systolic BP remains significantly associated with the outcomes in the 4 models (UAER: R = 0.402 R_a^2 = 0.118, P = 0.029; interventricular septum thickness: R = 0.380 R_a^2 = 0.086, P = 0.022; posterior wall thickness: R = 0.404 R_a^2 = 0.107, P = 0.045 and left ventricular mass: R = 0.322 R_a^2 = 0.043, P = 0.049). When the systolic office was the BP included in the model, it did not continue to be significantly associated with the outcomes (P >0.05). When both office systolic and daytime systolic BP were included simultaneously in each one of the models, only the daytime systolic BP remain significantly associated to the renal and cardiac outcomes.

The second approach was to stratify the patients according to office systolic BP in normal-high (130 – 140 mm Hg) and normal-low (<130 mm Hg) BP groups. These values were adopted for the reason that they are current goals of BP treatment in DM patients and, at the same time, capture the higher values of BP (i.e., the group that could confound the results). The presence of high-normal office systolic BP was not associated with UAER [11.2 (1 – 1223.5) vs. 8.4 (1.7 – 169.6) µg/min, P = 0.074], interventricular septum thickness (0.96 ± 0.16 vs. 0.97 ± 0.12 cm, P = 0.830), left posterior wall thickness (0.92 ± 0.11 vs. 0.91 ± 0.11 cm, P = 0.660) or left ventricular mass (142.4 ± 32.3 vs. 145.2 ± 25.2 g/1.73 m^2, P = 0.635). Likewise, the presence of high-normal office BP did not discriminate the patients with diabetic nephropathy (micro- or macroalbuminuria) [odds ratio (OR) = 1.83, 95% confidence interval (CI) 0.87 - 3.85, P = 0.108]. In contrast, patients with masked hypertension had a significant increase in the risk for this complication (OR = 3.74, 95% CI 1.72 - 8.14, P = 0.001). These analyses suggest that the

effect observed for masked hypertension cannot be attributed only to the small increase observed in office BP.

Conclusions

In this sample of normotensive type 2 DM patients, approximately one third of the individuals had masked hypertension and it was associated with target-organ damage, represented by higher UAER, as well as greater interventricular septum and posterior wall thickness. These associations remain after adjustments for possible confounding factors and cannot be attributed only to elevations of the office BP levels.

The linkage of BP levels and micro- and macrovascular DM complications is well known (1). The development of portable ambulatory BP equipment has allowed the accumulation of evidence showing that 24-h BP values present better correlation to outcomes than office BP (3; 4). In addiction, ABPM allows the separation of the population into four groups: true normotensives (normotension in both office and 24-h ABPM), true hypertensives (hypertension in both the office and 24-h ABPM), white-coat hypertensives (hypertension in office and normotension in 24-h ABPM) and, more recently, the masked hypertensives (normotension in office and hypertension in 24-h ABPM). Patients in this peculiar group have otherwise not been identifiable, since their routine office BP exam is normal and physicians would not be aware they belong to a high-risk group.

Masked hypertension is reported to affect 2 to 26% of the population (8; 14-18). This large variation might be due to differences in the definition of normal ambulatory BP levels, as well as variations in patient demographic characteristics, such as age and BMI (16; 19). The data from the *Pressione Arteriose Monitorate e Loro Associazioni* (PAMELA) (8) study, the larger cohort of individuals (n = 2051) evaluated by ABPM,

showed a prevalence of 9% in the general population and 14.5% among normotensives. The frequency of masked hypertension in the DM population had not been evaluated previously and the present data suggests a high prevalence (30%) among type 2 DM patients. Therefore, association of masked hypertension and chronic complications in type 2 DM patients had also not been analyzed. As far as we know, this is the first report of an increased UAER and ventricular wall thickness in type 2 DM patients with masked hypertension.

In previous reports in non-diabetic patients, masked hypertension has been associated with diminished sensitivity of arterial baroreflex (14), aortic stiffness (verified by carotid-femoral pulse wave velocity) (20), increased left ventricle mass index (7; 16) and cardiovascular mortality (8). Patients with masked hypertension have shown an adverse clinical and metabolic profile in some contexts (8; 14; 16). In children and adolescents, the diagnosis of masked hypertension was associated with increased BMI and a parental history of hypertension (16). In non-diabetic adults, there is a progressive increase in male sex prevalence, age, BMI, total cholesterol and blood glucose throughout the spectrum of BP abnormalities, from the truly normotensive group across the white-coat hypertension, masked hypertension and truly hypertensive groups (8). Moreover, most previous reports identified higher levels of office BP in masked hypertension patients (8; 14; 16). Based on this, it could be hypothesized the worst outcomes found in the masked hypertension group are explained solely by higher office BP levels, since it is well known that there is not a threshold for BP and target-organ lesion, as the two variables have a continuous correlation (21). However, our results, as well as those from the PAMELA study, remain significant after further adjustment for the difference in office BP as well as for other relevant clinical and laboratorial confounders (7; 8; 22).

The reason why some individuals have normal office BP and high values during the ABPM is at present unknown (23). One possibility is that some patients react to stressful daily activities with an elevation in BP. An increase in BP levels during exercise, as has been verified in offspring of type 2 DM patients with insulin resistance (24), could be one of the situations related to BP elevation during the day in masked hypertensive patients. On the other hand, the increase in BP during the day could be due to arterial stiffness, since the patients with masked hypertension, in this sample, had a higher pulse pressure, reflecting the isolated elevation of systolic BP.

There are two practical implications of the present results. The first one is that the simple office BP evaluation cannot identify patients with masked hypertension and thus cannot provide them with the potential benefits of anti-hypertensive treatment. Therefore, ABPM should be part of the initial evaluation of normotensive type 2 DM patients to identify those patients with masked hypertension. The second one is that type 2 DM patients with masked hypertension probably would benefit from anti-hypertensive interventions, in the same way as has been demonstrated in prehypertension non-diabetic subjects (25) and normotensive type 2 DM patients in the Micro- Heart Outcomes Prevention Evaluation (Micro-HOPE) study (26). The American Diabetes Association (ADA) position statement on DM treatment affirms that all patients >55 years of age should receive the prescription of an angiotensin converting enzyme inhibitor (ramipril) regardless of the obtained BP values (27) , and this might be particularly useful in patients with masked hypertension.

No association was found between masked hypertension and diabetic retinopathy, in contrast to the results of classical hypertension trials (1). This could be attributed to the fact that “any degree of diabetic retinopathy” was used as the outcome, which enclose mild retinal damage in opposition to more advanced retinal disease found

in the United Kingdom Prospective Study (UKPDS) (1). Furthermore, this sample is constituted from office normotensive patients and the results cannot be compared with those from hypertensive trials.

One possible limitation of this report is mainly the cross-sectional design, which holds off conclusions about the cause and effect relationship between masked hypertension and the renal and ecocardiographic outcomes. However, this limitation does not obscure the main results of this study.

In conclusion, type 2 DM patients with masked hypertension have elevated UAER values, a higher prevalence of high-normal, micro- and macroalbuminuria and enlargement of ventricular walls in comparison to normotensive patients. The evaluation of normotensive type 2 DM patients with 24-h ABPM, especially those with UAER ≥10 μg/min, seems to be important in order to identify this high-risk group. However, replication of these findings in different settings and clinical trials evaluating masked hypertension treatment are needed in turn to determine potential renal and cardiovascular protection.

Acknowledgments: This study was partially supported by Projeto de Núcleos de Excelência do Ministério de Ciência e Tecnologia (PRONEX), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundo de Incentivo a Pesquisa (FIPE) do Hospital de Clínicas de Porto Alegre. LHC was recipient of scholarship from CAPES (Programa de Apoio à Instalação de Doutores - ProDoc).

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Table 1: Clinical and laboratorial characteristics according to blood pressure classification

	Normotension n = 94	**Masked hypertension** n = 41	**P**
Age (years)	56.2 ± 10.5	56.1 ± 9.7	0.941
Diabetes duration (years)	9.5 ± 7.6	9.1 ± 6.2	0.762
Males - n (%)	42 (45)	29 (71)	0.005
Whites – n (%)	70 (75)	33 (81)	0.605
Smokers – n (%)	23 (25)	14 (35)	0.118
Waist circumference (cm)			
Males	98.9 ± 11.1	99.9 ± 10.2	0.717
Females	95.5 ± 9.4	94.2 ± 11.0	0.697
Body Mass Index (kg/m^2)	28.4 ± 4.4	28.0 ± 4.2	0.621
Diabetic Retinopathy- n (%)	26 (34)	9 (30)	0.678
UAER (μg/min)	8.1 (1.0 – 1143.4)	21.3 (2.5 – 1223.5)	0.001
Fasting Plasma Glucose (mg/dl)	153.9 ± 68.3	154.6 ± 55.2	0.955
A1c (%)	7.8 ± 2.0	7.8 ± 2.2	0.993
Total Cholesterol (mg/dl)	191.9 ± 40.5	203.3 ± 39.3	0.134
HDL cholesterol (mg/dl)	47.4 ± 12.7	45.3 ± 13.2	0.372
Triglycerides (mg/dl)	123.0 (46.0 – 974.0)	144.5 (43.0 – 475.0)	0.278
Creatinine (mg/dl)	0.8 (0.5 - 1.4)	0.9 (0.3 – 1.5)	0.911
eGFR (ml/min/1.73 m^2)*	98.6 ± 27.3	102.7 ± 46.4	0.606
Antihypertensive effect drugs- n (%)	21 (22)	10 (24)	0.715

Data available for Diabetic Retinopathy n = 106 (normotension = 76 and masked hypertension = 30)
UAER = urinary albumin excretion rate
* eGFR = estimated glomerular filtration rate measured by Modification of Diet in Renal Disease study (MDRD) equation.
Data expressed as the mean ± SD, median (minimum - maximum) or number of patients (%).

Table 2. Blood pressure characteristics according to blood pressure classification

	Normotension N = 94	**Masked hypertension** n = 41	**P**
Office			
systolic BP (mm Hg)	122.9 ± 10.2	127.8 ± 7.5	0.003
diastolic BP (mm Hg)	76.0 ± 7.2	77.4 ± 7.4	0.309
pulse pressure (mm Hg)	46.9 ± 9.2	50.4 ±8.1	0.041
24-h			
systolic BP (mm Hg)	119.7 ± 7.3	134.8 ± 9.5	<0.001
diastolic BP (mm Hg)	71.8 ± 6.1	81.9 ± 6.3	<0.001
pulse pressure (mm Hg)	47.9 ± 6.9	53.0 ± 10.0	0.003
systolic BP load (%)	10.7 (0 – 47.4)	48.8 (1.2 – 98.6)	<0.001
diastolic BP load (%)	3.2 (0 – 30.6)	23.9 (1.2 – 95.2)	<0.001
Daytime			
systolic BP (mm Hg)	122.3 ± 7.1	138.1 ± 7.8	-
diastolic BP (mm Hg)	74.3 ± 6.1	85.4 ± 6.3	-
pulse pressure (mm Hg)	47.9 ± 6.6	58.8 ± 10.1	-
systolic BP load (%)	4.7 (0 – 32)	47.2 (1.5 – 98.3)	-
diastolic BP load (%)	2.2 (0 – 50.3)	22.9 (1.5 – 95.8)	-
Nighttime			
systolic BP (mm Hg)	114.2 ± 10.3	127.3 ± 14.3	<0.001
diastolic BP (mm Hg)	65.5 ± 74.9	74.9 ± 9.5	<0.001
pulse pressure (mm Hg)	48.7 ± 7.7	52.4 ± 11.1	0.060
systolic BP load (%)	24.4 (0 – 100.0)	68.8 (0 – 100.0)	0.003
diastolic BP load (%)	0 (0 – 86)	26.3 (0 – 98.0)	<0.001

Data expressed as the mean ± SD or median (minimum - maximum).

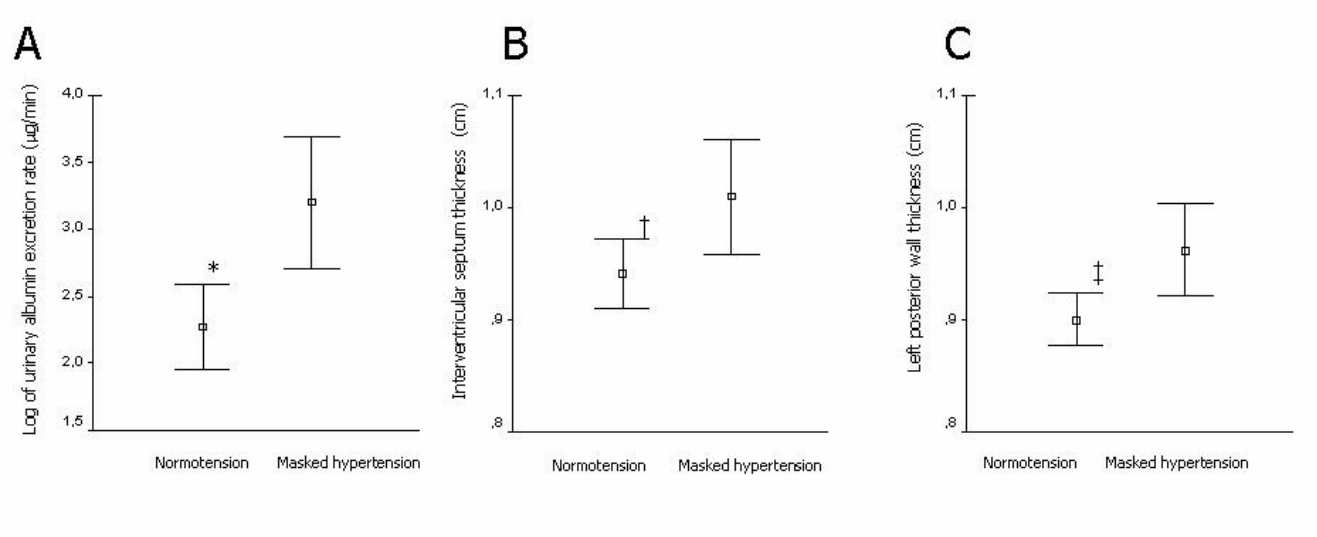

Figure 1. Urinary albumin excretion rate (A), interventricular septum thickness (B) and left posterior wall thickness (C) in the normotension and masked hypertension groups. * P = 0.001, † P = 0.015, ‡ P = 0.006.

Blood pressure means rather than nocturnal dipping pattern predict complications in type 2 diabetic patients

Running Title: Ambulatory blood pressure means and diabetes

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Word count: 2712

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Artigo enviado para publicação no periódio *Diabetic Medicine* em 27 de junho de 2007

Summary

Aim: To find out whether systolic and diastolic BP means, during ambulatory BP monitoring (ABPM), have better correlations with microvascular complications and echocardiographic structural alterations than the absence of nocturnal drop of BP.

Methods: A cross-sectional study was conducted in 270 type 2 DM outpatients who underwent clinical and laboratory evaluation, urinary albumin excretion rate (UAER) determination, echocardiography, office and 24-h ABPM (Spacelabs 90207).

Results: UAER was associated with office BP (systolic - R^2_a: 0.164, P <0.001; diastolic - R^2_a: 0.128, P <0.001) and ABPM (24-h systolic - R^2_a: 0.194, P <0.001; diastolic - R^2_a: 0.200, P <0.001) but not with a blunted nocturnal drop of BP (systolic - R^2_a: 0.064, P = 0.091; diastolic - R^2_a: 0.065, P = 0.078). Similar results were observed for echocardiographic parameters. The presence of retinopathy was associated only with nighttime BP values [systolic - odds ratio (OR): 1.119 and diastolic means – OR: 1.211 and blunted nocturnal BP decline – OR: 2.948].

Conclusions: UAER and echocardiographic structural alterations had more consistent correlations of a greater magnitude with systolic BP means than with the absence of nocturnal decline of BP. The nocturnal BP values appear to be more relevant for diabetic retinopathy. Treatment of hypertension in patients with type 2 DM should take into account the 24-h period rather than focusing on a specific fragment of BP homeostasis.

Key words: type 2 diabetes, ambulatory blood pressure means, nocturnal dipping pattern, microvascular complications and ventricular hypertrophy.

Introduction

Hypertension occurs frequently in patients with diabetes mellitus (DM) and is a major risk factor for the development of micro- and macrovascular complications [1]. Actually, in the United Kingdom Prospective Diabetes Study (UKPDS), intensive treatment of hypertension had a greater impact on the prevention of type 2 DM microvascular complications than intensive blood glucose control [2,3].

Twenty-four-hour ambulatory blood pressure (BP) monitoring (ABPM) is clinically useful since it provides a better definition of the cardiovascular risk profile in both hypertensives [4] and the general population [5] than ordinary office BP measurements. Furthermore, ABPM allows the analysis of various BP parameters such as 24-h, daytime and nighttime BP means and loads, nocturnal dipping patterns and presence of white-coat and masked hypertension, otherwise not documented by the office BP evaluation [6]. Each of these parameters has been associated with higher cardiovascular risk in non-diabetic patients [7,8].

In type 2 normoalbuminuric DM patients, the systolic ambulatory BP mean is independently associated with urinary albumin excretion rate (UAER) [9]. In addition, type 2 DM patients with masked hypertension (elevated daytime BP levels in office normotensive individuals) have higher UAER and left ventricle wall thickness than truly normotensive patients [10]. Other ambulatory BP parameters have been studied in DM patients and special attention has been given to the blunted nocturnal physiological drop of BP. It was associated with increased glomerular filtration rate (GFR) [11] as well as with higher incidence of microalbuminuria [12,13,14], diabetic retinopathy [13,15] and macrovascular complications [13] in both type 1 and type 2 DM patients. However, this issue is still controversial, since in most of these studies patients with blunted nighttime BP decline also had elevated 24-h ABPM means [13,14,16].

Therefore, we hypothesize that elevations in BP means during the 24-h period in ABPM are more relevant, regarding microvascular complications and echocardiographic structural alterations in type 2 DM patients, than nighttime/daytime (N/D) BP ratios, which reflects the blunted nocturnal decline of BP.

Patients and Methods

Patients

A cross-sectional study was performed on a cohort of 270 patients with type 2 DM who have been followed since 1994 in the outpatient clinic at Hospital de Clínicas de Porto Alegre. The inclusion criterion was the diagnosis of type 2 DM (>30 years of age at onset of DM, no previous episode of ketoacidosis or documented ketonuria and treatment with insulin only 5 years after diagnosis). Patients with creatinine >1.5 mg/dl, other renal diseases, cardiac arrhythmia or postural hypotension were excluded. The Ethics Committee of the hospital approved this study, and informed consent was obtained from all patients.

Patient evaluation

Patients underwent an interview and clinical examination to record demographic and anthropometrical data, as previously described [17]. Indirect ophthalmoscopy (n = 223) was performed through dilated pupils by an ophthalmologist and, for the purpose of this study, patients were classified only according to the presence or absence of any degree of diabetic retinopathy (DR).

BP evaluations were performed one week after withdrawal of all antihypertensive medications. Office BP was measured twice with a mercury sphygmomanometer, using the left arm and with the patient in a sitting position, after a 5-minute rest. ABPM was performed by oscillometry (Spacelabs 90207 serial numbers 207/024751 and 207/038016, with calibration certification), with a 15-minute interval in the daytime and 20-minute interval in the nighttime periods. ABPM was performed on an ordinary workday, and

patients were advised to maintain their usual daily activities. Sleep time was recorded as the period between the time when the patient went to bed and the time when the patient woke up the next morning. The means of 24-h, daytime and nighttime systolic and diastolic BP were recorded, as well as systolic and diastolic BP loads (percentage of 24-h and daytime BP ≥140/90 mm Hg and nighttime ≥120/80 mm Hg). The N/D BP ratios for systolic and diastolic BP were calculated dividing the nighttime by the daytime BP values. The patients' BP status was classified according to ABPM measurements into dippers: N/D BP ratio ≤0.90 and non-dippers: N/D BP ratio >0.90 [18].

Echocardiograms (n = 190) were obtained according to the recommendations of the American Society of Echocardiography [19] using standard parasternal and apical views with subjects in the partial left decubitus position using a commercially available instrument (Hewlett Packard Sonus 1000) by the same cardiologist. Left ventricular mass was calculated and adjusted to the body surface area. The cardiologist who performed the echocardiograms was unaware of the subjects' clinical or laboratory characteristics.

Laboratory methods

UAER was measured in 24 h-timed urine, by immunoturbidimetry (Microalb, Ames- Bayer, Tarrytown, NY, USA; intra- and interassay coefficients of variations were 4.5% and 11.0%, respectively) and the mean of 2 samples was employed for the analyses. The patients were classified as normoalbuminuric (UAER <20 μg/min), microalbuminuric (UAER 20-199 μg/min) and macroalbuminuric (UAER ≥200 μg/min). A1c was measured by an HPLC system [high performance liquid chromatography- Merck-Hitachi 9100 (normal range 4 - 6%)]. Fasting plasma glucose was measured by the glucose-peroxidase colorimetric enzymatic method (Biodiagnostica). Creatinine was measured by the Jaffé method and the lipid profile by a colorimetric method.

Statistical analysis

Data are expressed as mean ± SD except for UAER, triglycerides and BP loads [median (range)]. Quantitative variables without normal distribution were log transformed. Correlations were performed by Pearson test. Student t test or chi-square test were used to compare clinical and laboratory data between patients with and without diabetic retinopathy. Multivariate analyses were performed for the following dependent variables: log-UAER, left ventricular mass, interventricular septum thickness and left posterior ventricular wall thickness (multiple linear regression) and diabetic retinopathy (logistic regression). Separate models were constructed for each of the BP measurements with adjustments for the variables associated with the outcomes during the correlations or univariate analyses. P values of <0.05 (2-tailed) were considered significant. The strength of the correlations was analyzed based on a magnitude scale (weak: r <0.300, moderate: r = 0.300 – 0.599, strong: r = 0.600 – 0.899 and perfect: r ≥0.900) and a comparison of correlations test was employed to establish the differences among the correlations

Results

The main clinical and laboratory characteristics of the 270 patients enrolled are shown in Table 1. Fifty six percent (n = 150) of the patients were normoalbuminuric, 30% (n = 82) were microalbuminuric and 14% (n = 38) were macroalbuminuric. The prevalence of diabetic retinopathy was 35% (n = 94). Systolic non-dipping was observed in 65% (n = 175) and diastolic non-dipping in 43% (n = 114) of the patients.

Blood pressure parameters and urinary albumin excretion rate

Positive and significant correlations were found between UAER and office BP (systolic: r = 0.367, P <0.001; diastolic: r = 0.266, P <0.001) and ABPM parameters (24-h BP means for systolic: r = 0.418, P <0.001 and for diastolic: r = 0.343, P <0.001). Daytime, nighttime BP means and pulse pressures, as well as the BP loads, also had significant

correlations with UAER, which were comparable with those found for the 24-h parameters (data not shown). Since UAER was also correlated with DM duration (r = 0.201, P = 0.001), A1c test (r = 0.149, P = 0.023) and serum triglyceride levels (r = 0.129, P = 0.042), multiple linear regression models were performed for each of the BP values with adjustments for these confounding variables (Table 2). The association of UAER and all office BP, 24-h, daytime and nighttime BP levels were sustained.

Although N/D BP ratios have also shown a significant association with UAER (systolic: r = 0.159, P = 0.011 and diastolic: r = 0.157, P = 0.011) this was not maintained after adjustments for other possible influencing factors (DM duration, A1c test and serum triglyceride levels) in a multivariate regression analysis (systolic: R^2_a = 0.064, P = 0.091 and diastolic: R^{2a} = 0.065, P = 0.078).

Blood pressure parameters and echocardiographic structural alterations

The left ventricle mass had a positive moderate correlation with the systolic 24-h (r = 355, P <0.001), daytime (r = 0.354, P <0.001) and nighttime (r = 325, P <0.001) BP means, but not with N/D BP ratios (systolic: r = 0.058, P = 0.439 and diastolic: r = 0.100, P = 0.179). No other clinical or laboratorial variables were associated with the left ventricle mass in this sample. Nevertheless, multivariate analyses of independent variables with potential biological importance (age, DM duration and waist circumference) were performed, and office BP and ABPM means retained their associations with the left ventricle mass.

Similar results were found for the other echocardiographic characteristics. The systolic BP means had a stronger correlation with septum thickness (24-h: r = 0.358, P <0.001) than diastolic N/D BP ratio (r = 0.155, P = 0.037). These correlations were significantly different (P = 0.012). The systolic N/D BP ratio did not even reach a statistically significant correlation with this echocardiographic parameter (r = 0.105, P =

0.159). After the multivariate adjustments for the variables also correlated with interventricular septum thickness [DM duration, waist circumference and body mass index (BMI)], most of the BP means continue to present positive and significant correlations. However, the diastolic N/D BP ratio (R = 0.267, R^2_a = 0.055, P = 0.160) did not remain associated. Concerning posterior left wall thickness, moderate correlations were obtainable only with systolic ABPM values (data not shown). Likewise for the interventricular septum, the systolic N/D BP ratio did not attain a statistically significant association with the posterior left wall thickness (r = 0.057, P = 0.444) and the diastolic N/D BP ratio lost its association after corrections for age, DM duration, waist circumference and BMI (R^2_a = 0.124, P = 0.485).

Blood pressure parameters and diabetic retinopathy

BP values in patients with and without any degree of DR are described in Table 3. Systolic BP parameters measured either at the office or during ABPM, were consistently increased in those with retinopathy. Regarding diastolic BP, only the nighttime values were elevated. Logistic regression models were performed with the presence of diabetic retinopathy as the dependent variable and each of BP parameters and the other variables associated with retinopathy in this sample (DM duration, A1c test and current smoking – data not shown) as the independent ones. Only nighttime BP values [each increment of 5 mm Hg in systolic BP mean: odds ratio (OR) 1.119, 95% confidence interval (CI) 1.022 – 1.224, P = 0.015 and diastolic BP mean: OR 1.211, CI 1.045 – 1.404, P = 0.011; diastolic BP load: OR 1.571, CI 1.083 – 2.278, P = 0.017] and the absence of diastolic nighttime dipping pattern (OR 2.948, CI 1.540 - 5.642, P = 0.001) sustained the association. Office, 24-h and daytime systolic and diastolic BP measurements as well as nighttime systolic BP load and absence of systolic nighttime dipping pattern did not continue to be associated with diabetic retinopathy after the adjustments (data not shown).

Clinical and laboratory factors associated with higher blood pressure values

The 24-h systolic BP means had a positive and significant correlation with age (r = 0.134, P = 0.028), DM duration (r = 0.226, P <0.001), A1c test (r = 0.149, P = 0.022) and total cholesterol levels (r = 0.196, P = 0.002). No other clinical and laboratory variables were associated with the BP levels (data not shown).

Discussion

In this sample of type 2 DM patients, the systolic BP means were the most important parameters of ABPM associated with UAER and echocardiographic left ventricle structural abnormalities. Concerning diabetic retinopathy, the nocturnal BP levels seem to have a relevant role.

Efforts have been made to define which component of BP homeostasis would be the most relevant predictor of DM chronic complications in order to improve patients' treatment. The N/D BP ratio, which reflects the physiological nighttime BP decline, is the most frequently studied component. Associations between higher N/D BP ratio and micro- and macrovascular complications have been described in both type 1 and type 2 DM patients [11,13,14,15,16,20]. However, in some studies, these associations did not remain significantly correlated when confounding factors were taken into account. In one cohort of type 1 DM patients, the relationship between the N/D BP ratio and the development of microalbuminuria was lost after adjustments to DM duration [16]. In another prospective study, the increase in N/D BP ratio appears just before the increase in UAER, and it was not observed at the baseline [14], implying that the absence of a nocturnal BP drop is not a risk factor for diabetic nephropathy development, but its marker [21]. In addition, the daytime diastolic BP mean was elevated since the baseline evaluation of the patients and, therefore, the daytime diastolic BP was the real renal endpoint predictor and not the dipping status [14]. Regarding patients with type 2 DM, a progressive increase in the N/D

BP ratio was associated with the progression of micro- and macrovascular complications [13]. However, once again, the 24-h, daytime and nighttime BP means were elevated [13].

There are similar findings concerning retinal involvement. The nighttime diastolic BP means and N/D diastolic BP ratio were associated with severe retinopathy in type 1 DM patients [15]. However, the association was no longer found (P = 0.07) after adjustments for age, DM duration, A1c test and smoking status. In type 2 DM patients, greater retinal involvement was associated with higher N/D BP ratios but also with BP means and pulse pressure levels [13]. In the present report, there was a large difference (+10 mm Hg) in the systolic nighttime BP mean between patients with and without DR, which is clearly clinically relevant and more important than the 5% difference in nighttime BP drop also found between groups. It is not yet clear why the nighttime BP values are more important in diabetic retinopathy. One possible explanation could be that the decubitus, associated with vasodilatation that occurs during the night, causes higher nighttime BP in the DM deregulated retinal artery tree.

The higher 24-h systolic BP was also related to age, DM duration, A1c test and cholesterol. Higher levels of cholesterol and fasting plasma glucose were also associated with higher BP levels in the *Pressioni Arteriose Monitorate e Loro Associazioni* (PAMELA) study [22]. Each of these variables may be involved in arterial stiffness and could explain the elevation of systolic BP levels found.

None of the previous publications has compared the strength of the correlation between each AMBP mean and N/D BP ratios. In this way, the higher ABPM means have probably confounded the final results of most papers analyzing nighttime BP decline. Emerging data from large population-based surveys support the idea that BP has a continuous association with end-organ lesions and mortality in spite of the method employed (office, home or ABPM) [7] or the BP component analyzed (24-h, daytime or

nighttime) [8]. Therefore, overemphasizing a specific BP component seems not to add significant knowledge to the understanding of BP vascular damage or to the treatment of hypertension.

Based on the present study results, as well as previous data from other authors, a practical recommendation regarding ABPM role in type 2 DM evaluation could be made. Normotensive patients based on office evaluation might undergo a 24-h ABPM in order to identify the masked hypertensive individuals [10]. When high BP levels are found at office evaluation, the BP treatment must be intensified and an ABPM should be ordered to confirm whether BP levels attained during the day and night are appropriate. In patients with diabetic retinopathy the absence of a dipping pattern should not be overemphasized rather than obtaining adequate nighttime diastolic and systolic BP levels.

The possible limitation of this study is the cross-sectional design, which avoids establishing a cause and effect relationship between the risk factor and the outcome. However, this limitation does not prevent the comparison among BP levels, which is the main result of this report.

In conclusion, in type 2 DM patients the systolic ABPM means have a greater impact on UAER, ventricular mass and wall thickness than the N/D BP ratios. Concerning diabetic retinopathy, the nighttime BP means are more relevant than the office, 24-h and daytime means. The treatment of high BP in type 2 DM patients might focus on overall ABPM means and special attention must be paid to the systolic component in order to eliminate the increased morbidity and mortality associated with elevated BP levels in this high-risk group.

Acknowledgments: This study was partially supported by Projeto de Núcleos de Excelência do Ministério de Ciência e Tecnologia (PRONEX), Conselho Nacional de

Desenvolvimento Científico e Tecnológico (CNPq) and Fundo de Incentivo a Pesquisa (FIPE) do Hospital de Clínicas de Porto Alegre. LHC was the recipient of a scholarship from CAPES (Programa de Apoio à Instalação de Doutores - ProDoc). CBL had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Clinical and laboratory characteristics of the patients.

Age (years)	56.4 ± 9.3
Diabetes duration (years)	10.1 ± 6.6
Males - n (%)	144 (53)
Whites – n (%)	209 (77)
Smokers – n (%)	48 (19)
Hypertensives – n (%)	135 (50)
Body Mass Index (kg/m^2)	28.5 ± 4.6
Waist circumference	
Females	95.0 ± 9.8
Males	99.5 ± 11.4
Fasting Plasma Glucose (mg/dl)	156.5 ± 59.6
A1c (%)	8.2 ± 2.3
Total Cholesterol (mg/dl)	201.0 ± 52.0
HDL cholesterol (mg/dl)	47.0 ± 12.5
Triglycerides (mg/dl)	138 (39-1115)
Creatinine (mg/dl)	0.8 (0.3-1.5)

Table 2. Multiple linear regressions analyses of renal and echocardiographic outcomes.

	Urinary albumin excretion rate *		**Interventricular septum thickness †**		**Left ventricle mass ‡**	
	R^2_a	**P**	**R^2_a**	**P**	**R^2_a**	**P**
Office systolic blood pressure	0.164	<0.001	0.097	0.002	0.039	0.004
Office diastolic blood pressure	0.128	<0.001	-	-	-	-
24-h systolic blood pressure	0.194	<0.001	0.152	<0.001	0.138	<0.001
24-h diastolic blood pressure	0.200	<0.001	0.082	0.009	0.109	<0.001
Daytime systolic blood pressure	0.181	<0.001	0.156	<0.001	0.139	<0.001
Daytime diastolic blood pressure	0.177	<0.001	0.082	0.009	0.103	<0.001
Nighttime systolic blood pressure	0.197	<0.001	0.136	<0.001	0.108	<0.001
Nighttime diastolic blood pressure	0.189	<0.001	0.082	0.003	0.094	<0.001
Nighttime/daytime systolic ratio	0.064	0.091	-	-	-	-
Nighttime/daytime diastolic ratio	0.065	0.078	0.055	0.160	-	-

Boxes without data: absence of correlation (P >0.05) in simple correlations test.
Adjustments for *diabetes mellitus duration, A1c test and triglycerides; †diabetes mellitus duration, A1c test, waist circumference and body mass index and ‡age, diabetes mellitus duration and waist circumference

Table 3. Blood pressure values in patients with and without diabetic retinopathy.

	Retinopathy		
	Absent (n = 129)	**Present (n = 94)**	**P**
Systolic			
Office blood pressure	138.8 ± 20.7	147.5 ± 24.1	0.004
24-h blood pressure	130.4 ± 15.5	136.9 ± 18.1	0.004
Daytime blood pressure	133.6 ± 15.7	138.9 ± 18.4	0.023
Nighttime blood pressure	123.2 ± 16.7	132.8 ± 19.8	<0.001
Nighttime/daytime ratio	0.92 ± 0.06	0.97 ± 0.09	0.001
Diastolic			
Office blood pressure	84.4 ± 13.0	87.3 ± 14.1	0.112
24-h blood pressure	78.4 ± 9.1	79.3 ± 10.4	0.340
Daytime blood pressure	81.3 ± 9.5	81.4 ± 10.8	0.962
Nighttime blood pressure	71.2 ± 10.0	74.9 ± 11.5	0.011
Nighttime/daytime ratio	0.88 ± 0.08	0.92 ± 0.09	<0.001

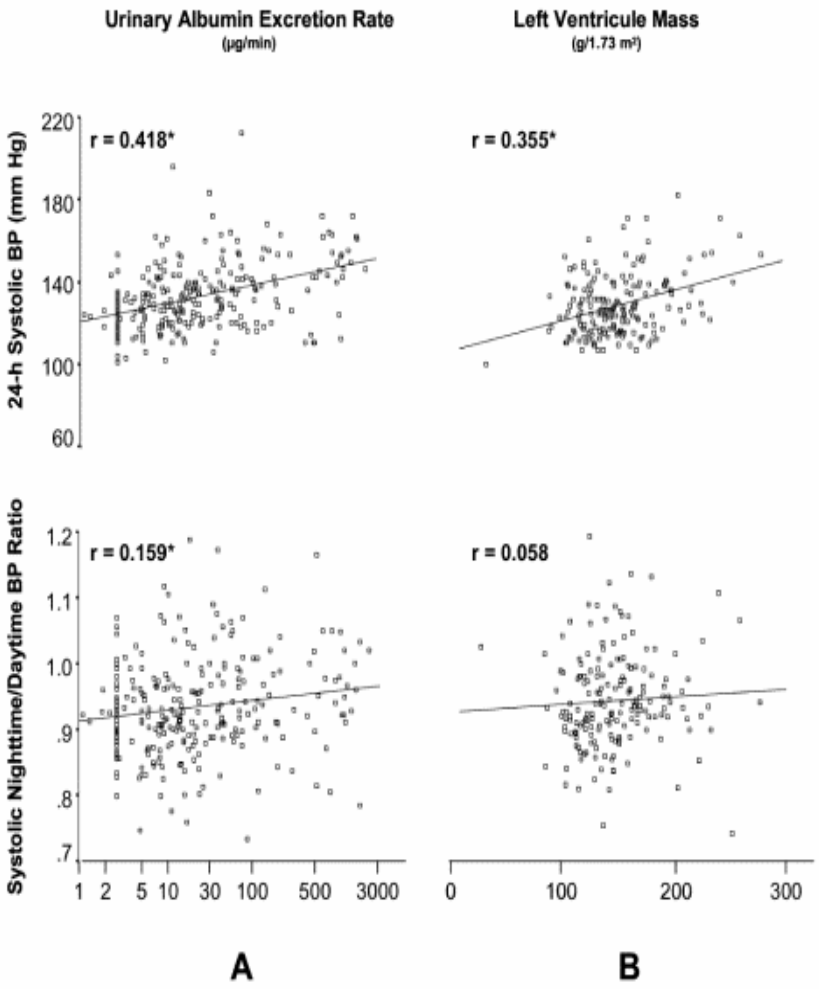

Figure 1. Urinary albumin excretion rate in log scale (A) and left ventricle mass (B) according to 24-h systolic blood pressure means or systolic nighttime/daytime blood pressure ratio. * P <0.05.

BP = blood pressure.