Glomerular hyperfiltration is associated with blood pressure abnormalities in normotensive normoalbuminuric IDDM patients[1]

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OBJECTIVE: To analyze the blood pressure patterns in normoalbuminuric IDDM patients with glomerular hyperfiltration.

PATIENTS AND METHODS: A controlled cross-sectional study of 38 normotensive normoalbuminuric (urinary albumin excretion rate <20 mg/min) IDDM patients (18 hyperfiltering [glomerular filtration rate > 134 ml × min^{-1}× 1.73m^{-2}] and 20 normofiltering) and 20 normal individuals matched for age, sex, and body mass index was performed. The 24-h ambulatory blood pressure was monitored using an auscultatory technique; the glomerular filtration rate was measured by ^{51}Cr-labeled EDTA method; extracellular volume by the distribution volume of ^{51}Cr-labeled EDTA; and 24-h urinary albumin excretion rate by radioimmunoassay.

RESULTS: Mean nocturnal diastolic blood pressure was higher in hyperfiltering IDDM patients (70.4 ± 7.8 mmHg), when compared with the control group (65.1 ± 5.3 mmHg, P *= 0.04). Diastolic blood pressure night:day ratio was higher in hyperfiltering IDDM patients (92.0 ± 8.6%), when compared with normofiltering IDDM patients (85.9 ± 4.8%) and control subjects (87.0 ± 6.8%,* P *= 0.02). In IDDM patients, the glomerular filtration rate significantly correlated with the diastolic blood pressure night:day ratio (*r *= 0.5,* P *= 0.002), extracellular volume (*r *= 0.4,* P *= 0.002), and HbA_1 (r = 0.3, P = 0.03). In stepwise multiple regression analysis, factors associated with glomerular filtration rate were diastolic blood pressure night:day ratio, extracellular volume, and HbA_1 (adjusted* r^2 *= 0.27,* P *= 0.003).*

CONCLUSIONS: Glomerular hyperfiltration is associated with higher nocturnal diastolic blood pressure and with a blunted nocturnal decrease in diastolic blood pressure levels in normotensive and normoalbuminuric IDDM patients.

Key-words: IDDM; UAER; blood pressure

A hiperfiltração glomerular está associada a alterações de pressão sangüínea em pacientes DMDI normotensivos

OBJETIVO: Analisar os padrões de pressão sangüínea em pacientes normoalbuminúricos DMDI com hiperfiltração glomerular.

PACIENTES E MÉTODOS: Foi feito um estudo controlado em cortes transversais com 38 pacientes normoalbuminúricos normotensivos (taxa de excreção urinária de albumina>20 mg/min) DMDI (hiperfiltração em 18 [taxa de filtração glomerular>134 ml x min^{-1} x 1,73m^{-2}] e normofiltração em 20), e de 20 indivíduos normais agrupados por idade, sexo, e índice de massa corporal. A pressão sangüínea ambulatorial foi monitorada em 24 h pelo método

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auscultatório; a taxa de filtração glomerular foi medida através do método ^{51}Cr-EDTA; o volume extracelular, através do volume de distribuição do ^{51}Cr-EDTA; e a taxa excreção urinária de albumina em 24 h, por radioimunoensaio. RESULTADOS: A média da pressão sangüinea diastólica noturna foi mais alta em pacientes DMDI com hiperfiltração (70,4 ± 7,8 mmHg), quando comparada à do grupo controle (65,1 ± 5,3 mmHg, P=0,04). A relação diurna:noturna da pressão sangüínea diastólica foi mais alta em pacientes DMDI com hiperfiltração (92,0 ± 8,6%) quando comparada a mesma relação dos pacientes DMDI com normofiltração (85,9 ± 4,8%) e controles (87,0 ± 6,8%, P=0,02). Os pacientes DMDI apresentaram uma taxa de filtração glomerular significativamente correlacionada com a relação diurna:noturna de pressão diastólica (r=0,5, P=0,002), com o volume extracelular (r=0,4, P=0,002), e com HbA_1 (r=0,3, P=0,03). Na análise de regressão múltipla escalonada, os fatores associados com a taxa de filtração glomerular foram: relação diurna:noturna de pressão sangüinea diastólica, volume extracelular, e HbA_1 (ajustado r^2=0,27, P=0,003).

CONCLUSÕES: Hiperfiltração glomerular está associada à pressão sangüínea diastólica noturna elevada e a uma diminuição noturna abrupta dos níveis de pressão sangüínea diastólica em pacientes normotensivos e em pacientes DMDI normoalbuminúricos.

Unitermos: DMDI; taxa de excreção urinária de albumina; pressão sangüínea.

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Introduction

An increased glomerular filtration rate (GFR) has been considered a risk factor for the development of diabetic nephropathy in IDDM patients (1). However, the role of glomerular hyperfiltration remains controversial. In a 10-year prospective study, baseline albumin excretion rate and blood pressure (BP) were the main risk factors for renal outcome. Baseline GFR was an independent determinant of final blood pressure (2).

Increased levels of arterial BP were detected in normoalbuminuric IDDM patients who progress to microalbuminuria (3). Alterations in ambulatory BP (ABP) parameters were observed in normoalbuminuric IDDM patients (4-6) and have been associated with diabetes duration (6) and with higher urinary albumin excretion rate (UAER) levels (4), although within the normal range. Abnormalities of circadian BP variation were also described in microalbuminuric IDDM patients (7-9). However, GFR was not taken into account in these studies.

It can be hypothesized that if there was an association of glomerular hyperfiltration and abnormalities of BP homeostasis, it would be possible to identify IDDM patients with a higher risk for the development of diabetic nephropathy. Therefore, the aim of the study was to analyze BP patterns in normoalbuminuric normotensive IDDM patients with glomerular hyperfiltration.

Patients and methods

This study followed a controlled cross-sectional design. Thirty-eight IDDM patients followed between 1986 and 1989 at the diabetes outpatient clinic at Hospital de Clínicas de Porto Alegre (a tertiary care center) were studied. The GFR and UAER of these patients are being measured at ~1-year intervals (10). Informed consent was obtained from each patient, and the protocol was approved by the ethics committee. The definition of IDDM was based on World Health Organization criteria (11), i.e., onset of diabetes age < 40 years, a previous episode of ketoacidosis or documented ketonuria, and

obligatory use of insulin for life maintenance. The inclusion criteria were as follows: diabetes duration for > 1 year; >18 years of age; 24-h UAER <20 μg/min on at least two different occasions; office ambulatory BP <140/90 mmHg; absence of coronary heart disease (normal maximal exercise electrocardiogram) or other cardiac disease; absence of renal disease (normal urinary sediment and negative culture); and absence of autonomic neuropathy (more than one abnormal result out of five cardiovascular autonomic reflex tests) (12). None of the patients were obese (BMI < 30 kg/m^2). Patients were conventionally treated with one or two daily subcutaneous insulin injections, except for one patient who took four injections per day. Office auscultatory BP was measured twice in a sitting position after a 10-min rest, with a standard 12.5-cm cuff mercury sphygmomanometer (phases I-V), and the mean BP value was used. These patients were classified as hyperfiltering (n=18) and as normofillering (n = 20) according to the upper limit of normal GFR range previously established in normal volunteers at our unit (mean + 2 SD = 134.0 ml × min^{-1} ×1.73 m^{-2}) (13). The condition of hyperfiltration and normofiltration was confirmed at least three times before the experiment, and 20 healthy individuals matched to the patients for age, sex distribution, BMI, ethnicity, smoking habit, and use of oral contraceptive formed the control group.

The same researcher installed the 24-h ABP monitors in the morning. Patients and control subjects were asked to continue their daily activities and to complete a 24-h report on values of home glucose monitoring (before breakfast, lunch, dinner, at 10:00 P.M, and if hypoglycemia was suspected), number of cigarettes smoked and other exceptional activities (for instance, extra physical activity or arguing).

The 24-h ABP was measured with a lightweight battery-operated ambulatory BP monitoring device (Pressurometer IV, Del Mar Avionics, Irvine, CA) using an auscultatory technique. Before sampling, the pressurometer programmer, a computer used with the Pressurometer IV program was used to test and program the monitor. The programmer is also used together with the test kit to calibrate the pressurometer against a mercury manometer to ensure proper transducer placement and sensitivity. After sampling, the programmer can be interfaced with a printer to generate a comprehensive tabular report showing sampling times and unedited systolic, diastolic, and heart rate readings. The monitor was programmed to take measurements every 10 min from 7:00 A.M. to 11:00 P.M. and every 15 min from 11:00 P.M. to 7:00 A.M.. The mean diurnal and nocturnal BP and heart rate were calculated based on each

Table1. Clinical characteristics of IDDM patients and control group[a]

	Hyperfiltering	Normofiltering	Control
n	18	20	20
Age (years)	32.1 ± 6.4 (22-40)	34.8 ± 7.8 (22-51)	32.7 ± 6.0 (22-47)
Sex (F/M)	10/8	9/11	10/10
Ethnicity (black/white)	4/14	1/19	2/18
BMI (kg/m^2)	24.3 ± 3.8 (18.2-30.0)	22.0 ± 2.1 (18.4-24.8)	23.6 ± 2.3 (20.0-27.5)
Smokers	6	3	4
Ambulatory monitoring on working day	12	15	15
Familial history of hypertension	12	7	9
Oral contraceptive use	3	3	2
Duration of diabetes (years)	6.5 ± 4.4 (1-15)	8.4 ± 4.7 (1-17)	-
Insulin dose (U × kg^{-1}× day^{-1})	0.7 ± 0.2 (0.4-1.1)	0.7 ± 0.3 (0.3-1.5)	-
Background retinopathy	4	2	-
Peripheral neuropathy	3	2	-

[a]Data are n or mean ± SD (range). All *P* values are nonsignificant.

patient's self-recorded time for going to bed and rising in the morning.

The GFR was measured using the ^{51}Cr-labeled EDTA single injection technique (coefficient of variation [CV] = 11.2%) and calculated as a monoexponential function of the plasma disappearance curve according to Chantler and Barrat (14). Extracellular volume (ECV) was estimated as the distribution volume of ^{51}Cr-labeled EDTA (15). UAER was determined by radioimunoassay (DPC, Los Angeles, CA; inter-and intra-assay CV = 2.3 and 2.8%, respectively) in 24-h sterile specimens. Glucose was measured by the glucose-oxidase method, HbA_1 by a microchromatographic system (Labtest; normal range 5.3-8.0%), and fructosamine by a colorimetric method (NBT reduction, Labtest; normal range: 1.87-2.87 mmol/l), creatinine by Jaffe's reaction, urinary urea by a kinetic reaction, urinary sodium by flame photometry and cholesterol, HDL, and triglycerides by a colorimetric method.

Statistical analysis

The three groups were compared by analysis of variance (ANOVA) followed by the Student-Newman-Keuls (SNK) test. Student's t test or Mann-Whitney's ranksum test was used to compare normofiltering and hyperfiltering IDDM patients. Differences between groups for discrete variables were evaluated by the Fisher's exact test and the χ^2 test. Pearson's correlation test was used for the correlation between GFR and systolic and diastolic BP night:day (N:D) ratios. To examine a nonlinear relation between the GFR and diastolic BP N:D ratio, a statistical method to determine the breakpoint of two lines (a changepoint model) was used (16). Stepwise multiple linear regression analysis were carried

Table 2. Laboratory features of IDDM patients[a]

	Hyperfiltering	Normofiltering	P value
n	18	20	
GFR (ml × min ×1.73m^{-2})	158.2 ± 13.9 (138.5-180.4)	117.4 ± 13.1 (94.4-133.0)	<0.001
ECV (1/1.73m^{-2})	23.0 ± 3.7 (17.4-30.9)	19.6 ± 2.5 (14.6-23.1)	0.002
UAER (mg/min)	4.4 (0.3-15.9)	4.7 (0.1-16.5)	NS
HbA_1 (%)	8.9 ± 2.2 (5.3-13.0)	8.7 ± 1.8 (5.0-11.4)	NS
Fasting plasma glucose (mmol/l)	7.8 ± 4.9 (3.0-11.5)	8.1 ± 4.8 (2.4-12.2)	NS
Home glucose monitoring (mmol/l)	7.9 ± 2.8 (4.4-13.9)	7.7 ± 1.6 (4.2-9.72)	NS
fructosamine (mmol/l)	3.75 ± 0.84 (2.23-5.91)	3.48 ± 0.64 (2.39-4.77)	NS
Cholesterol (mmol/l)	4.4 ± 1.0 (3.0-6.6)	4.4 ± 0.7 (3.3-6.1)	NS
HDL (mmol/l)	1.4 ± 0.5 (0.7-2.5)	1.3 ± 0.3 (0.8-2.0)	NS
Triglycerides (mmol/l)	0.7 ± 0.3 (0.2-1.3)	1.1 ± 0.6 (0.5-2.3)	0.04
Creatinine (mmol/l)	76.9 ± 15.9 (53.0-106.1)	90.2 ± 10.6 (70.7-106.1)	0.007
Urinary sodium excretion (mEq/h)	9.1±2.8 (5.4-14.3)	7.6±2.7 (3.6-14.1)	NS
24-h urinary urea (g)	21.6±8.3 (11.9-33.8)	20.0±7.9 (8.0-30.0)	NS

[a]Data are mean ± SD (range). For UAER data are expressed as median range. Home glucose monitoring represents the mean of four measurement per day.

out to determine the effects of different variables on GFR variation. Data were expressed as means ± SD, except for the UAER analysis, for which median and range were used. $P < 0.05$ was considered significant.

Results

The clinical characteristics of IDDM patients and control subjects are shown in Table 1. No difference was observed when comparing age, sex, ethnicity, BMI, smoking habits, number of valid 24-h ABP readings, family history of hypertension, and the number of tests performed on leisure days (day-off) or working days (day-in) among the three groups ($P > 0.05$).

When clinical and laboratory features were compared between hyper- and normofiltering patients (Table 2), the only differences observed were lower levels of triglycerides and serum creatinine and higher ECV levels in hyperfiltering patients. By definition, GFR was different for the two groups.

ABP and heart rate values are described in Table 3. The nocturnal diastolic BP was significantly higher in hyperfiltering patients when compared with the control group (ANOVA, $P = 0.04$; SNK < 0.005). Differences in the diurnal variation of ABP were addressed by calculating the N:D ratio. The diastolic BP N:D ratio was higher in hyperfiltering patients (92.0 ± 8.6%), when compared with normofiltering patients (85.9 ± 4.8%) and the control group (87.0 ± 6.8%). There was no difference between normofiltering and control patients (ANOVA; $P = 0.02$; SNK < 0.05). Individual values of diastolic BP N:D ratios are shown in Figure 1. These results did not change when the control subject with the lower value of diastolic BP N:D ratio was excluded from the analyses. The systolic BP N:D ratio was also higher in hyperfiltering patients (88.4 ± 8.1%) as compared with normofiltering patients (81.5 ± 10.5%) and with the control group (83.6 ± 6.8%), but it did not reach the conventional statistical significance level (ANOVA, $P = 0.055$). The proportion of nondippers, defined in this study as the subjects in whom the reduction of diastolic BP was < 10% from day to night, was higher in hyperfiltering patients (10/18) when compared with normofiltering patients (3/20) and the control group (6/20) (χ^2, $P = 0.02$), without any difference between normofiltering patients and the control group.

In the group of diabetic patients, correlations (Pearson's tests) were calculated for GFR and diastolic BP N:D ratio (Figure 2A; $r = 0.5$, $P = 0.002$), ECV (Figure 2B; $r = 0.4$, $P = 0.002$), HbA_1 ($r = 0.3$, $P = 0.03$), diabetes duration ($r = -0.05$, $P = 0.4$), log AER ($r = 0.1$, $P = 0.2$), and urinary sodium ($r = 0.09$, $P = 0.3$). Variables with a P value <0.10 were entered in a stepwise multiple linear regression analysis with GFR as the dependent variable. The results were as follows: diastolic BP N:D ratio (adjusted $r^2 = 0.19$, $F = 9.4$, $P = 0.004$), diastolic BP N:D ratio + ECV + HbA_1 (adjusted $r^2 = 0.27$, $F = 57$, $P = 0.003$). A

Table 3. Ambulatory blood pressure and heart rate patterns of IDDM patients and control group[a]

	Hyperfiltering	Normofiltering	Control
n	18	20	20
24-h sBP (mmHg)	122.9 ± 10.1	114.9 ± 10.9	111.2 ± 9.5
24-h dBP (mmHg)	74.7 ± 6.7	75.3 ± 6.6	72.2 ± 5.6
24-h heart rate (beats/min)	71.3 ± 6.7	68.6 ± 5.6	68.9 ± 5.2
Diurnal sBP (mmHg)	116.5 ± 11.9	119.9 ± 10.9	116.4 ± 10.6
Diurnal dBP (mmHg)	76.9 ± 7.1	78.4 ± 6.6	75.0 ± 6.1
Diurnal heart rate (beats/min)	74.3 ± 6.2	71.2 ± 5.3	70.7 ± 4.6
Nocturnal sBP (mmHg)	102.2 ± 10.2	97.7 ± 14.3	97.7 ± 14.3
Nocturnal dBP (mmHg)	70.4 ± 7.8	67.1 ± 6.3	65.1 ± 5.3[b]
Nocturnal heart rate (beats/min)	67.4 ± 9.1	62.2 ± 6.9	65.0 ± 10

[a]Data are means ± SD. sBP, systolic blood pressure; dBP, diastolic blood pressure.
[b]$P = 0.02$, hyperfiltering vs. control.

statistical analysis to determine the breakpoint in the correlation of GFR and diastolic BP N:D ratio disclosed that a broken line fitted significantly (F = 57.1) better than a straight line. The breakpoint was 140 ml × min^{-1} × 1.73 m^{-2}, and GFR values under this level were not correlated with diastolic BP N:D ratio.

Conclusions

In this study, IDDM patients with glomerular hyperfiltration presented higher levels of nocturnal diastolic BP. GFR was associated with a blunted decrease in diastolic BP, with increased

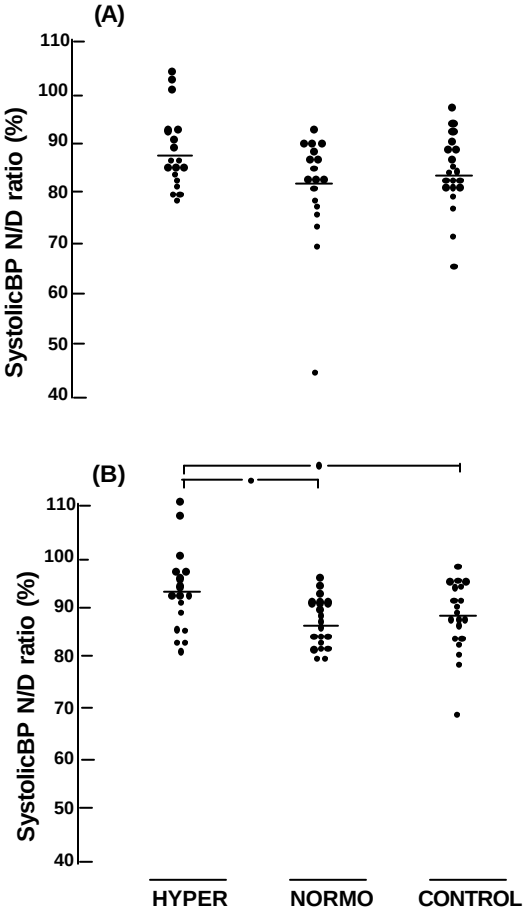

Figure 1. Individual night:day ratio for systolic (A) and diastolic (B) blood pressure in IDDM patients and healthy control subjects. HYPER, hyperfiltering patients (n = 18); NORMO, normofiltering patients (n = 20); CONTROL, control subjects (n = 20). Horizontal lines indicate the means. *P < 0.005.

ECV and HbA_1. The diastolic BP N:D ratio was the main factor contributing for GFR variation. There is probably a threshold in GFR values above which there is an association with BP abnormalities. The breakpoint analysis disclosed

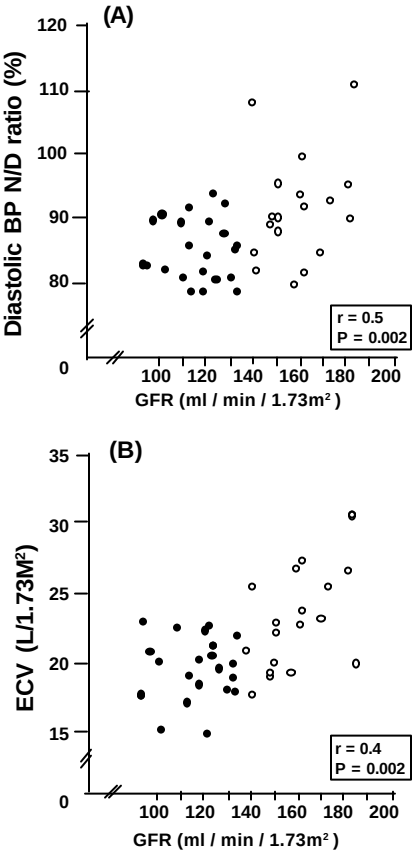

Figure 2. Correlations (Pearson's tests) between GFR and diastolic BP N:D ratios (A) and ECV (B) in IDDM patients. ●, normofiltering patients; ○, hyperfiltering patients.

that only GFR values > 140 ml × min^{-1} × 1.73 m^{-2} presented a significant correlation with the diastolic BP N:D ratio. This GFR value is closer to the upper limit of GFR previously established in our unit, of 134 ml × min^{-1} × 1.73 m^{-2} (13).

It is well known that GFR is influenced by the degree of metabolic control in IDDM (17) and NIDDM patients (18). In the present study, HbA_1 variation accounted only for about 3% of the GFR variation. The relationship between GFR and ECV has already been reported by us (19) and others (20). Theoretically, the observed expansion of ECV could explain the abnormalities of the BP pattern in hyperfiltering IDDM patients. However, the blood volume was not different in a similar group of normofiltering and hyperfiltering IDDM patients (19). It could be speculated that during the night, in a recumbent position, there could be a redistribution of ECV leading to a transient increase in blood volume.

Higher levels of nocturnal BP in normotensive normoalbuminuric IDDM patients were also reported by other authors (5,6). In the

study by Gilbert et al. (5), there is no mention as to whether ABP monitoring was performed on working or nonworking days. Another study (6) evaluated only male patients, and the authors did not mention smoking habits, the number of tests performed on working days, and the criteria used to define the night period. The authors compared patients with a diabetes duration of 12 years with patients with a diabetes duration of 2.4 years.

Diabetes duration has been reported to influence ABP patients in normoalbuminuric IDDM patients (6, 21). In those studies, the night heart rate was higher in patients with a longer duration of diabetes, possibly indicating the presence of vagal neuropathy. Neither of these studies had performed proper autonomic function tests. It has already been shown that autonomic dysfunction is associated with blunted decrease of nocturnal diastolic BP in normoalbuminuric IDDM patients (22). In our study, the patients did not present abnormalities in autonomic cardiovascular tests or a higher nocturnal heart rate. However, we could not exclude an early autonomic dysfunction if more sensitive methods had been applied. The effect of the longer duration of diabetes could, in fact, represent the presence of autonomic neuropathy.

Other authors have not found any significant difference in the BP N:D ratio between normoalbuminuric IDDM patients and healthy control subjects (24,24). In the study by Hansen et al. (23), ABP monitoring was performed more often on nonworking days (71% in IDDM patients and 75% in control subjects) than in the present study (24% in IDDM patients and 29% in the control group; $P < 0.01$ for both comparisons). The duration of diabetes was also longer (18 years) than in our subjects (7.5 years). In another study (24), the number of patients and healthy individuals was small (12 in each group), fixed night periods were used to calculate the nocturnal BP mean (11:00 P.M. to 7:00 A.M), and all the patients were admitted to the hospital for the night measurements. The authors did not mention whether normal individuals were also admitted.

The GFR was not measured in any of the studies mentioned above.

The association between GFR and an altered circadian BP rhythm could identify a subset of IDDM patients more susceptible to future development of diabetic nephropathy. Prospective studies of this particular group of patients should be conducted. In conclusion, in normotensive and normoalbuminuric IDDM patients, glomerular hyperfiltration is associated with a higher nocturnal diastolic BP and with a blunted nocturnal decrease in diastolic BP levels.

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