Cardiovascular Autonomic Neuropathy Is Associated With Microalbuminuria in Older Patients With Type 2 Diabetes

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OBJECTIVE — Cardiovascular autonomic neuropathy is associated with microalbuminuria in young and middle-aged patients with type 2 diabetes. We examined this relationship and the potential mediating role of blood pressure in older patients.

RESEARCH DESIGN AND METHODS — At least two of three components of cardiovascular autonomic testing were completed by 132 patients (mean age 70 ± 5.6 years). Relative rankings on each of the components were averaged to create a summary heart rate variability (HRV) measure. The urine microalbumin-to-creatinine ratio (milligrams albumin/grams creatinine) was calculated. Blood pressure was measured at rest and by 24-h ambulatory recording.

RESULTS — Urine microalbumin-to-creatinine ratio was higher in those with lower HRV (mean urine microalbumin-to-creatinine ratio 28, 56, and 191 mg/g from the highest to lowest tertile of HRV; $P < 0.0001$). Resting and ambulatory blood pressure levels were negatively correlated with HRV and positively correlated with urine microalbumin-to-creatinine ratio. In multivariate analysis adjusting for age, duration of diabetes, HbA_{1c}, and HDL cholesterol, HRV and blood pressure were both independently associated with urine microalbumin-to-creatinine ratio, with no evidence that either mediates the effect of the other.

CONCLUSIONS — Cardiovascular autonomic neuropathy and blood pressure are independently associated with microalbuminuria in older patients with type 2 diabetes.

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Cardiovascular autonomic neuropathy has a prevalence of ~17–22% in patients with type 1 and type 2 diabetes (1,2), and its presence has been associated with substantially increased risk of cardiovascular and all-cause mortality in patients with type 2 diabetes (3). Approximately 65% of people with diabetes die of cardiovascular disease (4), and cardiovascular disease is the leading cause of death among patients with type 2 diabetes who are diagnosed with cardiovascular autonomic neuropathy (3,5). The clinical manifestations of cardiovascular autonomic neuropathy include orthostatic hypotension, abnormalities in heart rate control, and decreased heart rate variability (HRV) on 24-h monitoring or provocative testing (1,6,7).

Cross-sectional studies in young and middle-aged patients have found associations between diabetic cardiovascular autonomic neuropathy and microalbuminuria (8–10). Results from longitudinal studies are conflicting; data from patients with type 1 diabetes show that cardiovascular autonomic neuropathy predicts deterioration of renal function (11,12), and data from older patients with type 2 diabetes show no predictive effect (13). Microalbuminuria is strongly associated with increased risk of cardiovascular complications, including atherosclerotic coronary artery disease, stroke, peripheral vascular disease, and cardiovascular mortality (14). Abnormalities in 24-h ambulatory blood pressure pattern, particularly loss of normal sleep decrement in systolic pressure ("nondipping"), are also associated with diabetic microalbuminuria (15,16). It has been hypothesized that autonomic neuropathy impairs both renal function and the normal diurnal blood pressure pattern (10).

The purpose of this study was to examine the association between cardiovascular autonomic neuropathy and microalbuminuria in an older population with type 2 diabetes and the potential role of blood pressure in mediating this relationship.

RESEARCH DESIGN AND METHODS

— We studied a subset of patients enrolled in the Informatics for Diabetes Education and Telemedicine (IDEATel) Study (17). IDEATel is a federally funded study to assess telemedicine as a means of managing the care of older Medicare beneficiaries with diabetes (age ≥55 years) who reside in medically underserved areas of New York State. Exclusion criteria for the IDEATel study include end-stage renal disease; impairment of speech, hearing, vision, or cognition; and life-threatening comorbidities.

The two IDEATel clinical centers are at Columbia University in New York City and SUNY Upstate Medical University in Syracuse, New York. IDEATel participants underwent fasting baseline examination between October 2000 and October 2002. Prescription drug use was ascertained by interviewer-administered

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Abbreviations: ECG, electrocardiogram; HRV, heart rate variability; IDEATel, Informatics for Diabetes Education and Telemedicine; SBP, systolic blood pressure.

questionnaire. Height, weight, and seated blood pressure were measured, blood and spot urine samples were collected, and 24-h ambulatory blood pressure monitoring was performed.

Potential participants for the cardiovascular autonomic neuropathy study were randomly sampled within two age-defined strata (58–74 and 75–84 years) from IDEATel participants who completed the baseline examination before 30 April 2002. Subjects with a normal nocturnal blood pressure dipping pattern (dippers) were oversampled to achieve a ratio of dippers to nondippers of at least 1:2. Subjects were excluded if they had a nocturnal mean systolic blood pressure (SBP) decrement >20% of mean daytime SBP, atrial fibrillation or flutter, second- or third-degree heart block, resting tachycardia (≥120 bpm), cardiac pacemaker, self-reported myocardial infarction within the previous year, severe respiratory illness (emphysema, chronic bronchitis, or asthma), laser ophthalmic surgery within the previous 3 months, inability to stand independently, or inability to complete at least two of the three cardiovascular autonomic tests. Of the 336 participants invited for autonomic testing, 160 agreed to participate and 132 completed at least two of the three components of cardiovascular autonomic testing. These 132 subjects completed cardiovascular autonomic testing within 1 year of the IDEATel baseline examination and were clinically stable in the interval between the baseline examination and cardiovascular autonomic testing. Both the IDEATel and the cardiovascular autonomic neuropathy studies were approved by the institutional review boards of Columbia-Presbyterian Medical Center and the SUNY Upstate Medical University.

Laboratory measures

Urine albumin level was measured using the immunoprecipitin method (Diasorin, Stillwater, MN) from a random spot urine sample collected at the baseline examination. Values <5.7 mg/dl (n = 34 of 160) were assigned a value of 4.0 mg/dl. Urine creatinine level was measured using the picric acid colorimetric method. Both analyses were performed using a Roche/Hitachi 717 automated analyzer (Roche Diagnostics, Indianapolis, IN). The urinary microalbumin-to-creatinine (milligrams of albumin/grams of creatinine) ratio was calculated. HbA_{1c} was analyzed by boronate affinity chromatography with the Primus CLC 385 (Primus, Kansas City, MO). Total cholesterol, triglyceride, and HDL cholesterol levels were measured using enzymatic colorimetric methods (Vitros; Johnson & Johnson, New Brunswick, NJ). LDL cholesterol level was calculated using the Friedewald equation for subjects with triglyceride level <400 mg/dl and measured directly using a homogeneous assay (Polymedco, Cortlandt Manor, NY) for those with triglyceride level ≥400 mg/dl. Biochemical analyses were performed at Penn Medical Laboratory (currently Medstar Medical Laboratory) in Washington, DC.

Resting blood pressure measurement

Resting blood pressure was measured at the IDEATel baseline examination using the Dinamap Monitor Pro 100 (Critikon, Tampa, FL) automated oscillometric device. Three measurements were obtained after 5 min of rest using a standardized protocol. The average of the second and third measurements was recorded as the resting blood pressure.

Resting electrocardiography

A standard 12-lead electrocardiogram (ECG) was obtained using a GE/Marquette MAC500 (GE Medical Systems, Milwaukee, WI). ECGs were read blindly by one of the investigators (W.P.) using standard diagnostic criteria for the presence of left ventricular hypertrophy, left bundle branch block, and prior myocardial infarction.

Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring was performed using a Spacelabs 90207 oscillometric monitor (SpaceLabs, Redmond, WA) following a published protocol (18). Blood pressure was recorded every 20 min for a 24-h period with the machine programmed to deflate in 8-mmHg bleed steps. Sleep and wake intervals were defined based on diary entries or from a telephone interview on the morning when monitoring ended. Nocturnal dipping was defined as a ratio of mean sleep to mean awake SBP of 0.80–0.90, inclusive (a decrease in sleep SBP of 10–20% relative to awake SBP). Nondipping was defined as a ratio <0.90 (19). Patients with a nocturnal SBP decrement >20% were excluded because of evidence suggesting that they constitute a subgroup with different pathophysiologic features (20).

Cardiovascular autonomic testing

Cardiovascular autonomic function was tested using the Anscore device (Boston Medical Technologies, Wakefield, MA). The Anscore device records an ECG tracing, relative breath flow, and expiration pressure. Participants were asked to fast for 2 h before the examination and to avoid taking insulin, caffeine, or over-the-counter cold medications. Participants experiencing fever on the day of testing were rescheduled. Other medications known to affect the autonomic nervous system were not withheld. The cardiovascular autonomic assessment comprised three tests.

- Deep breathing test: the expiration-to-inspiration heart rate ratio was determined during a 1-min period in which the participant was instructed to breath at a rate of six breaths per minute. The expiration-to-inspiration heart rate ratio is the average heart rate from expiration to inspiration within each breath cycle.
- Valsalva test: the participant was asked to blow into a mouthpiece with a constant pressure of ~40 mmHg for 15 s. The Valsalva ratio is the ratio of the highest heart rate during (or shortly after) the forced expiration to the lowest heart rate occurring after the maneuver.
- Stand test: consists of active standing from a supine position. The 30:15 ratio is the ratio of the longest R-R interval ~30 s after standing to the shortest R-R interval ~15 s after standing.

The Anscore device has reported coefficients of variation of 4.30, 6.26, and 6.66% for deep breathing, Valsalva, and stand test, respectively, in younger subjects (21).

Test data were transferred by modem to Boston Medical Technologies' remote processing center, where artifacts were removed, heart rates were interpolated from the ECG waveform, and ratios were calculated. For each test, a low ratio indicates poorer cardiovascular autonomic function. An abnormal test result was defined as HRV ratio <5th percentile for age-, sex-, and device-specific range based on normal ranges established using this device in individuals without diabetes (21). American Diabetes Association

diagnostic criteria for cardiovascular autonomic neuropathy require results of two or more of these three tests to be abnormal (22).

We calculated each participant's percentile rank from 0 to 100% on each of the three component tests and a summary measure of HRV as the average of the percentile ranks for the three tests. Of the 160 subjects, 25 did not complete any of the tests, 3 completed one test, 28 completed two tests, and 104 completed all three tests. The 28 subjects who completed one or no tests were excluded from the analysis. For the 28 subjects who completed two of the three tests, the summary score for each of these individuals was estimated using the observed percentile ranks of the two completed tests and coefficients derived from regressions, fitted among the $n = 104$, of the summary score on the percentile rank scores of these same two tests. Chronbach's α for the percentile ranks of the three cardiovascular autonomic tests was 0.72 in the 104 participants who completed all three tests.

Statistical analysis

Two-group comparisons were made using χ^2 or Fisher's exact tests (when any expected cell frequency was <5) for categorical variables and Student's *t* tests or one-way ANOVA for continuous variables. The nonparametric Kruskall-Wallis test was used for highly skewed continuous variables. The 132 subjects were divided into tertiles of the summary measure of HRV. Mean values of other variables were compared across tertiles, using one-way ANOVA or Kruskal-Wallis for continuous variables and χ^2 or Fisher's exact tests for categorical variables. Multivariate stepwise linear regression and logistic regression analyses were performed with the microalbumin-to-creatinine ratio as the dependent variable (log transformed for linear regression and categorized into two groups for logistic regression) and the summary HRV measure and bivariately associated blood pressure measures as the predictors. Potential confounding factors that were bivariately associated ($P < 0.05$) with HRV and/or microalbumin-to-creatinine ratio were included in both multivariate models. Two-tailed *P* values are reported. In additional models, statistical interactions of the summary HRV measure with each of the covariates were tested. Statistical analyses were performed using SPSS statistical software (SPSS, Chicago, IL) and SAS (SAS Institute, Cary, NC).

RESULTS — The 132 subjects who completed at least two of the three components of the cardiovascular autonomic testing did not differ with respect to age, sex, or resting blood pressure from the 28 excluded subjects who completed fewer than two tests. The mean age of these 132 subjects included in the remaining analyses was 70 years; 55% were women, and 77% were Hispanic (Table 1). Mean duration of diabetes was 11.6 years, and 57 subjects (43%) reported taking β-blockers, calcium channel blockers, or both. This group did not differ in demographic characteristics from the 75 subjects who reported taking neither class of drugs but did have a lower ranking on the summary HRV measure.

Lower summary HRV score was associated with higher microalbumin-to-creatinine ratio; a nearly 7:1 ratio existed between the mean microalbumin-to-creatinine ratio in the lowest tertile relative to the highest tertile of HRV ($P < 0.0001$). Given the substantial skew in the distribution of the microalbumin-to-creatinine ratio, this comparison of means may exaggerate the group differences. However, the median of the microalbumin-to-creatinine ratio in the bottom tertile (38.3 mg/g) was ~4.9 times that of the top tertile (7.8 mg/g). Differences across categories of HRV were also found for glycosylated Hb level, HDL cholesterol level, and duration of diabetes but not for resting blood pressure level. Although no statistically significant differences among HRV tertiles were found in the ambulatory blood pressure measures, including presence/absence of nocturnal dipping, the continuous summary HRV score was significantly associated with sleep ambulatory SBP ($r = -0.20$, $P = 0.02$), sleep-to-awake SBP ratio ($r = -0.18$, $P = 0.04$), and dipping status (Student's *t* test, $P = 0.04$). Ambulatory diastolic blood pressure measures were not associated with HRV tertiles or the continuous HRV score.

As shown in Fig. 1, log-transformed urine microalbumin-to-creatinine ratio was inversely correlated with the summary HRV measure. Urine microalbumin-to-creatinine ratio was also associated with mean sleep SBP ($r = 0.37$, $P < 0.0001$) but not with dipping status (Student's *t* test, $P = 0.22$).

Stepwise regression analysis predicting higher log-transformed microalbumin-to-creatinine ratio showed significant associations with the summary HRV score, glycosylated Hb, HDL cholesterol, and resting SBP (Table 2). The coefficient of the summary HRV score decreased by only 2% with the addition of resting SBP to the equation. Similarly, when resting SBP was forced into the equation first, its coefficient decreased by only 2% with the inclusion of the HRV score. This observation, together with the lack of a significant association between HRV score and resting SBP, indicates that HRV and SBP were independently related to the microalbumin-to-creatinine ratio and that neither mediated the relationship of the other with microalbumin-to-creatinine ratio. Because a threshold for microalbumin-to-creatinine ratio of ≥30 mg/g has clinical implications (23), we also performed a logistic regression analysis with urine microalbumin-to-creatinine ratio dichotomized at this value as the dependent variable. The results were substantively the same as in the linear multiple regression model. Tests for interaction showed that the associations of summary HRV score and resting SBP with microalbumin-to-creatinine ratio did not vary with level of age, duration of diabetes, HbA_{1c}, or HDL cholesterol level.

CONCLUSIONS — The main finding of this study is that diminished HRV, as measured by provocative cardiovascular autonomic testing, is associated with microalbuminuria in older patients with type 2 diabetes. This association remained significant after multivariate adjustment for other clinical factors predictive of microalbuminuria. There was no evidence that blood pressure level, as measured at rest or by 24-h ambulatory monitoring, mediated this relationship. We also found an independent relationship of resting blood pressure level to microalbumin-to-creatinine ratio that was not mediated by HRV.

Previous research has explored the relationships between cardiovascular autonomic neuropathy, variables derived from 24-h blood pressure recordings, and microalbuminuria (10). Spallone et al. (10) found that normotensive patients with type 1 diabetes and cardiovascular

Table 1—*Selected characteristics of 132 subjects with type 2 diabetes categorized by tertile of summary HRV measure, Cardiovascular Autonomic Neuropathy Study, New York, 2001–2002*

		Tertiles of summary HRV measure				Continuous	
	Overall	Lowest tertile	Middle tertile	Highest tertile	*P**	*r*	*P*
n	132	44	44	44			
Age (years)	70 ± 5.6	71 ± 5.3	70 ± 5.0	70 ± 6.4	0.51	−0.13	0.13
Sex (men)	60 (45)	21 (48)	22 (50)	17 (39)	0.53	−0.10	0.27
Race/ethnicity							
Hispanic	101 (77)	30 (68)	35 (80)	36 (82)			
Non-Hispanic white	11 (8)	6 (14)	2 (5)	3 (7)	0.49	—	—
African American	20 (15)	8 (18)	7 (16)	5 (11)			
Use of either β-blocker, calcium channel blocker, or both	57 (43)	22 (50)	20 (45)	15 (34)	0.30	−0.17	0.05
Use of ACE inhibitor or angiotensin II receptor blocker	63 (61)	20 (67)	22 (59)	21 (57)	0.70	−0.04	0.69
Microalbumin-to-creatinine ratio	94.8 ± 257.5	191 ± **404**	65.6 ± 137.7	28.2 ± 72.4	**0.0001**	−0.28	**0.001**
Ln microalbumin-to-creatinine ratio	3.12 ± **1.48**	3.85 ± **1.60**	3.19 ± 1.30	2.34 ± 1.11	**0.0001**	−0.44	**0.0001**
Micoalbumin-to-creatinine ratio ≥18	59 (45)	29 (66)	21 (48)	9 (20)	**0.0001**	−0.41	**0.0001**
Micoalbumin-to-creatinine ratio ≥30	47 (36)	24 (55)	17 (39)	6 (14)	**0.0003**	−0.39	**0.0001**
HbA_{1c} (%)	7.8 ± 1.7	8.3 ± 1.7	8.0 ± 1.8	7.3 ± 1.4	**0.02**	−0.20	**<0.05**
Duration of diabetes (years)	11.6 ± 8.9	14.8 ± 10.0	12.4 ± 8.6	7.6 ± 6.3	**0.001**	−0.37	**0.0001**
BMI (kg/m^2)	28.5 ± 5.1	28.5 ± 6.0	28.2 ± 4.4	29.0 ± 4.6	0.78	0.03	0.72
Total cholesterol (mg/dl)	174.9 ± 37.5	168.9 ± 33.5	177.6 ± **40.3**	177.9 ± 38.5	0.46	0.06	0.47
HDL cholesterol (mg/dl)	45.6 ± 12.5	43.0 ± 10.3	43.7 ± 13.4	49.7 ± 12.7	**0.02**	0.19	**<0.05**
LDL cholesterol (mg/dl)	102.4 ± 33.9	99.1 ± 30.5	105.5 ± 33.5	102.4 ± 37.7	0.69	0.01	0.90
Triglycerides (mg/dl)	157.9 ± 86.8	168.3 ± 88.7	171.0 ± 110.2	134.9 ± 46.1	0.10	−0.14	0.12
Smoking							
Ever smoked	73 (55)	26 (59)	24 (55)	23 (52)	0.81	−0.05	0.56
Current smoker	16 (12)	7 (16)	6 (14)	3 (7)	0.40	−0.13	0.12
Left ventricular hypertrophy on ECG	8 (6)	4 (9)	1 (2)	3 (7)	0.44	−0.03	0.70
Left bundle branch block on ECG	10 (8)	5 (11)	3 (7)	2 (5)	0.60	−0.13	0.15
Prior myocardial infarction on ECG	12 (9)	6 (14)	4 (9)	2 (5)	0.39	−0.08	0.34
Office blood pressure							
Resting systolic blood pressure (mmHg)	139.9 ± 21.0	140.8 ± 22.7	138.3 ± 18.2	140.4 ± 22.3	0.84	−0.03	0.76
Resting diastolic blood pressure (mmHg)	72.2 ± 9.5	71.0 ± 9.9	71.8 ± 9.4	73.8 ± 9.1	0.37	0.13	0.15
Ambulatory blood pressure monitoring							
Mean wake SBP (mmHg)	136.7 ± 14.0	138.3 ± 13.5	137.4 ± 15.3	134.5 ± 13.1	0.41	−0.12	0.18
Mean sleep SBP (mmHg)	128.3 ± 16.9	132.4 ± 16.5	127.0 ± 17.3	125.5 ± 16.5	0.13	−0.20	**0.02**
Sleep-to-wake SBP ratio	0.94 ± 0.08	0.96 ± 0.08	0.92 ± 0.07	0.93 ± 0.08	0.11	−0.18	**0.04**
Nondipper	**84 (36)**	33 (75)	26 (59)	25 (57)	0.15	−0.18	**0.04**

Data are *n* (%) or means ± SD. **P* for differences among tertiles. *P* values for age, log-transformed microalbumin-to-creatinine ratio, HbA_{1c}, cholesterol and triglyceride measures, BMI, and continuous blood pressure measures were derived from ANOVA; *P* values for categorical variables were derived from χ^2 or Fisher's exact test. *P* values for the microalbumin-to-creatinine ratio, duration of diabetes, and neuropathy symptom scales were calculated using the nonparametric Kruskal-Wallis test. Data in bold type are significant.

autonomic neuropathy had decreased nocturnal dipping. These investigators proposed that cardiovascular autonomic neuropathy blunts nocturnal blood pressure dipping and that the kidneys are more vulnerable to overall blood pressure burden in the absence of proper neural control of renal blood flow. We found only modest relationships between HRV and sleep-related measures derived from 24-h ambulatory blood pressure monitoring. We did find, however, that HRV was associated with microalbuminuria independent of blood pressure level, suggesting that cardiovascular autonomic impairment may be involved in the pathogenesis of diabetic renal disease through mechanisms independent of blood pressure. The renal vasculature is extensively innervated by the sympathetic nervous system. Our findings are consistent with the hypothesis suggested by others that impairment of autonomic function leads to increased renal blood flow (24), glomerular hyperfiltration, and sodium excretion, all of which accelerate progression to diabetic microalbuminuria (25,26). Alternatively, the metabolic and vascular changes associated with diabetes may adversely affect both renal and cardiovascular autonomic function through other mechanisms.

Consistent with previous studies, we found bivariate associations of age, HbA_{1c}, HDL cholesterol, resting blood pressure, and mean sleep SBP with mi-

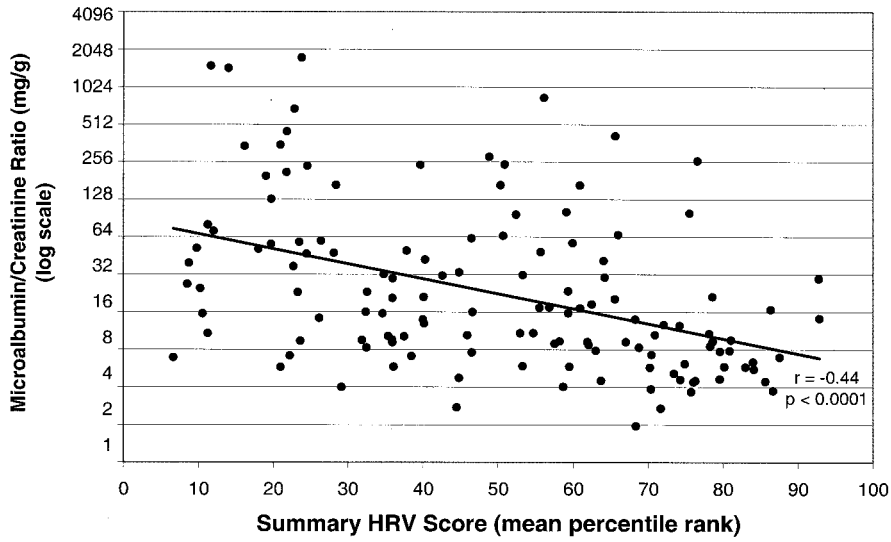

Figure 1—*Bivariate relationship of urine microalbumin-to-creatinine ratio with summary HRV measure.*

croalbuminuria (13,27,28). Previous studies have also found relationships between higher ambulatory blood pressure, especially night blood pressure, and diabetic microalbuminuria (16). Torbjornsdotter et al. (29) obtained 24-h blood pressure recordings and renal biopsy specimens in 41 normoalbuminuric patients with type 1 diabetes and found that nocturnal mean arterial blood pressure correlated directly with early evidence of nephron basement membrane thickening and mesangial matrix hyperplasia. Nielsen et al. (30), in a longitudinal study of 23 patients with type 1 diabetes, found that increases in microalbuminuria were proportionate to increases in systolic and diastolic 24-h blood pressure. Lurbe et al. (16) found that elevated sleep SBP predicted the development of microalbuminuria in normotensive, normoalbuminuric adolescents with type 1 diabetes. Whereas several of these studies measured both ambulatory blood pressure and cardiovascular autonomic neuropathy (10,15), none compared these two factors in a multivariate model with microalbuminuria as the outcome variable. In our study, in multivariate models that included resting blood pressure and HRV, none of the 24-h ambulatory blood pressure measures was significantly related to microalbuminuria. It is possible that age, use of antihypertensive medications, or presence of more advanced comorbidities weakened this association in our sample.

We did not find a significant association between abnormal 24-h blood pressure pattern (loss of nocturnal dipping) and cardiovascular autonomic neuropathy in multivariate analysis adjusting for other variables, including resting SBP (Table 2). It is possible that this negative finding resulted from exclusion of "extreme dippers" (nocturnal SBP >20% less than daytime SBP) or from exclusion of subjects who were unable to complete at least two of the three components of the cardiovascular autonomic testing, if the excluded subjects had a greater degree of autonomic neuropathy than subjects who were able to complete at least two testing components.

Several limitations should be considered in interpreting our findings. Whereas the cardiovascular autonomic tests used in our study are standard (7), these tests may not assess aspects of cardiovascular autonomic function captured by either short-term power spectral analysis or 24-h evaluations of HRV. Another limitation is that few of our subjects (10.6%) had two or more abnormal tests. This prevalence is lower than the 17–22% reported in studies of younger patients (1,2). Therefore, we based our analysis on a composite score based on HRV rankings, rather than the proportions of subjects with abnormal tests, limiting comparability to studies focusing on the numbers of abnormal cardiovascular autonomic tests (6,8,10). Although we did not obtain multiple spot urine samples or a 24-h urine collection to assess microalbuminuria, the random microalbumin-to-creatinine ratio has high reported sensitivity and specificity compared with 24-h urine microalbumin testing (31). Another issue is that patients were sampled for our study based on their 24-h blood pressure pattern (nocturnal dipping versus nondipping), but this seems unlikely to have affected the findings of the multivariate analysis. The number of normotensive subjects was too small to support analysis of whether features of the 24-h blood pressure recording were associated with microalbuminuria in patients with normal range resting blood pressures. Finally, our design is cross sectional and does not provide predictive data.

In conclusion, cardiovascular autonomic neuropathy and higher resting blood pressure are both associated with microalbuminuria in older patients with type 2 diabetes, consistent with the hypothesis that cardiovascular autonomic neuropathy and blood pressure are linked to microalbuminuria by different biological pathways.

Table 2—***Results of multivariate analyses predicting urine microalbumin-to-creatinine ratio in 132 subjects with type 2 diabetes, Cardiovascular Autonomic Neuropathy Study, New York, 2001–2002: Linear regression model results (natural logarithm transformation of urine microalbumin-to-creatinine ratio)***

Covariate	β	SE	*P*
Constant	0.260	1.527	0.86
Age (10 years)	0.029	0.204	0.89
Duration of diabetes (10 years)	0.040	0.131	0.76
HbA_{1c} (%)	0.189	0.065	<0.01
HDL cholesterol (10 mg/dl)	−0.194	0.088	<0.05
Summary HRV measure (10 percentage points)	−0.219	0.050	0.0001
Resting SBP (10 mmHg)	0.222	0.054	0.0001

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