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ORIGINAL ARTICLE

Usefulness of ambulatory blood pressure monitoring in predicting the presence of autonomic neuropathy in type I diabetic patients

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This study investigated whether nondipping (defined as a day–night change in blood pressure (BP) $\leqslant$0%) could be assumed as a diagnostic index for autonomic neuropathy, and assessed its accuracy in discriminating between type I diabetic patients with and without autonomic neuropathy. In 87 type I diabetic patients with normal renal function (age 36$\pm$11, duration 17$\pm$9 years, serum creatinine 67.2$\pm$15.9 μmol/l), four cardiovascular tests and 24-h BP monitoring were performed, and the percentage day–night change (Δ) in systolic (SBP) and diastolic BP (DBP) was calculated. Sixteen patients had ΔSBP and/or ΔDBP $\leqslant$0%. In a multiple logistic regression with adjustment for sex, age, and body mass index, the odds ratio for having autonomic neuropathy was seven times higher in patients with ΔSBP $\leqslant$0% as opposed to those without (odds ratio 6.97, CI 1.4–34.9, $P=0.018$). Using Receiver Operating Characteristic (ROC) analysis, ΔBP showed an acceptable accuracy in discriminating between patients with and without autonomic neuropathy (area under the ROC curve 0.69$\pm$0.06 and 0.72$\pm$0.05 for ΔSBP and ΔDBP, respectively). Adequate cutoff values were 0% for ΔSBP (sensitivity, 26%; specificity, 95%; positive predictive value, 87%) and 5% for ΔDBP (sensitivity, 26%; specificity, 92%; positive predictive value, 81%). In type I diabetic patients with normal renal function, a value of ΔSBP $\leqslant$0% identifies the presence of autonomic neuropathy with a very high chance. Nondipping at the cutoff proposed could be considered an adjunctive marker of autonomic neuropathy provided with a high specificity and low sensitivity.
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Keywords: autonomic neuropathy; type I diabetes; nondipping; blood pressure monitoring; diagnosis

Introduction

Ambulatory blood pressure (BP) monitoring (ABPM) has been gradually gaining acceptance in the routine management of hypertensive patients and is endorsed by the latest guidelines of official bodies.[1–3] Thus, it is commonly performed in diabetic patients,[4] and the prognostic meaning of the reduced nocturnal fall of BP (nondipping) is well known in diabetes.[5]

A blunted or reversed circadian pattern of BP has been increasingly described in diabetic patients and related to autonomic neuropathy[6,7] or to overt nephropathy.[8–12] Although some uncertainty still persists about the whole pathophysiology of the nondipping phenomenon, a series of studies have allowed to show the main pertinence of nondipping to diabetic autonomic neuropathy.[13–18] Notwithstanding, the predictive value of nondipping with regard to the presence of autonomic neuropathy has not been established.

Observation in wide population studies of hypertensive and normotensive subjects has led to some criticism about the 10% threshold dividing dippers and nondippers.[19,20] According to the distribution of the day–night variation in BP in the general population, it has been proposed to lower the cutoff for the definition of nondipping to 0%, that identifies a complete loss of the day–night change in BP and corresponds to the 95th percentile of the distribution in a large international database in normotensive subjects.[20]

Thus, we investigated whether nondipping could be assumed as a diagnostic index for autonomic neuropathy, and assessed its accuracy in discriminating between type I diabetic patients with and without autonomic neuropathy. Moreover, we evaluated the best cutoff of the percentage nocturnal BP fall in identifying patients with autonomic neuropathy.

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Materials and methods

We consecutively recruited 87 type I diabetic patients among outpatients attending the diabetic clinic of the Tor Vergata University, Rome. Inclusion criteria were age under 60 years and diabetes duration more than 5 years, a urinary albumin concentration on three early morning urine collections in the range of normo- or microalbuminuria (0–200 mg/l). Exclusion criteria were macroalbuminuria (urinary albumin concentration >200 mg/l), impaired renal function (serum creatinine >115 μmol/l), haematuria, urinary infection, clinically significant abnormality of hepatic, haemopoietic, respiratory or endocrine function, history and/or evidence of cerebrovascular or coronary heart disease, arrhythmias, use of drugs affecting cardiovascular or autonomic nervous function apart from antihypertensive drugs used by three patients. The study was approved by the Ethics Committee of Tor Vergata University and informed consent was obtained from all participants.

The 87 patients, 40 men, had a mean age of 36 ($\pm$11) years, a diabetes duration of 17 ($\pm$9) years, a body mass index of 24 ($\pm$4) kg/m^2, a fair glycaemic control (HbA1c 7.9$\pm$1.7%, normal range 4.3–5.9%), normal serum creatinine (67.2$\pm$15.9 μmol/l), normal casual BP (119/73$\pm$14/9 mm Hg). Forty patients had retinopathy, 23 microalbuminuria, nine hypertension, but only three were treated with antihypertensive drugs (i.e. ACE inhibitors) at the time of BP measurement, 33 were current smokers.

Neurological assessment

Autonomic function was assessed by four cardiovascular tests, deep breathing, lying to standing, Valsalva manoeuvre, and postural hypotension, which were performed according to standard procedure[21] and evaluated using age-related reference values.[22] An autonomic score was obtained from the sum of scores given to each of the four tests (0 for a normal result, 1 for a borderline result, and 2 for an abnormal result), range 0–8.[22,23] Type I diabetic patients were divided according to the autonomic tests results into two groups with autonomic neuropathy (one or more abnormal tests) and without autonomic neuropathy (less than one abnormal test).

BP monitoring

Non-invasive 24-h ABPM was performed using an oscillometric recorder (SpaceLabs 90207, Redmond, WA, USA) satisfying the validation requirements for ABPM Systems.[24] The device was programmed to measure BP every 20 min for 24 h. Systolic (SBP) and diastolic BP (DBP) measurements were averaged for the day and the night periods, according to the patients' reported time of waking up and going to bed. In addition, the day–night difference (Δ) in SBP and DBP as a percentage of day values was calculated ((day BP$-$night BP)$\times$100/day BP). Patients with a value of 0% or less were considered as nondippers.

Laboratory assessment

In addition to routine laboratory assessment, we measured the 24-h urinary albumin excretion (UAE) by a double-antibody radioimmunoassay (Albumin RIA 100, Pharmacia AB, Uppsala, Sweden) on timed 24-h urine collections.

Presence of non-proliferative or proliferative retinopathy was determined by ophthalmoscopic examination.

Statistical analysis

Data are expressed as means$\pm$s.d. Unpaired Student's *t*-test was used as test of significance for means in the case of variables showing normal distribution, and the χ^2 test was used for categorical variables. Mann–Whitney-*U* test was used for those variables, which did not satisfy the assumption of a normal distribution. Linear regression analysis was used to relate different variables. Logarithmic transformation was applied to UAE (decimal logarithm), a non-parametric variable, before using linear regression analysis. Multiple linear regression analyses were performed to determine the relative contribution of different independent variables to ΔBP, both main clinical parameters and all those variables found to be related in univariate analysis. Multiple logistic regression was used to calculate the odds ratio for having autonomic neuropathy.

All statistical analyses were done using the program StatView IV (SAS Institute Inc., Cary, NC, USA) on a Macintosh iBook G4 computer. A value of $2P<0.05$ was considered significant.

Receiver Operating Characteristic (ROC) analysis has been widely accepted to assess and compare diagnostic validity of tests and has been included in the checklist for reporting on studies of diagnostic accuracy.[25,26] ROC analysis was used to assess the accuracy of the ΔBP in distinguishing between type I diabetic patients with and without autonomic neuropathy, through the measurement of the area under the ROC curve, which incorporates both components of accuracy, that is, sensitivity and specificity, into a single measure.[27] Moreover, we calculated sensitivity, specificity, positive predictive value, negative predictive value, and the likelihood ratio for a positive result for three different cutoff values of ΔBP, selected on the basis of the ROC analysis for predicting autonomic neuropathy (i.e. 0, 5 and 10%). The likelihood ratio for a positive result is the ratio of the chance of a positive result if the patient has the disease to the chance of a positive result if he/she does not have the disease, and is calculated as the ratio of sensitivity to (1$-$specificity). A high likelihood ratio for a positive result suggests that the test provides useful information.[28]

Results

According to cardiovascular tests, 18 patients had early autonomic neuropathy (at least one abnormal test), 32 definite AN (at least two abnormal test results), and 37 had normal tests.

The averaged values of day (122.3/77.1±13.4/7.9 mm Hg), night (113.5/66.7±14.5/9.3 mm Hg), and 24-h SBP and DBP (119.0/72.9±13.1/7.9 mm Hg), were all within the standards for normal BP monitoring (day ⩽135/85, night ⩽120/79, 24-h ⩽130/80 mm Hg).[2] The averaged day–night difference was 7.2±7.5% for SBP and 13.5±8.8% for DBP.

Figure 1 displays as a dot-plot the distribution of the individual values of day–night difference in SBP and DBP according to the presence or absence of autonomic neuropathy. Nondipping for SBP was present in 15 patients (17.2%), nondipping for DBP in nine patients (10.3%), and nondipping for combined SBP and DBP in eight patients (9.2%). Finally, 16 patients (18.4%) were nondippers for SBP and/or DBP. All nondippers had autonomic neuropathy with the exception of two out of the 15 systolic nondippers and two out of the nine diastolic nondippers. When choosing the most widely used cutoff value for systolic nondipping (i.e. 10%), nondipping for SBP was present in 54 patients (62%), 35 with and 15 without AN, respectively (χ^2 test, $P=0.12$).

Compared to dippers, nondippers for SBP and/or DBP had a greater prevalence of retinopathy, microalbuminuria, autonomic neuropathy, and hypertension, and higher values of 24-h UAE, and of autonomic score, with a high degree of significance for this latter parameter, whereas no differences were present in the other ones including casual BP (Table 1). Thus, nondipping proved to be associated with all diabetic complications.

However, in a multiple regression analysis including as independent variables the parameters found to be associated with nondipping or related in univariate regression to nocturnal fall in BP, that is age (vs ΔDBP: $r=-0.22$, $P=0.04$), retinopathy, microalbuminuria, hypertension, 24-h UAE (log) (vs ΔSBP and ΔDBP: $r=-0.25$, $P=0.03$), serum creatinine levels (vs ΔSBP and ΔDBP: $r=-0.24$, $P=0.03$), and autonomic score (vs ΔSBP and ΔDBP: $r=-0.46$, $P<0.0001$), the only variables still related to nocturnal BP fall were autonomic score for SBP, age, hypertension, and autonomic score for DBP (Table 2). Thus, autonomic neuropathy remained the only determinant of day–night change in SBP and the main determinant of day–night change in DBP.

At this point, to ascertain the diagnostic value of nondipping for the diagnosis of autonomic neuropathy, we started by considering whether nondipping was predictive for autonomic neuropathy. In a multiple logistic regression after adjustment for the clinical correlates known to affect nocturnal BP fall in the general population,[20] that is sex, age, and body mass index, the odds ratio for having autonomic neuropathy was seven times higher in

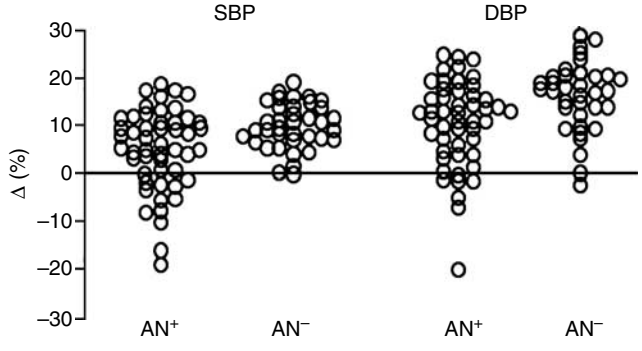

Figure 1 Distribution of the individual values of the day–night difference (Δ) in SBP and DBP according to the presence (AN^+) or absence of autonomic neuropathy (AN^-).

Table 1 Clinical parameters of dippers and nondippers

Type 1 patients	*Dippers*	*Nondippers*
n	71	16
Sex (M:F)	33:38	7:9
Age (years)	35.6±10.9	40.7±11.0
Duration (years)	16.7±10.1	18.1±6.1
BMI (kg/m^2)	24.4±3.5	23.6±3.9
HbA1c (%)	7.9±1.7	8.2±1.8
Creatinine (mmol/l)	66.3±17.7	71.6±17.7
LDL cholesterol (mg/dl)	105.9±33.6	101.7±31.7
With retinopathy (%)	40	75*
With microalbuminuria (%)	21	50*
24-h UAE (μg/min)	5.8 (1–185)	32 (2–200)**
With AN (%)	52	81*
Autonomic score	1.2±1.8	3.9±2.3***
With hypertension (%)	7	25*
Casual SBP (mm Hg)	118.9±13.9	119.8±13.6
Casual DBP (mm Hg)	73.0±9.1	74.9±8.5
Smokers (%)	37	44

Abbreviations: *n*, number; AN, autonomic neuropathy; BMI, body mass index; LDL, low-density lipoprotein; UAE, urinary albumin excretion.
Data are mean±s.d. or median (range).
*$P<0.05$ χ^2 test; **$P=0.01$ Mann–Whitney-*U* test; ***$P<0.0001$ Student's *t*-test.

Table 2 Multivariate regression analysis for ΔSBP and ΔDBP as dependent variables

	ΔSBP	*ΔDBP*
	$r^2=32\%$, F=*4.9*	$r^2=37\%$, F=*6.1*
Independent variables	*P*-value	*P*-value
Age (years)	0.142	**0.034**
Retinopathy (yes 1)	0.866	0.804
Microalbuminuria (yes 1)	0.461	0.509
Hypertension (yes 1)	0.194	**0.042**
Creatinine (mg/dl)	0.383	0.435
24-h UAE (log)	0.868	0.957
Autonomic score	**0.004**	**0.009**

Abbreviations: UAE, urinary albumin excretion.
Bold indicates significant *P*-values.

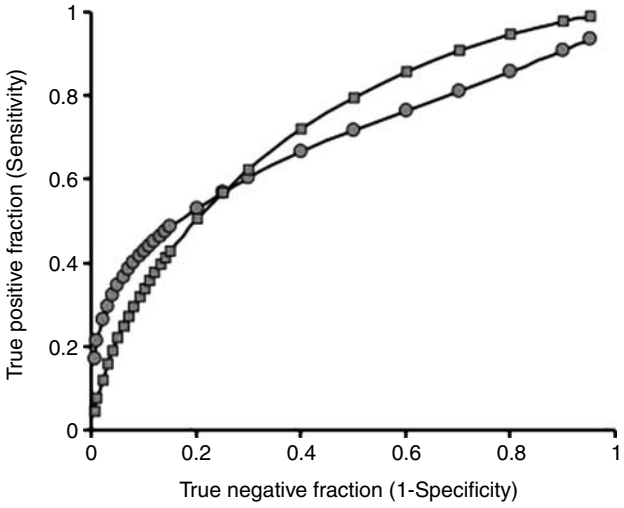

Figure 2 ROC curves for ΔSBP (●) and ΔDBP (■). Plots of all sensitivity/specificity pairs over the entire range of observation of ΔSBP and ΔDBP are represented. The *x* axis is the false-positive fraction (1−specificity) of the group without AN, and the *y* axis the true positive fraction (sensitivity) in the group with AN. The areas under the curves were 0.69 (95% CI 0.57–0.79) and 0.73 (95% CI 0.61–0.82) for ΔSBP and ΔDBP, respectively.

systolic nondippers as opposed to systolic dippers (odds ratio 6.97, 95% CI 1.4–34.9, $P=0.018$).

Moreover, using ROC analysis we evaluated the diagnostic accuracy of day–night difference in BP. Figure 2 represents plots of all sensitivity/specificity pairs over the entire range of observation of ΔSBP and ΔDBP. ROC analysis showed an acceptable accuracy of ΔBP in differentiating between patients with and without autonomic neuropathy. In fact, the areas under the ROC curves were 0.69 and 0.73 for ΔSBP and ΔDBP, respectively.

Then, we calculated sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio for positive result, for three different cutoff values of ΔSBP and ΔDBP, selected on the basis of the ROC analysis for predicting autonomic neuropathy, that is 0, 5, and 10% (Table 3). The best cutoff values seemed to be 0% for ΔSBP (sensitivity, 26%; specificity, 95%) and 5% for ΔDBP (sensitivity, 26%; specificity, 92%), in that they showed the best likelihood ratio, 5.2 and 3.3, respectively, whereas the cutoff of 10% had a very low specificity. A likelihood ratio of 5.2 indicates that the test is useful, in that a positive value, ΔSBP $\leqslant$0%, is more than five times as likely to occur in a patient with autonomic neuropathy as opposed to one without.

Discussion

In these non-proteinuric type I diabetic patients with normal kidney function, autonomic neuropathy still proved to be the most powerful determinant of nocturnal BP fall, confirming previous reports.[14,18] A lot of evidence has been gathered that

Table 3 Diagnostic characteristics of different cutoff values for ΔBP

Cutoffs of ΔBP	*Sensitivity (%)*	*Specificity (%)*	*PPV (%) (CI)*	*NPV (%) (CI)*	*LR*
ΔSBP 0%	26	95	87 (70–104)	49 (37–60)	5.2
ΔSBP 5%	42	86	81 (66–96)	52 (39–64)	3
ΔSBP 10%	70	51	66 (48–84)	56 (43–68)	1.4
ΔDBP 0%	14	95	78 (51–104)	45 (34–56)	2.8
ΔDBP 5%	26	92	81 (62–100)	48 (36–59)	3.3
ΔDBP 10%	40	78	71 (54–88)	49 (36–62)	1.8

Abbreviations: CI, confidence intervals; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

points to a strong link between nondipping phenomenon and autonomic neuropathy, even with a suggestion of a pathogenetic meaning,[13,15–17,29] though some uncertainty still exists about all the pathogenetic mechanisms involved. Nevertheless, recently in 61 type I diabetic subjects, Stella *et al.*[30] did not find any independent relationship between autonomic neuropathy and nondipping and suggested again a primary link between nondipping and diabetic nephropathy regardless of autonomic neuropathy but modified by low-density lipoprotein cholesterol and hypertension. However, in that study, the inclusion of a number of patients with overt nephropathy or end-stage renal disease, and of 20 patients undergoing antihypertensive treatment, and also the choice of a cutoff value of 10% for defining nondipping, partially accounts for the lack of evidence of a direct link between nondipping and autonomic neuropathy. Although the present study was not designed to assess the relationship between autonomic neuropathy and nondipping, it does support the view of a keen association between autonomic neuropathy and circadian BP behaviour in type I diabetes.

The aim of this study was instead to ascertain the potential utility of nondipping as a diagnostic tool for autonomic neuropathy. Until now, no data have ever been provided on this specific aspect. In this study, systolic nondipping, defined as a percentage day–night difference in SBP $\leqslant$0%, represented a strong predictor for autonomic neuropathy with an odds ratio of 7. Moreover, using ROC analysis, day–night difference in BP showed an acceptable diagnostic accuracy in distinguishing between patients with and without autonomic neuropathy, with areas under the ROC curves of 0.69 and 0.73, for day–night difference in SBP and DBP, respectively.

Finally, the best diagnostic cutoff values were 0% for ΔSBP (sensitivity, 26%; specificity, 95%) and 5% for ΔDBP (sensitivity, 26%; specificity, 92%), in that they had the highest values of likelihood ratio, 5.2 and 3.3, respectively. Thus, a nocturnal fall in BP $\leqslant$0% for SBP or $\leqslant$5% for DBP indicate with a high chance the presence of autonomic neuropathy. Moreover, this study shows that the cutoff value still widely used for defining nondipping

(i.e. 10%)[31] has specificity which is too low to be acceptable in identifying patients with autonomic neuropathy. The cutoff values of day–night difference in BP that we found to be more appropriate for identifying patients with autonomic neuropathy, approximate to the 95th percentile of the distribution of day–night variation in BP in a large international database in normotensive subjects.[20] Moreover, Hansen *et al.*[32] found that in 137 normoalbuminuric normotensive adult type I diabetic patients, the 95th percentile level of the day–night difference in SBP and DBP were 3 and 6%, respectively, which as values are rather similar to those identified by us as appropriate diagnostic cutoff points for autonomic neuropathy (i.e. 0 and 5%).

We preferred a cutoff value with low sensitivity and high specificity because ABPM for obvious reasons cannot be proposed as a screening test for autonomic neuropathy. Instead, if an ABPM revealed a low nocturnal fall in BP, we need to know which value of day–night difference in BP is more predictive for autonomic neuropathy. In this case, we prefer specificity to sensitivity.

Similar data of sensitivity and specificity for the diagnosis of diabetic autonomic neuropathy have been reported for QTc interval in a wide meta-analysis of 17 studies involving 4584 diabetic patients. The pooled sensitivity and specificity for autonomic neuropathy of QTc $>441\pm8$ ms were 28 and 86%, respectively.[33] Thus, it could be argued that it is much easier and less expensive to obtain the same predictive information on autonomic neuropathy by performing QTc assessment rather than ABPM. In actual fact, the present study should not lead to the promotion of an indiscriminate resorting to ABPM in order to screen for autonomic neuropathy, also because it shows that nondipping is an insensitive marker of autonomic neuropathy. Moreover, there are defined recommendations to perform ABPM, as stated by official bodies.[2,34] However, given the rather widespread use of ABPM in the general and diabetic population[4] and conversely the still limited application of routine diagnosis of diabetic autonomic neuropathy,[35] it is helpful to know that nondipping status suggests a high probability of the presence of autonomic neuropathy. Thus, a nondipper diabetic patient should be considered at high risk of autonomic neuropathy and should undergo, by way of confirmation, a standard diagnostic approach with cardiovascular tests and an intensive therapeutic strategy, aimed at providing good glycaemic control, correcting cardiovascular risk factors, and guaranteeing good BP control for the whole 24-h period.[36]

In conclusion, nondipping can be considered an additional marker of autonomic neuropathy, with high specificity and low sensitivity features, and the day–night difference in BP at the cutoff values proposed, can be accepted as a diagnostic tool for autonomic neuropathy, in that it is provided with enough usefulness, as proved by the high likelihood ratio, and enough accuracy, as indicated by the area under the ROC curve. Thus, it can be used legitimately to diagnose autonomic neuropathy. In addition to the practical value of ABPM in providing useful information in managing patients' BP, assessment of day–night change of BP can be introduced as an accurate diagnostic tool for autonomic neuropathy, which despite not being sensitive is highly specific.

Part of the study was presented at the 41st Annual Meeting of the European Association for the Study of Diabetes, Athens, Greece, 10–15 September 2005 and published as an abstract form (Diabetologia 48 (Suppl 1): A361, 2005).

What is known about topic
- Ambulatory BP monitoring is widely used in diabetic patients.
- Diabetic autonomic neuropathy is the major determinant of nondipping in diabetic patients.
- The predictive value of nondipping with regard to the presence of autonomic neuropathy in diabetes has not been established so far.

What this study adds
- Day–night difference in BP at the cutoff values of 0% for SBP and 5% for DBP is an accurate diagnostic tool for autonomic neuropathy in type I diabetic patients, highly specific albeit not sensitive.
- A nondipper type I diabetic patient should be considered at high risk of autonomic neuropathy and deserves intensive therapeutic strategy.
- Ambulatory BP monitoring is a useful tool in identifying a diabetic complication burdened by adverse prognostic value.

Abbreviations: BP, blood pressure; DBP, diastolic BP; SBP, systolic BP.

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