A Novel Association Between Nondipping and Painful Diabetic Polyneuropathy

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**OBJECTIVE**
We hypothesized the meaningful coexistence of neuropathic pain and nondipping in painful diabetic polyneuropathy (PDPN).

**RESEARCH DESIGN AND METHODS**
In 113 patients with PDPN, with painless diabetic polyneuropathy (DPN+) and without DPN (DPN⁻), neuropathic pain, sleep, risk for obstructive sleep apnea (OSA), autonomic function, and blood pressure (BP) circadian pattern were assessed using the Douleur Neuropathique en 4 Questions (DN4), the Medical Outcomes Study Sleep Scale, the Berlin Questionnaire, cardiovascular reflex tests, and ambulatory BP monitoring.

**RESULTS**
Patients with PDPN showed higher nighttime systolic BP (130.4 ± 15.6 mmHg) than both DPN⁻ (119.9 ± 10.6 mmHg; *P* < 0.0001) and DPN⁺ patients (124.2 ± 12.3 mmHg; *P* < 0.05), and lower day–night difference (∆) in systolic BP (5.5 ± 6.5 vs. 8.6 ± 7.7%; *P* < 0.05) and diastolic BP than DPN⁻ patients. In a stepwise regression analysis, orthostatic hypotension, high risk for OSA, and PDPN (DN4 interview) were independent determinants of ∆ in systolic BP (*r* = 0.46; *P* = 0.0001), ∆ in diastolic BP, and nighttime systolic BP.

**CONCLUSIONS**
PDPN is associated with higher nocturnal systolic BP and impaired BP circadian pattern independent of pain-related comorbidities, suggesting a condition of high cardiovascular risk.

Sleep problems are common in painful diabetic polyneuropathy (PDPN) (1) and contribute to the effect of pain on quality of life. Nondipping (the absence of the nocturnal decrease in blood pressure [BP]) is a recognized feature of diabetic cardiac autonomic neuropathy (CAN) and is attributed to the abnormal prevalence of nocturnal sympathetic activity (2). Both sleep problems and nondipping are burdened with a negative prognostic value (2–4).

This study aimed to evaluate the relationship of the circadian pattern of BP with both neuropathic pain and pain-related sleep problems in PDPN, without ignoring the role of possible confounders such as obstructive sleep apnea (OSA) (4). We hypothesized the meaningful coexistence of neuropathic pain and nondipping in PDPN.

**RESEARCH DESIGN AND METHODS**
We selected 113 patients with diabetes after excluding neuropathies or pain unrelated to diabetic polyneuropathy (DPN) and severe comorbidities (Supplementary Information).

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RESULTS

Patients with PDPN (n = 34) comprised a higher proportion of women and shorter duration of diabetes than patients with DPN (DPN⁺; n = 33); a smaller percentage of physically active people and higher BMI and systolic BP than those without DPN (DPN⁻; n = 46). Patients with PDPN had higher scores in neuropathic symptoms and signs than DPN⁻ patients but similar CARTs results (Supplementary Table 1).

Patients with PDPN achieved worse scores for MOS-SS items than both other groups (Supplementary Fig. 2 and Supplementary Table 2). In a stepwise regression analysis, the DN4 interview (P = 0.0004) and high risk for OSA (P < 0.0001) were independent determinants of SPI-9. Patients with PDPN showed higher nighttime systolic BP (130.4 ± 15.6 mmHg) than both DPN⁻ (119.9 ± 10.6 mmHg; P < 0.0001) and DPN⁺ patients (124.2 ± 12.3 mmHg; P < 0.05), as well as lower Δ in systolic BP (5.5 ± 6.5% vs. 8.6 ± 7.7%; P < 0.05) and diastolic BP (10.8 ± 8.1% vs. 14.2 ± 6.7%; P < 0.05) than the DPN⁻ group, whereas no differences in any ABPM results between DPN⁺ and DPN⁻ patients were found (Supplementary Fig. 3 and Supplementary Table 2).

Nondipping status, present in 8 patients (7%), was associated with PDPN (χ² = 7.22; P = 0.007), more so than with DPN (χ² = 4.35; P = 0.037), and a higher autonomic score (3.00 ± 3.16 vs. 1.30 ± 1.84; P = 0.020).

High risk for OSA was present in 44 patients and associated with higher nighttime systolic BP (P = 0.0032) and lower Δ in systolic BP (P = 0.0116) and diastolic BP (P = 0.0351). In the subgroup assessed for depression, no association between depression and ABPM measures was found.

In a stepwise regression analysis, orthostatic hypotension, high risk for OSA, and DN4 interview were independent determinants of Δ in systolic BP (Table 1). The subgroup assessed for depression gave the same results when including Beck Depression Inventory II score instead of SPI-9 in the model. Using a model similar to that used for Δ in systolic BP, 24-h BP, high risk for OSA, PDPN, and orthostatic hypotension were independent determinants of nighttime systolic BP (Table 1). Similarly, when including diastolic instead of systolic BP, the analysis confirmed DN4 interview and orthostatic hypotension as independent determinants of Δ in diastolic BP (data not shown).

CONCLUSIONS

Investigating the relationship between PDPN and BP circadian pattern, we found patients with PDPN exhibited impaired nocturnal decrease in BP compared with those without neuropathy, as well as higher nocturnal systolic BP than both those without DPN and with painless DPN. Although the Δ in BP between PDPN and DPN⁻ groups failed to reach statistical significance (P = 0.090),
nondipping (Δ ≤ 0%) was more strictly associated with PDPN than DPN; in multivariate analysis including comorbidities and most potential confounders, neuropathic pain was an independent determinant of Δ in BP and nocturnal systolic BP.

As previously shown (2), in this study nondipping also was associated with CAN, and orthostatic hypotension was the major determinant of Δ in systolic BP and an independent determinant of nighttime systolic BP. Therefore, PDPN could behave as a marker for the presence and severity of CAN. However, no differences in single CARTs or autonomic score between patients with PDPN and DPN were found, confirming our previous observation (13). Furthermore, the relationship of BP circadian pattern with PDPN was independent of orthostatic hypotension. Nevertheless, since we did not measure baroreflex sensitivity or heart rate variability (6), we cannot exclude greater autonomic dysfunction in patients with PDPN, which is detectable only through more sensitive tests, as recently observed (14).

Sleep polysomnographic alterations have been associated with nondipping and higher nocturnal BP (15). Thus, neuropathic pain might affect the BP circadian pattern through its effects on sleep, which was clearly documented in our study where DN4 interview was a major determinant of SPI-9. However, according to multivariate analyses, the relation of PDPN with Δ in BP and nocturnal BP was independent from sleep problems.

Evidence suggests a relationship between OSA and both hypertension and attenuated decrease in BP at night (4). In our study, high risk for OSA was associated with a smaller nocturnal decrease in BP. However, in multivariate analysis, there emerged an independent role for both risk for OSA and neuropathic pain in determining Δ in BP and nocturnal systolic BP.

In our study patients with PDPN were proportionally less active than DPN patients. However, dippers were not more active than non-dippers (27% vs. 11%; P = 0.782), and although physical activity was included in multivariate analysis, the independent role of neuropathic pain was confirmed.

The limitations of our study include 1) the lack of polysomnography and nerve conduction studies to confirm the diagnosis of OSA and DPN, respectively; 2) no objective measurements of physical activity using actigraphy; 3) assessment of depression in only a subgroup and no measure of anxiety at all; and 4) the difference of some clinical and neurological variables between the PDPN, DPN, and DPN- groups, although all variables were included as potential confounders in multivariate analyses. Conversely, our study’s strengths are 1) accurate PDPN diagnosis and 2) consideration of most possible confounders in the relationship between pain and BP.

In conclusion, the novel association of PDPN with higher nocturnal systolic BP and nondipping is independent from pain-related sleep problems and diabetes-related comorbidities such as CAN and OSA. Neuropathic pain might affect circadian BP pattern by worsening a pre-existing sympathovagal imbalance and through other unknown mechanisms. The prognostic burden of nondipping and higher nocturnal BP (4) heightens that of other pain comorbidities such as sleep disturbance (3). Thus, PDPN should increasingly be regarded as a condition of high cardiovascular risk.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. C.D.A. designed the study; researched, extracted, and analyzed data, and wrote the manuscript. R.M. designed the study, researched data, and reviewed the manuscript. F.D.G. researched and analyzed data. C.G. researched data. G.A.M. researched data, contributed to the discussion, and reviewed the manuscript. V.S. designed and conducted the study, researched and analyzed data, and wrote the manuscript. V.S. is the guarantor of this work and, as such, had full access to all 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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References