Nocturnal Blood Pressure Is Associated With Cerebral Small-Vessel Disease in Type 1 Diabetes

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Although vascular complications are a hallmark of diabetes, cerebral small-vessel disease (cSVD) in type 1 diabetes remains scarcely studied. We recently showed that cSVD is more common in individuals with type 1 diabetes than healthy control subjects and is associated with systolic office blood pressure (BP) (1). Hence, we aimed to further evaluate the impact of BP on cSVD in type 1 diabetes.

This substudy of the Finnish Diabetic Nephropathy (FinnDiane) Study aims to assess early markers of cerebrovascular disease in people with type 1 diabetes and has previously been described in detail (1). Of the 191 neurologically asymptomatic study participants, 73 volunteered for a 24-h ambulatory BP monitoring (ABPM). All participants underwent a clinical study visit, and brain MRI assessed for markers of cSVD (white matter hyperintensities, lacunar infarcts, and cerebral microbleeds) (1,2).

The 24-h ABPM was conducted in accordance with current standards (3). After ABPM-quality validation, we calculated average BP, mean arterial pressure (two-thirds of diastolic + one-third of systolic BP), pulse pressure (PP) (systolic − diastolic BP), BP variability (average real variability), and nocturnal dipping ([1 − nocturnal systolic / diurnal systolic BP] × 100%). Elevated BP and masked hypertension were defined as described by the European Society of Hypertension (3).

We observed cSVD in 20 (27.4%) participants, of whom 14 had cerebral microbleeds, 9 white matter hyperintensities, and 2 lacunes. Table 1 includes clinical characteristics as well as main results for BP measurements based on presence or absence of cSVD. In addition, participants with cSVD more often had nocturnal hypertension (12 [60.0%] vs. 16 [32.0%], $P = 0.031$) that was independently associated with cSVD (odds ratio 4.09 [95% CI 1.27–13.2], $P = 0.019$) after adjustment for age, antihypertensive medication, and ABPM quality. The same was true for masked hypertension (10 [50.0%] vs. 12 [25.0%], $P = 0.030$, and odds ratio 3.74 [95% CI 1.17–12.0], $P = 0.020$). No association was seen for elevated office BP, diurnal BP, or 24-h BP (data not shown).

Our findings were more prominent in participants on antihypertensive therapy, among whom participants with cSVD had higher systolic BP (median 127 mmHg [interquartile range 119–132] vs. 113 mmHg [108–117], $P = 0.001$), higher diastolic BP (75 mmHg [70–78] vs. 67 mmHg [64–73], $P = 0.021$), and a higher prevalence of nocturnal and masked hypertension (7 [78.5%] vs. 7 [35.0%], $P = 0.033$, and 6 [75.0%] vs. 5 [23.8%], $P = 0.028$, respectively). In participants without antihypertensive medication, BP did not differ between those with or without cSVD.

This study indicates a link between nocturnal BP and asymptomatic microvascular disease of the brain in type 1 diabetes. As novel findings, we show that higher nocturnal systolic and diastolic BP and mean arterial pressure, as well as

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Table 1—Comparison of individuals with versus without cSVD

	Small-vessel disease	No small-vessel disease	*P**
n	20	53	
Male, *n* (%)	10 (50.0)	30 (56.6)	0.613†
Age, years	42.2 (39.3–46.2)	39.6 (33.4–45.2)	0.113†
Diabetes duration, years	20.9 (19.2–32.1)	21.2 (19.9–23.9)	0.748†
Diabetes manifestation age, years	19.9 (10.7–24.1)	15.5 (11.0–22.8)	0.638†
HbA_{1c}, % [mmol/mol]	8.2 (7.5–8.7) [66 (59–72)]	8.0 (7.4–8.7) [64 (57–72)]	0.647†
eGFR, mL/min/1.73 m^2	106 (95–115)	111 (104–117)	0.122†
BMI, kg/m^2	26.6 (24.6–28.5)	27.1 (24.7–30.4)	0.421†
Current smoker, *n* (%)	0 (0.0)	1 (1.9)	>0.999†
Microvascular complications, *n* (%)	4 (20.0)	11 (20.8)	>0.999†
Macrovascular complications, *n* (%)	0 (0.0)	0 (0.0)	—
Total cholesterol, mmol/L	4.1 (3.7–4.8)	4.4 (4.0–5.0)	0.104†
LDL cholesterol, mmol/L	2.1 (1.4–2.6)	2.3 (2.1–3.0)	0.067†
HDL cholesterol, mmol/L	1.5 (1.3–1.9)	1.5 (1.2–1.8)	0.603†
Triglycerides, mmol/L	0.9 (0.7–1.5)	0.9 (0.7–1.3)	0.946†
Lipid-lowering medication, *n* (%)	6 (30.0)	12 (22.6)	0.551†
Antithrombotic medication, *n* (%)	2 (10.0)	4 (7.5)	0.528†
Antihypertensive medication, *n* (%)	8 (40.0)	21 (39.6)	0.792‡
Office SBP, mmHg	133 (124–139)	130 (123–142)	0.270
Office DBP, mmHg	79 (83–75)	81 (74–85)	0.503
Office pulse, bpm	69 ± 12	69 ± 12	0.778
24-h SBP, mmHg	127 (124–135)	122 (118–129)	0.078
Diurnal SBP, mmHg	130 (127–140)	127 (122–132)	0.173
Nocturnal SBP, mmHg	117 (111–124)	110 (107–116)	0.010
24-h DBP, mmHg	79 (76–86)	79 (76–83)	0.356
Diurnal DBP, mmHg	82 (79–89)	82 (79–87)	0.648
Nocturnal DBP, mmHg	72 (68–76)	67 (64–72)	0.009
Nocturnal dip, %	11 (6–15)	13 (9–17)	0.050
24-h pulse, bpm	73 (68–82)	72 (66–79)	0.509
Diurnal pulse, bpm	76 (70–86)	75 (70–84)	0.552
Nocturnal pulse, bpm	63 (58–68)	62 (56–68)	0.658
24-h MAP, mmHg	95 (90–101)	94 (90–98)	0.416
Diurnal MAP, mmHg	97 (93–104)	97 (93–102)	0.852
Nocturnal MAP, mmHg	86 (83–92)	81 (78–86)	0.006
24-h PP, mmHg	47 (44–52)	44 (41–48)	0.074
Diurnal PP, mmHg	47 (45–53)	44 (41–48)	0.091
Nocturnal PP, mmHg	45 (41–49)	44 (40–47)	0.176
24-h SBP ARV, mmHg	10 ± 3	10 ± 3	0.604
24-h DBP ARV, mmHg	8 (7–9)	7 (6–9)	0.351

Data are mean ± SD or median (interquartile range) unless otherwise indicated. Microvascular complications: albuminuria or retinal photocoagulation. Antithrombotic medication: aspirin or warfarin. Estimated glomerular filtration rate (eGFR): Chronic Kidney Disease Epidemiology Collaboration formula. ARV, average real variability; DBP, diastolic BP; MAP, mean arterial pressure; SBP, systolic BP. *Adjusted for age, antihypertensive medication, and ABPM quality. †Unadjusted *P*. ‡Adjusted for age and quality only.

nocturnal and masked hypertension, are associated with cSVD in type 1 diabetes. To this date, this is the only existing study on ABPM and brain MRI in type 1 diabetes.

In healthy elderly people, an association between increased ABPM and cSVD has previously been observed (4). In accordance with our results, this study showed an association between higher nocturnal BP and cSVD and, furthermore, that elevated diurnal and 24-h BP were associated with cSVD. These discrepancies could be due to the difference in age, BP levels, or use of antihypertensive medication between the study cohorts. Nocturnal BP is, however, recognized as a stronger predictor of cardiovascular events than diurnal BP (3). Our results indicate that elevated nocturnal BP is associated with early markers of cerebrovascular disease.

We observed no association between cSVD and PP, a marker of arterial stiffness. In type 1 diabetes, arterial stiffness has been associated with cerebral white matter hyperintensities, a marker of cSVD (5). In our younger cohort, white matter hyperintensities were too infrequent for any further subanalyses. The

different manifestations of cSVD (2) could potentially have different pathophysiology and, thus, also differ in their association with BP.

We observed more prominent findings in individuals on antihypertensive medication. No association was, however, found between cSVD and antihypertensive medication—as opposed to earlier observations (4). This may indicate that a higher nocturnal BP is a marker of a preexisting generalized circulatory dysregulation, or it may be due to taking BP-lowering medication during daytime.

The study limitations include the lack of power to detect more subtle differences between the groups and the cross-sectional design that limits the interpretation of causality. Nonetheless, the strengths of our study are the well-characterized study population and the detailed evaluation of both BP and cSVD.

Our findings show that cSVD in type 1 diabetes is associated with nocturnal BP and masked hypertension. Whether the link is causal or simply reflects vasculopathy and/or BP dysregulation needs further investigation.

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References

1. Thorn LM, Shams S, Gordin D, et al.; FinnDiane Study Group. Clinical and MRI features of cerebral small-vessel disease in type 1 diabetes. Diabetes Care 2019;42:327–330

2. Wardlaw JM, Smith EE, Biessels GJ, et al.; STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013;12:822–838

3. O'Brien E, Parati G, Stergiou G, et al.; European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension position paper on ambulatory blood pressure monitoring. J Hypertens 2013; 31:1731–1768

4. Avet J, Pichot V, Barthélémy JC, et al. Leukoaraiosis and ambulatory blood pressure load in a healthy elderly cohort study: the PROOF study. Int J Cardiol 2014;172:59–63

5. van Elderen SGC, Brandts A, Westenberg JJM, et al. Aortic stiffness is associated with cardiac function and cerebral small vessel disease in patients with type 1 diabetes mellitus: assessment by magnetic resonance imaging. Eur Radiol 2010;20:1132–1138