Blood pressure variability and white matter hyperintensities after ischemic stroke

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ABSTRACT

Background: High blood pressure variability (BPV) may be a risk factor for stroke and dementia in patients with ischemic stroke, but the underlying mechanism is unknown. We aimed to investigate whether high BPV is associated with presence and progression of white matter hyperintensities (WMH).
Methods: We performed a post-hoc analysis on the MRI substudy of the PRoFESS trial, including 771 patients with ischemic stroke who underwent MRI at baseline and after a median of 2.1 years. WMH were rated with a semi-quantitative scale. Visit-to-visit BPV was expressed as the coefficient of variation (interval 3–6 months, median number of visits 7). The association of BPV with WMH burden and progression was assessed with linear and logistic regression analyses adjusted for confounders.
Results: BPV was associated with burden of periventricular WMH (β 0.36 95%CI 0.19–0.53, per one SD increase in BPV) and subcortical (log-transformed) WMH (β 0.25, 95%CI 0.08–0.42). BPV was not associated with periventricular (OR 1.09, 95%CI 0.94–1.27) and subcortical WMH progression (OR 1.15, 95%CI 0.99–1.35). Associations were independent of mean BP.
Conclusion: High visit-to-visit BPV was associated with both subcortical and periventricular WMH burden in patients with ischemic stroke, but not with WMH progression in this study.

1. Introduction

Blood pressure variability (BPV) is associated with an increased risk of stroke and dementia beyond mean blood pressure (BP) values [1,2]. The exact mechanism underlying this association is unknown. A possible explanation is that high BPV contributes to development and progression of white matter hyperintensities (WMH) [3], which is a known risk factor for cognitive decline and dementia [4]. Antihypertensive treatment limits progression of WMH [5]. Previous studies have investigated BPV and WMH in the general population [3,6], but few have specifically addressed patients with recent ischemic stroke. If indeed BPV increases WMH progression, this has implications for BPV monitoring and choice of antihypertensive treatment that minimizes BPV. We aimed to investigate the association of BPV with burden and progression of WMH in patients with ischemic stroke.

2. Methods

We performed a post-hoc analysis on the MRI substudy of the Prevention Regimen for Effectively avoiding Second Strokes (PRoFESS) trial [7,8]. The PRoFESS trial randomized patients with non-cardioembolic ischemic stroke to telmisartan or placebo. Additional antihypertensive medication was given at the discretion of the treating physician. The MRI substudy included 771 patients who underwent MRI at baseline and study close-out. Patients were followed-up at regular intervals after one, three and six months, and every six months thereafter. BP was measured at each visit in a standardized manner. BPV was defined as the systolic coefficient of variation (CV, standard deviation (SD)/mean*100). Presence, severity and location of WMH were rated independently by two neuro-radiologists with use of a semi-quantitative scale (Supplementary Methods), blinded to clinical data [9]. For this study, the outcome of interest was burden of periventricular and subcortical WMH at follow-up, and progression of WMH between baseline and follow-up, defined as at least 0.5 point increase in periventricular WMH score, or any increase in subcortical WMH volume between baseline and follow-up in milliliters. All patients provided written informed consent prior to inclusion in the PRoFESS trial and MRI substudy.

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Table 1

Association between BPV and WMH.

	Periventricular WMH burden	Subcortical log(WMH) burden	Periventricular WMH progression	Subcortical WMH progression
CV, per standard deviation	0.36 (0.19–0.53)	0.25 (0.08–0.42)	1.09 (0.94–1.27)	1.15 (0.99–1.35)
Quintiles of CV				
Q1	Ref	Ref	Ref	Ref
Q2	0.17 (−0.36–0.69)	−0.06 (−0.59–0.46)	0.85 (0.53–1.35)	1.11 (0.70–1.78)
Q3	0.21 (−0.32–0.73)	0.57 (0.04–1.09)	1.05 (0.66–1.67)	1.10 (0.68–1.76)
Q4	0.83 (0.30–1.36)	0.53 (0.01–1.06)	1.22 (0.76–1.95)	1.35 (0.84–2.17)
Q5	0.72 (0.19–1.25)	0.51 (−0.02–1.03)	0.99 (0.62–1.57)	1.43 (0.88–2.32)

CV coefficient of variation; Q quintile; Ref reference; WMH white matter hyperintensities. Results are presented for the adjusted model (adjusted for age, sex, diabetes, smoking, mean systolic BP (SBP) and antihypertensive drug use at baseline, the models on WMH progression are also adjusted for baseline WMH).
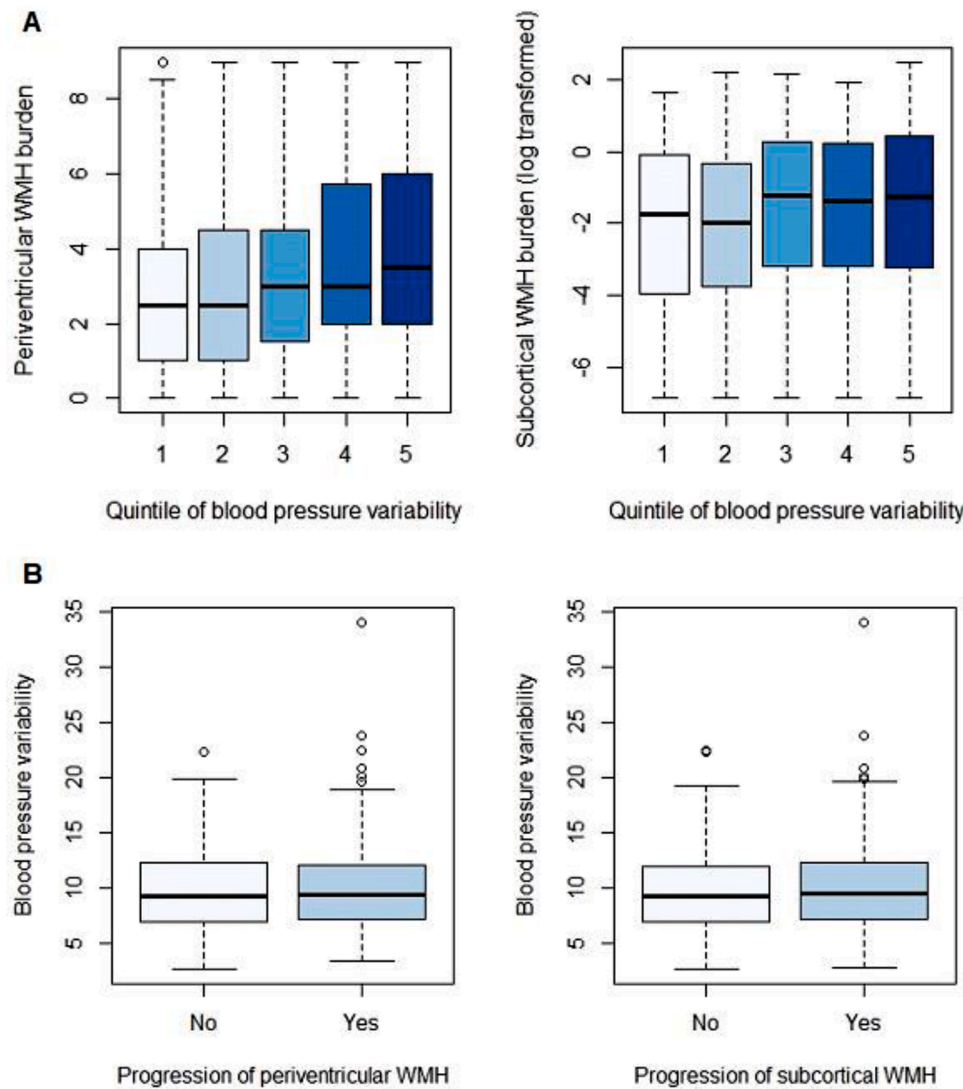
Fig. 1. Association of BPV with WMH burden (A) and progression (B).

2.1. Statistical analysis

We analyzed the data as a single cohort, because treatment with telmisartan did not influence progression of WMH [7]. Subcortical WMH volume was log-transformed to obtain a normal distribution. We performed linear regression analysis to study the association of BPV with burden of subcortical and periventricular WMH, and logistic regression to investigate the association of BPV with WMH progression. The first model was unadjusted, whereas in the second model we adjusted for

age, sex, diabetes, smoking, mean systolic BP (SBP) and antihypertensive drug use at baseline. The model for WMH progression was additionally adjusted for WMH burden at baseline. Results are presented per SD increase in BPV. Next, we studied the association between BPV in quintiles and WMH to explore non-linear associations. We performed subgroup analyses stratified for median SBP at baseline, antihypertensive medication use, etiology of index stroke (small vessel occlusion versus other) and median WMH load at baseline. Last we performed a sensitivity analysis after exclusion of eight patients with cardio-embolic

stroke. Analyses were performed with R version 4.1.1.

3. Results

771 patients were included in the study. Mean age was 65 years, 64% were male (Supplementary Table 1). The median number of BP measurements was 7 (range 4–11). During a median follow-up of 2.1 years (range 1.1–4.1), 52% of patients had progression of periventricular WMH (395 of 758 patients, missing in 13) and 56% (429 of 771 patients) had progression of subcortical WMH.

Higher BPV was associated with a higher periventricular WMH score at follow-up (β 0.36; 95% confidence interval (CI) 0.19–0.53, per SD increase in BPV, Table 1). The burden of periventricular WMH was significantly higher among patients in the highest two quintiles of BPV (Table 1). This association was independent of mean SBP. Similarly, high BPV was associated with a larger volume of subcortical WMH at follow-up (β 0.25; 0.08–0.42 for logWMH volume per SD increase in BPV). Patients in the second and third quintile of BPV had a significantly higher volume of periventricular WMH compared to patients in the lowest BPV quintile (Table 1, Fig. 1A). Analyses based on tertiles or quartiles showed similar results.

There was no association between BPV and progression of periventricular (OR 1.09; 0.94–1.27) or subcortical WMH (OR 1.15; 0.99–1.35, Table 1, Fig. 1B).

Subgroup analyses suggest that the association between BPV and periventricular WMH may be stronger for patients with small vessel disease compared to other stroke subtypes, although the interaction did not reach statistical significance (p = 0.08). Subgroup analyses according to WMH burden, SBP and antihypertensive drug use did not show any differences (Supplementary Table 2, 3). Results were essentially similar after exclusion of eight patients with cardio-embolic strokes, although the association of the second and third quintile with subcortical WMH was no longer statistically significant (Supplementary Table 4).

4. Discussion

Higher visit-to-visit BPV is associated with a higher burden of periventricular and subcortical WMH in patients with ischemic stroke at follow-up, but not with WMH progression in our study.

Our findings add to the knowledge from two systematic reviews and meta-analyses in the general population, showing that high BPV is associated with an increased burden of WMH [3,6]. WMH may be a mediator linking BPV to stroke and dementia. It has been suggested that large fluctuations expose the vessels to chronic stress, specifically in the presence of arterial stiffness or atherosclerosis [10]. This may subsequently lead to chronic hypoperfusion and impaired blood-brain barrier function, resulting in WMH. Interestingly, the effect of BPV on WMH tended to be stronger in patients with stroke due to small vessel disease, suggesting that patients with vascular damage of deep perforating vessels are more vulnerable to BP fluctuations.

The lack of an association between BPV and WMH progression in our study suggests that the effect of BPV on WMH burden is (at least partly) explained by baseline WMH volume. This provides some argument against the hypothesis that BPV is on the causal pathway to WMH, or may imply that BPV is the consequence of WMH rather than the cause (e. g. reverse causality). It is hypothesized that impaired autonomic function caused by cerebrovascular damage may lead to large blood pressure variation [6,11,12]. However, we cannot exclude that the lack of an association between BPV and WMH progression in our study is explained by the use of a visual rating scale for WMH, which is less accurate to detect progression over time. Furthermore, the time interval between baseline and follow-up imaging was relatively short to detect changes. Last, defining progression as binary endpoint instead of on a continuous scale may also have reduced power to detect an association. Previous studies on BPV and WMH progression in ischemic stroke

patients have shown conflicting results [13–15]. Studies that did find an association assessed short-term BPV and applied home-based instead of office-based BP measurements [14,15], suggesting that timing and method of BP measurement matters.

A strength of our study is the large sample size and the rating of MRI scans by two experienced neuro-radiologists. Limitations include the relatively short follow-up and the use of a semi-quantitative rating scale. Also, the study is conducted in a population of trial participants. The population was relatively young, mostly had mild stokes and almost two-thirds of the patients were Asian, all of which may limit the generalizability of the findings.

In conclusion, high BPV is associated with a higher burden of WMH but not with WMH progression in patients with ischemic stroke in this study. These results suggest that BPV may be a marker of cerebrovascular damage, but it remains uncertain whether BPV is causal to WMH. Future studies with long-term follow-up and automatic segmentation of WMH are needed to definitively establish the association between BPV and WMH progression.

Disclosures

None

CRediT authorship contribution statement

Nina A Hilkens: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing – original draft. **Frank-Erik de Leeuw:** Supervision, Writing – review & editing. **Catharina JM Klijn:** Supervision, Writing – review & editing. **Edo Richard:** Conceptualization, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cccb.2024.100205.

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