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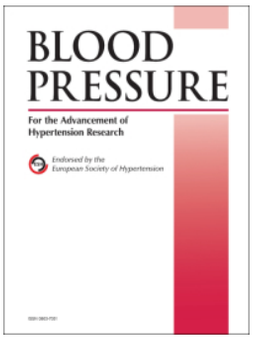

Blood Pressure

ISSN: 0803-7051 (Print) 1651-1999 (Online) Journal homepage: www.tandfonline.com/journals/iblo20

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To cite this article: Theresa J. van Lith, Esther Janssen, Jan-Willem van Dalen, Hao Li, Mats Koeneman, Wouter M. Sluis, Naomi T. Wijers, Marieke J. H. Wermer, Menno V. Huisman, H. Bart van der Worp, Frederick J. A. Meijer, Anil M. Tuladhar, Sebastian J. H. Bredie & Frank-Erik de Leeuw (2025) Higher blood pressure variability during hospitalisation is associated with lower cerebral white matter integrity in COVID-19 patients, Blood Pressure, 34:1, 2493828, DOI: 10.1080/08037051.2025.2493828

To link to this article: https://doi.org/10.1080/08037051.2025.2493828

BLOOD PRESSURE
2025, VOL. 34, NO. 1, 2493828
https://doi.org/10.1080/08037051.2025.2493828

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RESEARCH ARTICLE

Higher blood pressure variability during hospitalisation is associated with lower cerebral white matter integrity in COVID-19 patients

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ABSTRACT

Background: High blood pressure variability (BPV) is associated with cerebrovascular damage and dementia, but it is unknown whether short-term BPV during hospitalisation is also associated with cerebral white matter (WM) damage. We examined whether BPV, measured in-hospital using continuous monitoring, is associated with WM microstructural integrity in COVID-19 patients.

Methods: We included hospitalised COVID-19 patients from the CORONavirus and Ischemic Stroke (CORONIS) study who underwent continuous vital signs monitoring using a wearable device during hospital admission and had an MRI shortly after discharge. Systolic BPV was calculated as Average Real Variability (ARV) and Coefficient of Variation (CV) with 1-, 5- and 20-minute intervals. We used diffusion tensor imaging to assess fractional anisotropy (FA) and peak width of skeletonised mean diffusivity (PSMD) as markers of WM integrity. Associations between BPV and WM integrity were examined with linear regression adjusted for age, mean systolic blood pressure (BP), number of BP measurements and type of respiratory support.

Results: We included 47 COVID-19 patients (mean age: 59.6 years). BP was measured 6306 ± 4343 times per patient (median admission: 11 days (Interquartile Range [IQR] 7.5–15.0). Both higher ARV and CV were associated with lower WM microstructural integrity, reflected by lower FA (ARV: $\beta = -0.40$, $p = .010$; CV: $\beta = -0.33$, $p = 0.026$) and higher PSMD (CV: $\beta = 0.28$, $p = .038$) after adjustment for confounders. Correction for WM hyperintensities did not change these results.

Conclusions: High BPV during hospitalisation is associated with lower WM integrity in COVID-19 patients, although causality needs to be demonstrated. Our findings need validation in hospitalised patients without COVID-19 to examine generalisability.

PLAIN LANGUAGE SUMMARY

- Hypertension is very common in older individuals and is a risk factor for strokes and dementia. BP fluctuates over time rather than remaining constant. This is called BP variability.
- Earlier research has revealed that higher BP variability is linked to an increased risk of dementia, strokes, cardiovascular events and even death. Significant BP swings are likely harmful to the brain. When patients are hospitalised, their BP often becomes more unstable, but whether this instability can harm the brain is unclear. This study explored whether large BP variations during hospital stays are connected to brain damage.
- To investigate this, we measured BP continuously in COVID-19 patients in the hospital with a wearable monitoring system on the arm. Afterwards, we conducted MRI scans to examine the integrity of the brain.
- Our results indicate that patients with greater BP variability exhibit lower brain integrity after hospitalisation.
- This implies that BP fluctuations can indeed harm the brain.

ARTICLE HISTORY

Received 21 February 2025
Revised 9 April 2025
Accepted 10 April 2025

KEYWORDS

Blood pressure variability; magnetic resonance imaging; diffusion-weighted imaging; COVID-19; cerebral small vessel disease

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/08037051.2025.2493828.

- However, based on these results, it is not possible to determine whether BP variability causes brain damage or results from it. Additional research is needed to establish the chronological order of this association.
- If BP variability may indeed damage the brain, we should focus more on maintaining stable BP levels in hospitalised patients.

Introduction

Hypertension is a major risk factor for cardiovascular disease and dementia [1]. Accumulating evidence suggests that large fluctuations in blood pressure (BP), often referred to as blood pressure variability (BPV), increase the risk of cardiovascular disease, dementia and ischaemic stroke independent of mean BP, indicating the susceptibility of the brain to BP fluctuations [2–6]. Several systematic reviews have linked BPV with MRI markers of cerebral small vessel disease (SVD) such as white matter hyperintensities (WMH), but also with lower white matter (WM) integrity assessed with diffusion tensor imaging (DTI) [7–9]. Areas of WM with reduced microstructural integrity are shown to converse into WMH, which are associated with worse (cognitive and functional) outcomes [10]. Additionally, lower WM integrity after COVID-19 infection has been reported, which is possibly associated with worse outcomes, but the association with BPV remains unknown [11]. Investigation of this relationship can provide insights into the aetiology of adverse outcomes or help with therapeutic strategies for both the general population and those affected by COVID-19.

BPV includes short-term (during 24 h, including beat-to-beat, minute-to-minute, hour-to-hour and circadian rhythm), mid-term (multiple days) and long-term (weeks, months or years) variability with different underlying mechanisms and clinical consequences [6]. Previous studies mainly investigated relationships between WM integrity and BPV measured over months or years. The clinical applicability of this approach is limited, since data measured over several years is often not available. The emergence of devices that can reliably measure BPV continuously has facilitated the assessment of (short-term) BPV over prolonged durations, both in clinical settings and at home, offering great promise for monitoring and management of BP and BPV [12].

BPV assessment during hospital admission has emerged as a valuable tool. A recent study in over 80.000 hospitalised patients showed that high BPV during hospital admission is linked to increased risk of dementia within two years [13]. In hospitalised stroke and COVID-19 patients, BPV was associated with in-hospital mortality and intensive care unit (ICU) admission [14,15]. How increased BPV during hospitalisation affects the brain and if this is clinically relevant, especially in COVID-19 patients, remains unclear. Therefore, our objective was to investigate whether high short-term BPV, measured using continuous monitoring during hospitalisation in patients with COVID-19 was associated with lower microstructural integrity of the brain while also assessing the reproducibility of these results using BPV data from only the initial 24 h.

Methods

Study design

This study was part of the CORONavirus and Ischemic Stroke (CORONIS) study, a multicentre, prospective observational study investigating MRI markers of cerebrovascular disease and long-term clinical outcomes in patients hospitalised with COVID-19. A detailed study protocol has been published previously [16]. The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study on 01-04-2021 (NL75780.091.20). All patients provided written informed consent.

Study population and procedures

In the CORONIS study, adult patients hospitalised between April 2021 and September 2022 in one of three centres in the Netherlands because of laboratory-confirmed SARS-CoV-2 infection were included. Exclusion criteria comprised: MRI and contrast contraindications, pregnancy, limited life expectancy (<3 months), major disease interfering with study participation or follow-up or inability to provide informed consent. For the current analysis, we only included participants from the Radboudumc hospital ($n = 73$) who wore a non-invasive wearable vital sign monitoring system (ViSi Mobile) during hospital admission and underwent multi-shell MRI diffusion weighted imaging (DWI), which was not performed in the other participating centres. Patients with clinically overt stroke were excluded from this analysis. Demographic and lifestyle information, education, medical history and data regarding hospital

admission were collected at the initial assessment as reported previously [16].

Blood pressure (variability) monitoring and assessment

BP was continuously monitored on the general ward using an FDA-cleared non-invasive wearable vital signs monitoring system (ViSi Mobile, Sotera Wireless LTD, San Diego, CA) of which the validity has been described previously [17]. BP was measured cuffless by a pulseoxy sensor with calibration using an upper arm cuff two times a day. Pseudonymized data were retrieved from the research storage (Sotera's Amazon Web server) for analysis. BP readings that were considered potentially non-physiologic (systolic BP > 300 or <40 mmHg) were excluded. ViSiMobile was not available in the ICU, so in case of ICU admission during hospitalisation, BP data was only used until transfer to the ICU for better comparison of data. To ensure accuracy, we excluded 3 min before and after VisiMobile calibration from the BPV calculations.

Two indices of BPV were calculated: Coefficient of Variation (CV) and the Average Real Variability (ARV), to examine consistency of results independent of BPV metric since there is currently no consensus on the most reliable metric to use. We used the following formulas to calculate these measures:

$$\mathrm{CV} = \left(\frac{\mathrm{SD}}{\mathrm{mean}}\right) \times 100$$

$$\mathrm{ARV} = \frac{\sum \left|\mathrm{BP}_{k+1} - \mathrm{BP}_{k}\right|}{n}$$

where n is the number of valid BP measurements and k is the order of measurements. Both measures were calculated across various time intervals to examine the robustness of this measure in continuous data. First, they were calculated using minute-to-minute BP measurements. Additionally, calculations were performed for 5-minute intervals, considering values only at the first and last minutes within each 5-minute span, for example, 12:00, 12:05, 12:10 and so on. Similarly, analyses were conducted for 20-minute intervals, including readings at the 1st and 20th minutes (i.e. 12:00, 12:20, 12:40 and so on).

MRI protocol

Brain MRI scans were conducted during hospital stay or shortly after discharge (<3 months after positive PCR-test). The imaging details have been described previously [16]. MR images were acquired on a 3T MRI (Siemens, Prisma), using the following scan protocol: 3D T1 weighted (T1W) space fatsat (0.9 ms isotropic voxel size, repetition time (TR) = 700 ms, Echo Time (TE) = 9 mm); 3D fluid-attenuated inversion recovery (FLAIR) (1 mm isotropic voxel size, TR = 500 ms, TE = 394 ms); multi-shell DWI (80 diffusion-weighted directions [$40\times b=1000$ and $40\times b=2000$s/mm^2], $6\times b=0$ images, 2.0 mm isotropic voxels, TR = 4600 ms, TE = 80 ms).

MRI processing and outcomes

We pre-processed diffusion MRI data starting with denoising and Gibbs artefacts. Additionally, we corrected for head motion, eddy currents-induced distortion, susceptibility-induced distortion (top-up) and intensity bias using the MRtrix 3.0 software, Functional Magnetic Resonance Imaging of the Brain Software Library (FSL) software and Advanced Normalisation Tools [18–20]. Top-up was conducted based on synthesised b0 image from the T1 image using Synb0-DISCO, since no reversed phase-encoding b0 DWI image was available [21]. We calculated two DTI metrics with the pre-processed diffusion data (only $b=0$ and 1000 volumes): (1) mean diffusivity (MD) and (2) fractional anisotropy (FA). Tract-Based Spatial Statistics (TBSS) pipeline within FSL was employed to create a WM skeleton representing the centres of all tracts shared across the population [20,22,23]. Next, MD was projected into the WM skeleton using the 'tbss_non_FA' function within TBSS tool of FSL, resulting in aligned maps of MD. Next, this WM skeleton was used to extract the mean MD/FA values, representing the global average WM microstructural abnormalities for each participant. In addition, we calculated Peak width of Skeletonised Mean Diffusivity (PSMD) values using the PSMD tool (http://www.psmd-marker.com/) [24]. For segmentation and calculation of WMH volumes, we used the automated k-nearest neighbours algorithm (UBO Detector) using bias-corrected T1 and FLAIR images [25]. The segmentations were visually reviewed for errors and artefacts. We did not adjust for intracranial volume, since the UBO detector calculated WMH volumes in SPM's DARTEL space.

Statistical analysis

Baseline characteristics are presented as numbers and proportions (%) and continuous measurements are reported as mean (SD) or median (IQR), based on whether they were normally distributed. To assess

whether the three intervals (1/5/20 min) measures consistently represent BPV or if they differ significantly across different intervals, we examined the intercorrelations among the BPV metrics using correlation coefficients. Univariable and multivariable linear regression was used to analyse the relationship between BPV measures and continuous MRI diffusion outcomes (FA, MD, PSMD). Multivariable models were adjusted for baseline age, mean systolic BP during hospitalisation, number of BP measurements and type of ventilation. Type of ventilation was categorised into three categories thought to reflect the severity of COVID-19: (1) non-invasive respiratory support (nasal cannula or non-rebreathing mask), (2) non-invasive ventilation (Optiflow) and (3) invasive ventilation (intubation). Non-invasive ventilation was also available on the general COVID ward instead of ICU only. Several sensitivity analyses were conducted. First, we calculated CV and ARV (over 1/5/20 min intervals) only including the BP measurements conducted in the first 24 h after admission to examine if BP measurements of a shorter period are also sufficient to assess effects of BPV. Second, we used multivariable linear regression with additional adjustment for WMH volume to correct for pre-existing MRI markers of SVD. Third, we examined effect modification of WMH volume and pre-existing hypertension using interaction terms. Missing data was not imputed. We considered two-sided *p*-values less than .05 statistically significant. Data were analysed with R version 4.3.1.

Results

We included 47 COVID-19 patients with a mean age of 59.6 years (SD 12.9) (Table 1) of whom 16 (34.0%) were female (Figure 1). Patients were hospitalised with COVID-19 infection for 11 days [median, IQR 7.5–15.0]. During this hospitalisation, BP was measured on average 6306 times (SD 4343). Fourteen participants (30%) were admitted to the ICU. Median time between positive SARS-CoV-2 PCR test and baseline MRI was 39 days [IQR 27.0, 51.0]. In Supplementary figure 1, correlations between CV and ARV measured over different intervals are shown. CV measured over 1, 5 or 20 min are very highly correlated ($r > 0.98$). ARV1 and 5 are strongly correlated ($r = 0.97$), but correlate less strong with ARV20 ($r = 0.75/r = 0.78$). CV and ARV are only moderately correlated (correlation coefficients between 0.35 and 0.43).

Table 1. Baseline characteristics.

	Patients
n, (%)	47 (100.0)
Age in years, mean (SD)	59.6 (12.9)
Women, *n* (%)	16 (34.0)
Education, *n* (%)	7 (14.9)
Low (≤low-level secondary education)	26 (55.3)
Middle (average-level secondary education	14 (29.8)
High (≥high level secondary education/university)	
Duration of hospital admission in days, median [IQR]	11.0 [7.50, 15.0]
Time between admission and baseline MRI, median [IQR]	32.0 [21.5, 42.5]
Highest required respiratory/ventilation therapy during admission, *n* (%)	24 (51.1)
Nasal cannula, oxygen mask, non-rebreathing mask	15 (31.9)
Non-invasive ventilation (Optiflow)	8 (17.0)
Invasive ventilation (intubation)	
ICU admission, *n* (%)	14 (29.8)
Cardiovascular risk factors	
Hypertension, *n* (%)	19 (40.4)
BMI in kg/m^2, mean (SD)	28.50 (4.34)
Hyperlipidemia, *n* (%)	20 (42.6)
Diabetes mellitus, *n* (%)	9 (19.1)
(Previous) smoker, *n* (%)	27 (57.4)
Pulmonary diseases (COPD/asthma), *n* (%)	21 (44.7)
Antihypertensive medication during admission, *n* (%)	19 (40.4)
Type of antihypertensive medication used during admission (multiple options are possible per patient), *n* (%)	
ACE-I	12 (25.5)
ARB	4 (8.5)
β-blocker	13(27.7)
CCB	14 (29.8)
Diuretic	8 (17.0)
Blood pressure metrics	
Days of continuous blood pressure monitoring, median [IQR]	6 [4–10]
Systolic blood pressure during hospitalisation (mmHg), mean (SD)	125.12 (13.6)
ARV 1-minute interval, mean (SD)	2.53 (0.90)
ARV 5-minutes interval, mean (SD)	5.04 (1.67)
RV 20-minutes interval, mean (SD)	7.34 (2.26)
CV 1-minute interval, mean (SD)	11.7 (2.8)
CV 5-minutes interval, mean (SD)	11.8 (2.8)
CV 20-minutes interval, mean (SD)	11.9 (2.9)
WMH volume mm^3, median [IQR]	1.337 [0.845–3.733]

ARB, angiotensin receptor blocker; ACE-I, angiotensin-coverting enzyme inhibitor; CCB, calcium channel blocker; BMI, body mass index; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; ARV, average real variability; CV, coefficient of variation; WMH, white matter hyperintensities; N/A, not applicable.

Association BPV and DTI outcomes

All measures of BPV were associated with lower FA in both univariable and multivariable models, as shown in Table 2. Only ARV20 was associated with higher MD after adjusting for confounders (Table 2). All measures of CV were associated with higher PMSD after adjusting for confounders, while no significant association between ARV and PSMD was observed (Table 2).

Sensitivity analyses

BPV in the first 24 h. There was no significant association between BPV in the first 24 h of hospitalisation and FA or PSMD. While there was a positive association between 24H BPV and MD in the univariable analyses this association was no longer present after adjusting for confounders, as shown in Table 3.

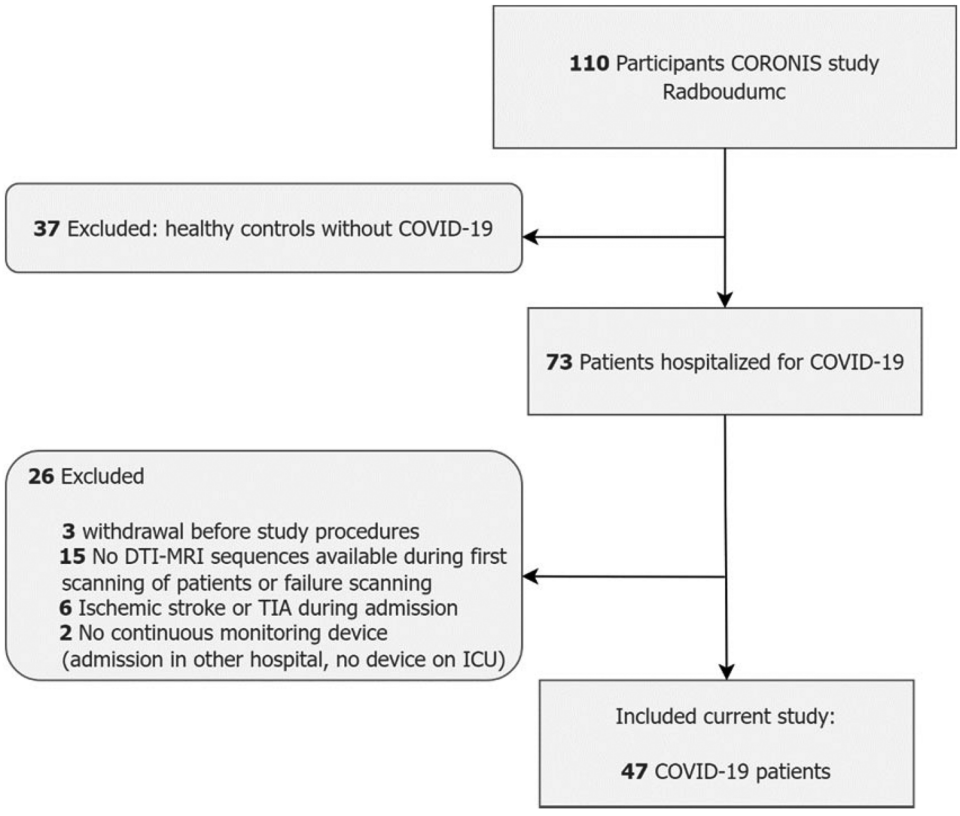

Figure 1. Flowchart of participant inclusion.

Table 2. Association of BPV metrics during hospital stay with white matter microstructural integrity metrics.

	Fractional anisotropy (FA)			
BPV metrics	Unadjusted Standardised β [95% CI]	*p*	Adjusted[a] standardised β [95% CI]	*p*
ARV1	−0.32 [−0.60 – −0.03]	**.029**	−0.40 [−0.70 – −0.10]	**.010**
ARV5	−0.39 [−0.67 – −0.12]	**.006**	−0.44 [−0.73 – −0.15]	**.004**
ARV20	−0.42 [−0.69 – −0.15]	**.003**	−0.47 [−0.75 – −0.19]	**.002**
CV1	−0.38 [−0.66 – −0.11]	**.008**	−0.33 [−0.61 – −0.04]	**.026**
CV5	−0.41 [−0.69 – −0.14]	**.004**	−0.36 [−0.64 – −0.08]	**.014**
CV20	−0.43 [−0.70 – −0.16]	**.003**	−0.38 [−0.67 – −0.10]	**.008**
	Mean diffusivity (MD)			
BPV metrics	Unadjusted Standardised β [95% CI]	*p*	Adjusted[a] Standardised β [95% CI]	*p*
ARV1	0.32 [0.03 – 0.60]	**.033**	0.23 [−0.06 – 0.53]	.122
ARV5	0.38 [0.10 – 0.66]	**.009**	0.26 [−0.03 – 0.55]	.074
ARV20	0.41 [0.14 – 0.69	**.004**	0.31 [0.02 – 0.59]	**.034**
CV1	0.17 [−0.13 – 0.46]	.256	0.14 [−0.14 – 0.42]	.315
CV5	0.20 [−0.09 – 0.49]	.179	0.17 [−0.11 – 0.45]	.224
CV20	0.22 [−0.07 – 0.51]	.137	0.20 [−0.08 – 0.48]	.152
	Peak width of skeletonised mean diffusivity (PSMD)			
BPV metrics	Unadjusted Standardised β [95% CI]	*p*	Adjusted[a] Standardised β [95% CI]	*p*
ARV1	0.20 [−0.10 – 0.49]	.187	0.12 [−0.19 – 0.42]	.447
ARV5	0.24 [−0.05 – 0.53]	.104	0.12 [−0.18 – 0.42]	.424
ARV20	0.26 [−0.03 – 0.55]	.078	0.15 [−0.14 – 0.45]	.296
CV1	0.36 [0.09 – 0.64]	**.012**	0.28 [0.02 – 0.55]	**.038**
CV5	0.39 [0.11 – 0.66]	**.007**	0.31 [0.04 – 0.58]	**.024**
CV20	0.41 [0.14 – 0.69]	**.004**	0.35 [0.09 – 0.61]	**.011**

[a]Adjusted for age, mean systolic BP, number of BP measurements and respiratory support. P-values < 0.05 are written in bold.

BPV and WMH volume. To examine if the association between BPV and DTI outcomes was independent of brain macrostructural changes, we performed an additional analysis adjusting for WMH volume. Results are shown in Table 4. Associations between all measures of BPV and FA are significant after additional adjustment for WMH volume. ARV1/5/20 was associated with higher MD, while ARV1 and CV1/5/20 was associated

Table 3. Association of BPV metrics first 24 h stay with white matter microstructural integrity.

BPV metrics	Unadjusted Standardised β [95% CI]	p	Adjusted[a] Standardised β [95% CI]	p
		Fractional anisotropy (FA)		
ARV1	−0.23 [−0.52 – 0.06]	.120	−0.19 [−0.64 – 0.14]	.250
ARV5	−0.26 [−0.55 – 0.03]	.073	−0.18 [−0.52 – 0.15]	.276
ARV20	−0.23 [−0.52 – 0.06]	.117	−0.18 [−0.52 – 0.16]	.287
CV1	−0.25 [−0.54 – 0.04]	.086	−0.19 [−0.52 – 0.14]	.248
CV5	−0.25 [−0.54 – 0.04]	.085	−0.18 [−0.52 – 0.15]	.277
CV20	−0.28 [−0.57 – 0.01]	.054	−0.20 [−0.54 – 0.13]	.220
		Mean diffusivity (MD)		
BPV metrics	Unadjusted Standardised β [95% CI]	p	Adjusted[a] Standardised β [95% CI]	p
ARV1	0.31 [0.03 – 0.60]	**.033**	0.10 [−0.21 – 0.42]	.516
ARV5	0.37 [0.09 – 0.65]	**.010**	0.15 [−0.16 – 0.47]	.339
ARV20	0.38 [0.10 – 0.66]	**.009**	0.18 [−0.14 – 0.50]	.261
CV1	0.31 [0.03 – 0.60]	**.032**	0.16 [−0.15 – 0.46]	.311
CV5	0.32 [0.03 – 0.60]	**.030**	0.15 [−0.16 – 0.46]	.331
CV20	0.34 [0.06 – 0.63]	**.018**	0.19 [−0.12 – 0.50]	.228
		Peak width of skeletonised mean diffusivity (PSMD)		
BPV metrics	Unadjusted Standardised β [95% CI]	p	Adjusted[a] Standardised β [95% CI]	p
ARV1	0.26 [−0.03 – 0.55]	.079	0.09 [−0.22 – 0.41]	.556
ARV5	0.28 [−0.01 – 0.57]	.057	0.06 [−0.26 – 0.38]	.702
ARV20	0.32 [0.04 – 0.61]	**.026**	0.17 [−0.14 – 0.49]	.236
CV1	0.23 [−0.06 – 0.52]	.116	0.06 [−0.25 – 0.38]	.676
CV5	0.25 [−0.05 – 0.54]	.096	0.07 [−0.24 – 0.39]	.654
CV20	0.28 [−0.01 – 0.57]	.056	0.11 [−0.20 – 0.42]	.483

[a]Adjusted for age, mean systolic BP, number of BP measurements and respiratory support. P-values < 0.05 are written in bold.

with higher PSMD after adjustment for WMH (Table 4).

The interaction term for BPV and WMH was not significant in any models assessing BPV measures and FA or MD as outcome (Supplementary Table 1). However, there was a significant interaction between BPV*WMH volume in models assessing CV and PSMD, indicating that the association between CV and PSMD is stronger with greater WMH volumes. The BPV*hypertension interaction term is only significant in the model assessing association between CV20 and PSMD (Supplementary Table 2). No other significant differences in the relationship between BPV and WM integrity were observed between individuals with and without hypertension.

Discussion

In this study, we showed that high BPV measured with continuous BP monitoring was associated with lower WM microstructural integrity (i.e. lower FA and higher PSMD) in hospitalised COVID-19 patients, independent of WMH. Our findings indicate that both CV and ARV as measurements of BPV are associated with WM damage. In the population-based Rotterdam Study, higher visit-to-visit BPV was significantly associated with lower FA and higher MD in the whole WM, while others have found lower FA only in the hippocampus and not in the whole WM [9,26]. We expand these findings by demonstrating that short-term BPV measured during hospitalisation because of COVID-19 is also associated with worse WM integrity.

BPV was associated with lower FA and higher PSMD, but not with MD. While FA quantifies the degree of anisotropy or directionality of water diffusion, known to be higher in organised WM pathways, MD is a measure of diffusion in each direction [27]. It is possible that alterations in tissue microstructure affect directionality of water diffusion (i.e. decreased FA) but do not substantially increase overall water diffusion (i.e. unchanged MD) [28]. In PSMD, histogram analysis is used to capture diffuse pathological changes based on the distribution of MD values across the brain [24]. This is suggested to be especially sensitive to microstructural damage observed in SVD, which may explain why we do observe an association with PSMD but not with MD 24. Overall, these changes in DTI measures suggest that high BPV is associated with lower integrity of the WM.

No evidence was found for an association between BPV in the first 24 h of admission and WM integrity. In the first 24 h, the VisiMobile device may not have been properly connected since COVID-19 patients often experienced turbulent ER and general ward admissions due to a shortage of beds and subsequent transfers between wards. Furthermore, administration of vasoactive medication and fluids in this time period may have caused suboptimal calibration of the device, leading to measurement errors. Alternatively, fluctuations in BP during the first 24 h may mostly reflect the stressors experienced by patients during admission, while at later time-points, measurements reflect

Table 4. Association of BPV metrics with white matter microstructural integrity, additionally adjusted for white matter hyperintensities.

	Fractional anisotropy (FA)		Mean diffusivity (md)		Peak width of skeletonised mean diffusivity (psmd)	
BPV metrics	Standardised β [95% CI]	*p*	Standardised β [95% CI]	*p*	Standardised β [95% CI]	*p*
ARV1	−0.44 [−0.72 – −0.11]	**.002**	0.28 [0.02 – 0.54]	**.035**	0.19 [0.01 – 0.38]	**.041**
ARV5	−0.47 [−0.77 – −0.21]	**.001**	0.30 [0.05 – 0.55]	**.021**	0.18 [0.00 – 0.36]	.053
ARV20	−0.47 [−0.75 – −0.19]	**.002**	0.29 [0.04 – 0.54]	**.022**	0.13 [−0.05 – 0.32]	.151
CV1	−0.29 [−0.57 – −0.02]	**.034**	0.10 [−0.15 – 0.35]	.417	0.22 [0.06 – 0.39]	**.010**
CV5	−0.33 [−0.59 – −0.06]	**.019**	0.13 [−0.13 – 0.38]	.315	0.24 [0.07 – 0.40]	**.006**
CV20	−0.34 [−0.61 – −0.07]	**.016**	0.14 [−0.11 – 0.39]	.273	0.25 [0.08 – 0.41]	**.004**

[a]P-values < 0.05 are written in bold.

the underlying conditions responsible for high BPV more accurately.

The relationship between (COVID-19) infection, BPV and cerebrovascular damage is complex and there are several potential explanations for our results. First, infection with COVID-19 may cause an excessive immune reaction in some patients which causes a cytokine storm [29]. This cytokine storm can disturb several physiological systems, including BP regulation, and cause higher BPV 30. In turn, high BPV caused by COVID-19 may damage the brain by causing mechanical stress on vessel walls, leading to greater arterial stiffness and therefore less dampening of blood flow. This may lead to microvascular damage. Second, COVID-19 infection may cause cerebral damage, in which case BPV may not have a causal effect on the brain but is simply a marker of worse COVID-19 infection. Much remains unknown about the effects of COVID-19 on the brain, but some studies report lower DTI metrics after COVID-19 infection [31]. However, as discussed previously, higher BPV is also associated with cerebral damage and worse clinical outcomes in many other studies evaluating individuals without COVID-19, for example with ischaemic stroke [7,32]. Moreover, lower BPV in COVID-19 patients was associated with less mortality, suggesting that BPV does have an adverse effect, although this was a retrospective study [30]. Third, reverse causality is possible, where subclinical brain damage may cause central autonomic dysfunction, resulting in higher BPV. It is possible that our participants already had cerebrovascular damage prior to hospitalisation, causing higher BPV. This is especially relevant if we consider that hospitalised COVID-19 patients often have a worse cardiovascular risk profile [33]. However, our results remained statistically significant after adjusting for WMH volumes, which results from long-term cerebrovascular damage, and there was no interaction with WMH volumes. This suggests that the association between BPV and microstructural integrity is independent of pre-existing cerebral damage. Despite the absence of MRI scans prior to COVID-19 to conform this, our findings align with a previous study that also describe this association independent of WMH 9. Finally, it is possible that increased BPV is a consequence of stress induced by hospitalisation with a severe illness and is not specific for infection with COVID-19.

Cuffless continuous BP monitoring systems, such as ViSiMobile used in this study, have great potential for measuring BPV 34. As BP is highly dynamic and regular BP measurements only provide snapshots of BP in static conditions, cuffless devices can be used to detect BP changes during daily activities and sleep. However, the European Society of Hypertension does not recommend using cuffless devices based on pulse wave analysis to measure BPV yet since this technique is inadequately validated [6]. Nonetheless, continuous vital sign monitoring is already integrated in many hospitals without requiring additional effort from medical staff. When cuffless BP measurement is further adopted, these devices could become the preferred method to assess average BP levels and BPV.

Many different indices can be used to quantify BPV and there is currently no gold standard, especially in continuous cuffless BP monitoring [6,35]. The CV is commonly used but does not account for the order in which the BP measurements were obtained [6]. ARV may therefore more accurately reflect the time series nature of BP data and is more commonly used in ambulatory BP monitoring [6]. While both ARV and CV were associated with lower FA, ARV was associated with higher MD while CV was associated with higher PSMD in our study. ARV and CV indices were only moderately correlated, which suggests that these indices capture different aspects of BPV. It remains to be determined which BPV index should be used in which context. Furthermore, we showed a consistent BPV based on CV and ARV calculated during any time interval (1/5/20 min). This is useful information for clinical practice, where minute-to-minute data is often not available.

There are some limitations we need to address. First, COVID-19 may affect BPV during admission and WM integrity itself. Although we adjusted for type of ventilation during admission as a reflection of COVID-19 severity, it

is crucial to validate our findings in a distinct study population without COVID-19 or other viral infections to examine the generalisability of our findings. Second, we have a relatively small sample size and our findings should be confirmed in a larger cohort. Third, based on our results we cannot conclude if there is a causal relationship. This should be examined in longer studies with sequential MRI scans with BPV measured in between. Fourth, we measured BP using pulse wave analysis, and as described earlier, this method has not been adequately validated to measure BP. Finally, we did not adjust our *p*-values for multiple comparisons, since the measures and outcomes we analysed are inherently related and not completely independent. Applying such a correction could therefore increase the risk of type II errors, thereby masking real effects. However, we believe this is not an issue as our results show the same trends across all measures.

Future research should examine if our findings apply to hospitalised patients without COVID-19. If so, BPV during hospitalisation could help identify those at risk of brain damage or ICU admission. BP management in hospitalised patients is currently focused on the absolute BP values whereas our study emphasises the potential additional importance of controlling BP fluctuations to achieve stable BP. There is evidence that calcium channel blockers (CCBs) and non-loop diuretics are most effective in reducing long-term BP in patients with hypertension [36]. However, 60% of our participants was normotensive prior to hospitalisation and there is no clear evidence on whether these treatments can also lower BPV in normotensive individuals. In hospitalised COVID-19 patients, use of CCBs was associated with lower BPV and maintaining low BPV had a protective effect on mortality [30]. It remains unknown if lowering BPV also has a protective effect on brain integrity. If so, an optimal therapeutic target for BPV would need to be determined, since some BP fluctuations are normal in healthy individuals.

In conclusion, we demonstrated that high BPV, measured using continuous cuffless BP monitoring during hospital admission for COVID-19, was associated with lower microstructural integrity of the WM in the brain. If a causal relationship would be established, continuous BP monitoring during acute care hospitalisation for determining BPV may be useful to identify patients at risk of cerebral damage.

Disclosure statement

Frank-Erik de Leeuw has received the VIDI Innovational Research grant (ZonMW 016-126-351), the Clinical established investigator Dutch Heart Foundation (DHF) grant (2014 T060) and is Associate Editor at the International Journal of Stroke. H Bart van der Worp reports support for consultancy from Bayer and TargED, paid to his institution, and grants from the European Union and the DHF. Marieke J. H. Wermer is supported by a personal grant from ZonMw (VIDI and Aspasia). All authors declare that they have no conflicts of interest.

Funding

This work is funded by The Netherlands Organisation for Health Research and Development (ZonMw) and The Heart Council (grant number 10430012010014).

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