Impact of Decreased Visibility of Deep Medullary Veins on White Matter Integrity in Patients with Cerebral Small Vessel Disease

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Abstract

**Background:** Based on susceptibility-weighted imaging (SWI) visibility, deep medullary vein (DMV) scores are related to white matter damage (WMD) in patients with cerebral small vessel disease (CSVD). However, whether mechanisms are associated with DMV changes is unclear. We examined extracellular fluid (ECF) roles in white matter associations between DMV scores and white matter integrity (WMI) in patients with CSVD. **Methods:** We examined magnetic resonance imaging (MRI) and clinical data from 140 patients with CSVD. DMV scores (0–18) were assigned on SWI according to DMV anatomic regions and signal continuity/visibility. WMI and ECF volumes were evaluated using free water (FW) and fractional anisotropy (FA) values by diffusion tensor imaging (DTI). **Results:** DMV scores were independently associated with FA after adjusting for vascular risk factors, age, white matter hyperintensity (WMH) volume, and CSVD burden [β (95% confidence interval (CI)): –0.219 (–0.375, –0.061), p = 0.006]. We also observed a significant indirect effect of DMV scores on FA in white matter (mediated by FW in white matter) after controlling for age, vascular risk factors, WMH volume, and CSVD burden. **Conclusions:** DMV scores were independently related to WMI and mediated by ECF in the white matter of patients with CSVD.

**Keywords:** cerebral small vessel disease; deep medullary vein; diffusion tensor imaging; extracellular fluid; susceptibility-weighted imaging; white matter integrity

1. Introduction

In older adults, cerebral small vessel disease (CSVD) is often implicated in dementia and cognitive impairment [1]. Despite its prevalence and negative impact on cognitive function, underlying CSVD mechanisms and effective treatments are limited. Previous studies have indicated that white matter damage (WMD) is a major contributor to cognitive impairment in CSVD [2–4], but the causes of such damage are not fully understood, multifaceted, and may include: low cerebral blood flow [5], blood-brain barrier leakage [6], neuroinflammation [7], and venous abnormalities [8]. These mechanisms have garnered significant research traction in recent years. The deep medullary vein (DMV) complex is of particular interest and is the main venous blood drain in periventricular white matter and the corona radiata. DMVs are perpendicular to the ventricle, have limited variation, and are often used to examine deep venous changes in cerebral vascular disease. Studies have reported that magnetic resonance imaging (MRI)-derived DMV scores, based on DMV visibility on susceptibility-weighted imaging (SWI), are associated with the presence and burden of CSVD [9]. Subsequently, studies also find that DMV scores are related to cognitive impairment or dementia in individuals with CSVD [10]. According to previous studies, a higher DMV score is associated with venous lumen stenosis and venous hypertension [11], which may obstruct venous drainage in white matter and cause extracellular fluid (ECF) accumulation [12]. Increased ECF may facilitate harmful substance accumulation (e.g., plasma protein and metabolic waste) and, critically, cause WMD [13]. Therefore, we hypothesized that decreased DMV visibility was associated with WMD when mediated by increased ECF.

To evaluate ECF volumes, diffusion tensor imaging (DTI) is widely used in nervous-system-disease research [12,14,15]. According to the free water (FW) elimination 2-compartmental model [16], FW reflects ECF volume corrected for partial volume effects in cerebrospinal fluid, while fractional anisotropy (FA) indicates white matter integrity (WMI) after removing FW signals.

Therefore, CSVD is a significant health challenge for older adults; thus, deeper mechanistic insights are warranted. This study focused on the DMV complex in CSVD-associated WMD and investigated relationships between...
DMV scores, ECF volumes, and WMI using advanced multimodal magnetic resonance imaging (MRI) approaches.

2. Materials and Methods

2.1 Participants

The Institutional Review Board of our hospital approved the study, and patients provided written informed consent. Between January 2022 and August 2022, imaging and clinical data were prospectively collected from patients. Enrolled patients had MRI scans to assess for ischemic attack, lacunar infarct (LI), or dizziness. Inclusion criteria were: age >40 years, adherence of CSVD MRI markers to STRIVE guidelines [17], and ≥1 vascular risk factors. Exclusion criteria were: confirmed demyelinating diseases, severe occlusion/stenosis of a large intracranial or internal carotid artery, other brain abnormalities, and lung/heart/kidney insufficiency. Clinical baseline characteristics included age, sex, and vascular risk factor information.

2.2 MRI Protocol

In patients, a multimodal MRI protocol included 3D T1 weighted imaging (T1WI), T2 Flair, T2 weighted imaging (T2WI), SWI, and DTI sequences on a 1.5 Tesla scanner (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare, Erlangen, Germany). Sequence parameters were: (1) SWI: repetition time (TR) = 27 ms; echo time (TE) = 20 ms; flip angle = 10; slice thickness = 2 mm; intersection gap = 0 mm; field of view (FOV) = 24 × 24 cm²; and matrix number = 512 × 512. (2) DTI: TR = 3600 ms; TE = 95 ms; slice thickness = 3 mm; FOV = 23 cm × 23 cm; matrix = 128 × 128; diffusion directions = 30 for every b value; b value = 0, 1000, and 2000 s/mm².

2.3 Image Analyses

Two blinded and experienced neuroradiologists independently reviewed images, and disagreements were resolved by consensus.

2.4 Total CSVD MRI Scores

From STRIVE guidelines [17], 4 CSVD MRI markers were identified: high-grade perivascular spaces (HPVS), high-grade white matter hyperintensities (HWMH), cerebral microbleeds (CMBs), and LIs. An LI finding indicated round or ovoid-shaped lesions (3–15 mm in diameter), which appeared as hypointensities on T1WI and hyperintensities on T2WI. HPVS were assessed as the maximum numbers of perivascular space (PVS) in unilateral basal ganglia and were represented by enlarged PVSs >10. When Fazekas scores in deep white matter and/or periventricular white matter were ≥2, HWMH were assigned. CMBs manifested as small, round, or ovoid hypointensities without surrounding edema. An average diameter = 3–5 mm (by SWI) was used to exclude abnormal iron deposits, such as cavernous hemangioma, calcification, and vascular cross-sections.

Total CSVD magnetic resonance (MR) scores were calculated and ranged from 0–4 accordingly, based on an absence (0)/presence (1) of each of the 4 CSVD markers. For example, a CSVD MR score of 4 was assigned when all the markers were identified on MR images. WMH volume was calculated on T2 Flair images using the WMH mask segmented by FSL BIANCA.

2.5 DMV Scores

SWI sequences were constructed (thickness = 10 mm) using minimum intensity projection, and DMV scores were assessed using constructed SWI images. To calculate scores, we selected 5 consecutive periventricular slices in patients which covered most DMVs, from the ventricle level above the basal ganglia to where ventricles disappeared.

Based on regional anatomy, the DMV complex was apportioned into 6 segments: frontal, parietal, and occipital regions bilaterally. In DMV scoring, we used a semi-quantitative approach [18] where each of the 6 segments were separately scored (0–3) based on observed continuity and visibility in SWI sequences (Fig. 1). Total DMV scores—individual scores summed from the 6 segments, ranged from 0–18. A DMV score = 0 indicated prominent DMV, while 18 suggested undetectable DMV.

2.6 ECF and FA in White Matter

Gibbs artifact removal, denoising, echo planar imaging (EPI) distortion, and eddy current correction pre-processing steps were conducted in Mrtrix3 software (https://mrtrix.org/). Pre-processed DTI images were analyzed for ECF and WMI in FW elimination 2-compartmental mode [19] (ECF and tissue compartment) in DIPY software (https://dipy.org/). FA and FW maps were generated, and 3D T1WI images co-registered with b = 0 s/mm² (b0) images. Finally, white matter mean FA and FW values were generated for patients using respective white matter masks segmented by FMRIB’s automated segmentation tool (FSL FAST) with the default probability threshold recommended (Fig. 2). Calculated FA and FW values ranged from 0–1. The FW value represented the white matter ECF volume, with values closer to 1 indicating a marked increase in white matter ECF volume. FA values reflected WMI, with lower values indicating significant WMI loss.

2.7 Statistical Analyses

Categorical variables were represented as percentages and frequencies. Continuous, normal distribution data were represented as the mean ± standard deviation, while non-parametric data were reported as median and interquartile range (IQR) values. Relationships between DMV scores, FW, and FA values were processed using Spearman’s or Pearson correlation coefficients and linear regression analyses. Mediation analyses (PROCESS for Statistical Package for Social Sciences (SPSS) (Model 4)) were performed.
Fig. 1. Typical images showing deep medullary vein (DMV) scoring. (A,E) DMV score = 0. The DMV signal is continuous and visible on susceptibility-weighted imaging (SWI). (B,F) DMV score = 1. The DMV signal is continuous with unequivocal visibility but has a non-homogeneous signal in at least 1 vein. (C,G) DMV score = 2. At least 1 vein is not continuous, is faintly visible, and contains spot-like hypointensities. (D,H) DMV score = 3. The DMV is invisible.

with 95% confidence levels and 5000 bootstrap samples to examine FW mediating roles between DMV scores and FA values. DMV scores were predictors, FW values were mediators, and FA values were outcomes. Covariates were age, vascular risk factors, and CSVD burden. Statistical significance = \( p < 0.05 \). SPSS for Windows, V. 20 (IBM Corp., Armonk, NY, USA) was used for data analyses.

3. Results

We enrolled 140 patients (mean age = 60 ± 12 years, and 66 were men) with CSVD. Baseline clinical and imaging characteristics are shown (Table 1). Thirty-two (22.9%) patients showed HWMH, 53 (37.9%) showed CMBs, 20 (14.3%) showed HPVS and 56 (40%) showed LIs. The median (IQR) DMV score was 3 (0, 7), and mean FW and FA values in white matter were 0.25 ± 0.01 and 0.56 ± 0.03, respectively.

3.1 Relationship between DMV Scores and FA Values

As indicated (Fig. 3), Spearman’s correlation coefficients identified a significant correlation between DMV scores and FA values in white matter (\( r = -0.251, p < 0.05 \)). DMV scores were independently related to FA after adjusting for vascular risk factors, age, WMH volume, and CSVD burden [\( \beta \) (95% confidence interval (CI)): \(-0.219 \) (\(-0.375, -0.061 \)), \( p = 0.006 \), Table 2].
Table 1. Patient baseline clinical and imaging characteristics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>n = 140</th>
</tr>
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<tbody>
<tr>
<td>Male, n (%)</td>
<td>66 (47.1)</td>
</tr>
<tr>
<td>Age, years</td>
<td>60 ± 12</td>
</tr>
<tr>
<td>Hypertension, yes, n (%)</td>
<td>76 (54.3)</td>
</tr>
<tr>
<td>Diabetes mellitus, yes, n (%)</td>
<td>25 (17.9)</td>
</tr>
<tr>
<td>Current smoking, yes, n (%)</td>
<td>33 (23.6)</td>
</tr>
<tr>
<td>Hyperlipidemia, yes, n (%)</td>
<td>36 (25.7)</td>
</tr>
<tr>
<td>LI, yes, n (%)</td>
<td>56 (40.0)</td>
</tr>
<tr>
<td>HPVS, yes, n (%)</td>
<td>20 (14.3)</td>
</tr>
<tr>
<td>HWMH, yes, n (%)</td>
<td>32 (22.9)</td>
</tr>
<tr>
<td>CMB, yes, n (%)</td>
<td>53 (37.9)</td>
</tr>
<tr>
<td>WMH volume, mL</td>
<td>12.29 ± 12.58</td>
</tr>
<tr>
<td>DMV score, median (IQR)</td>
<td>3 (0, 7)</td>
</tr>
<tr>
<td>FW</td>
<td>0.25 ± 0.01</td>
</tr>
<tr>
<td>FA</td>
<td>0.56 ± 0.03</td>
</tr>
</tbody>
</table>

LI, lacunar infarct; HPVS, high-grade perivascular spaces; HWMH, high-grade white matter hyperintensities; WMH, white matter hyperintensities; CMB, cerebral microbleed; DMV, deep medullary veins; FW, free water; FA, fractional anisotropy; IQR, interquartile range.

3.2 Relationship between DMV Scores and FW Values

As indicated (Fig. 4A), Spearman’s correlation coefficient analyses identified significant correlations between DMV scores and FW values in white matter ($r = 0.425, p < 0.001$). DMV scores were also independently associated with FW values after adjusting for age, vascular risk factors, CSVD burden, and WMH volume [$\beta$ (95% CI): 0.145 (0.019, 0.571), $p = 0.037$, Fig. 5].

3.3 Relationship between FW and FA Values

As indicated (Fig. 4B), Spearman’s correlation coefficient analyses identified significant correlations between FW and FA values in white matter ($r = -0.323, p < 0.001$). FW was also independently associated with FA after adjusting for age, vascular risk factors, CSVD burden, and WMH volume [$\beta$, 95% CI: $-0.316 (-0.505, -0.128)$, $p = 0.001$, Fig. 5].

3.4 Mediation Analyses on DMV Scores, FW, and FA Values

Mediation analyses were controlled by age, vascular risk factors, WMH volume, and CSVD burden and identified significant indirect effects of DMV scores toward FA in the white matter when mediated by FW in white matter (Fig. 5).

4. Discussion

DMV scores were independently associated with FA values in white matter and mediated by FW values in patients with CSVD. Also, mediation effects were independent of vascular risk factors, age, WMH volume, and CSVD burden. Thus, relationships existed between DMV damage, increased ECF, and WMI loss in patients with CSVD.

With rapid improvements in MRI technology, SWI is widely used to investigate cerebral vascular and neurodegenerative diseases [20,21]. Many studies have reported that MRI-based DMV scores may be correlated with CSVD presence and severity [9,18,22]. Higher DMV scores are putatively correlated with a higher CSVD probability and severity. Previous autopsy and animal studies indicated that DMV damage may be caused by collagen type I and III deposition on vessel walls, leading to a stenotic or occluded lumen [11,23,24]. Higher DMV scores may reflect this DMV damage, and DMV abnormalities may be implicated in CSVD development.
Fig. 4. Graphs showing relationships between deep medullary vein (DMV) scores, fractional anisotropy (FA), and free water (FW) values. A: There is a significant correlation between DMV scores and FW values in white matter ($r = 0.425, p < 0.001$). B: There is a significant correlation between FW and FA values in white matter ($r = -0.323, p < 0.001$).

DMV scores correlated with cognitive impairment in patients with CSVD [10], while associations between microstructure changes and WMI loss and cognitive impairment were reported in these patients [2]. However, the relationship between DMV damage and WMI loss and the precise influence of DMV scores on WMD remains unclear. Here, we identified links between DMV damage, increased ECF, and WMI loss in patients with CSVD. When a DMV abnormality was present, increased ECF initially occurred, followed by white matter demyelination and axonal damage.

Based on DMV structure and function, we suggest that DMV-associated white matter abnormalities occur when the DMV lumen narrows and venous pressure increases, causing obstructed venous drainage and increased vascular permeability [11], with increased PVS and ECF leakage volumes. It was previously believed that the index of diffusion tensor image along the PVS near the DMV was related to lymphatic system function [25]. Thus, a DMV abnormality may have caused lymphatic system dysfunction and increased ECF volume. However, venous hypertension may also have decreased cerebral blood flow and vascular edema, thereby increasing ECF. Either way, increased ECF volume may have facilitated harmful substance (e.g., plasma proteins and metabolic waste) accumulation, which elicited neuroinflammation, and further increased the ECF volume, thus ensuring a vicious circle. These substances can potentially damage white matter microstructures (e.g., myelin and axons), leading to WMI loss [13,26]. In considering WMI loss and cognitive impairment, identifying DMV abnormality and cognitive impairment steps may uncover new CSVD venous-related prevention and control mechanisms.

CSVD is related to aging and associated with one or more vascular risk factors [27]. WMH volume and CSVD burden were often correlated with more severe WMD [28]. Therefore, in mediation analyses, we adjusted for age, vascular risk factors, WMH volume, and CSVD burden. This approach enhanced the practicality of our findings and suggested that cerebral venous abnormalities initially occurred with increased ECF volume, followed by WMD. Further, this observation was consistent with other research [8], which confirmed links between DMV scores and FW and FA values in patients with CSVD. Although research has shown a correlation between WMH volume, CSVD burden, age, and cognitive decline [3,29], this study reveals that they are not independently associated with FA or WMI.

Fig. 5. Mediation model analyses exploring relationships between deep medullary vein (DMV) scores, fractional anisotropy (FA), and free water (FW) values ($p < 0.05$).
The possible explanation is that the underlying mechanism driving cognitive decline or WMI involves changes in the brain’s microenvironment and microstructure, contributing to the development of WMH volume and CSVD burden.

Our study was limited. It was conducted at a single center and had a small sample. Secondly, no follow-up was conducted to examine relationships between DMV scores, FW and FA values, and cognitive impairment. Thirdly, low cerebral blood flow and inflammatory edema may also increase FW [28,30]; however, we did not include these factors or adjust for them in our models, thus introducing potential bias. Fourthly, although the DMV scores system has now been used in the serial study, the software automatically detecting and measuring DMV scores may be better to quantitatively assess DMV changes. We mainly focused on extracellular FW, while intracellular water content was not analyzed. Finally, capillary blood perfusion may have affected extracellular FW values. Thus a 3-compartment model may improve FW estimations. To address the limitations mentioned above, more multi-center investigations with more patients are required.

5. Conclusions

DMV scores were independently associated with WMI and mediated by ECF volume in white matter in patients with CSVD. This observation may underpin a venous element of WMD pathogenesis in CSVD.

Abbreviations

SWI, susceptibility-weighted imaging; DMV, deep medullary vein; CSVD, cerebral small vessel disease; DTI, diffusion tensor imaging; FW, free water; FA, fractional anisotropy; HWMH, high-grade white matter hyperintensities; CMB, cerebral microbleeds; HPVS, high-grade perivascular spaces; LI, lacunar infarcts; WMD, white matter damage; WMI, white matter integrity.

Availability of Data and Materials

Study datasets are available upon reasonable request from the corresponding author.

Author Contributions

HW, XL and ZX designed the research. HW, HZ, ZC, YW and HL performed the research. HL and HZ assisted with the research. HW and ZX analyzed data. HW, XL and ZX wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted according to the Declaration of Helsinki and approved by the Institutional Review Board of Tongde Hospital of Zhejiang Province (2022-042-JY). Written informed consent was provided prior to participation.

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Conflict of Interest

The authors declare no conflict of interest.

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