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CONTEMPORARY REVIEW

Brain Enlarged Perivascular Spaces as Imaging Biomarkers of Cerebrovascular Disease: A Clinical Narrative Review

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ABSTRACT: Perivascular spaces or Virchow-Robin spaces form pathways along the subarachnoid spaces that facilitate the effective clearance of brain metabolic by-products through intracellular exchange and drainage of cerebrospinal fluid. Best seen on magnetic resonance imaging of the brain, enlarged perivascular spaces (EPVSs) are increasingly recognized as potential imaging biomarkers of neurological conditions. EPVSs are an established subtype of cerebral small-vessel disease; however, their associations with other cerebrovascular disorders are yet to be fully understood. In particular, there has been great interest in the association between the various parameters of EPVSs, such as number, size, and topography, and vascular neurological conditions. Studies have identified cross-sectional and longitudinal relationships between EPVS parameters and vascular events, such as ischemic stroke (both clinical and silent), intracerebral hemorrhage, vascular risk factors, such as age and hypertension, and neurodegenerative processes, such as vascular dementia and Alzheimer disease. However, these studies are limited by heterogeneity of data and the lack of consistent results across studied populations. Existing meta-analyses also fail to provide uniformity of results. We performed a qualitative narrative review with an aim to provide an overview of the associations between EPVSs and cerebrovascular diseases, which may help recognize gaps in our knowledge, inform the design of future studies, and advance the role of EPVSs as imaging biomarkers.

Key Words: cerebral small-vessel disease ■ imaging biomarkers ■ perivascular spaces ■ Virchow-Robin spaces

PERIVASCULAR SPACES: ANATOMY, IMAGING CHARACTERISTICS, AND QUANTIFICATION

Brain perivascular spaces or Virchow-Robin spaces are potential spaces between the brain vasculature and the meningeal layers and were first described by pathologists Rudolf Virchow and Charles Robin separately in the 19th century.[1] They form pathways along the subarachnoid spaces surrounding the arterioles and venules and facilitate the transport of cerebrospinal fluid and the exchange of intracellular substances for the effective clearance of brain metabolic by-products (Figure).[2] Although the human brain was thought to be devoid of a lymphatic drainage system, current evidence indicates that the brain-wide perivascular space pathway may function as a "glymphatic" system.[2] The process of "waste removal" involves the movement of cerebrospinal fluid into the periarterial spaces using bulk-flow dynamics followed by entry into the interstitial fluid compartment using aquaporin-4 channels. Herein, it undergoes admixture with the cellular metabolic products and subsequently drains by convection into the perivenular spaces and then into the larger downstream venous and lymphatic systems.[3] As a result, impaired glymphatic clearance of substances and enlarged perivascular spaces (EPVSs) have been studied and implicated as a marker for various neurological conditions, such as cerebrovascular disease, dementias, and demyelinating disorders and, interestingly, they have also been studied in systemic vascular conditions, such as hypertension and chronic kidney disease.[4]

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Nonstandard Abbreviations and Acronyms

CAA	cerebral amyloid angiopathy
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CSVD	cerebral small-vessel disease
EPVS	enlarged perivascular space
ICH	intracerebral hemorrhage
LADIS	Leukoaraiosis and Disability Study
NOMAS	Northern Manhattan Stroke Study
OxVasc	Oxford Vascular Study
PVS	perivascular space
SVD	small-vessel disease
TABASCO	Tel-Aviv Brain Acute Stroke Cohort
WMH	white matter hyperintensity

Perivascular spaces (PVSs) are usually a microscopic finding and are not visualized on imaging. Observation of PVSs on imaging, such as magnetic resonance imaging (MRI), typically results from enlargement attributable to age or other disease processes.[5] Although the current terminology seeks to avoid the use of the prefix *enlarged*, because PVS enlargement may not be necessary for pathology, we will use the term EPVS for the purpose of this review. Because EPVSs follow the course of the penetrating brain vessel, PVSs may appear linear when imaged in parallel to a vessel or ovoid-circular (usually <3 mm in diameter) when imaged perpendicularly. The most important differential diagnosis of EPVSs is chronic brain infarcts. We have proposed a pathology-informed algorithm to distinguish EPVSs from chronic infarcts. In this algorithm, chronic infarcts are more likely to be >5 mm; occur usually in the upper two-thirds of the basal ganglia, in the cortex, or in the brain stem; and have a hyperintense rim in fluid-attenuated inversion recovery imaging.[6] Another feature that favors an EPVS over a chronic lacunar infarct the absence of a central vessel sign on high-resolution imaging. However, EPVSs can enlarge to sizes exceeding 1 cm and may have a hyperintense rim resembling infarcts. In these situations, proton density imaging may be helpful in distinguishing infarcts from PVSs. Whether EPVSs can be classified as "lesions" is not conclusive because their association with neurological disorders is not consistent.[7]

EPVSs are usually quantified on MRI by visual rating. Not surprisingly, significant variability has emerged between visual rating scales and their results, which hinders the translation of EPVS-related research into clinical practice.[8] Most EPVS scales have been administered using 1.5-T MRI and a combination of axial T1, T2, or fluid-attenuated inversion recovery sequences, whereas some scales have used additional planes and sequences, such as coronal, sagittal, 3-dimensional fast low-angle shot, fast-field echo, and spectral presaturation with inversion recovery, which influence the sensitivity and specificity for recording EPVSs.[5,9] The anatomical locations of EPVSs included in these scales also vary. While the inclusion of the basal ganglia and centrum semiovale is common, other regions, such as the midbrain, hippocampus, insula, and white matter, are not uniformly studied. Furthermore, most EPVS quantification scales are ordinal, but the number of EPVSs under each ordinal value is heterogeneous.[8] Other limitations of visual rating scales include ceiling effect, floor effect, and suboptimal reliability.[10]

Segmentation-based machine-learning techniques are thought to be less time-consuming and more reliable in longitudinal settings.[11] The use of these fully and semiautomated methods is still experimental and needs to be validated against clinical outcomes in diverse populations and clinical settings.[12] Other promising novel imaging approaches to EPVS diagnosis include the use of 7-T high-resolution MRI, incorporation of diffusivity tensor imaging, and the use of gadolinium as a possible glymphatic tracer.[13–15]

EPVSs have been studied as imaging biomarkers mainly in cerebrovascular disorders, such as ischemic and hemorrhagic stroke, cerebral small-vessel disease (CSVD), cerebral amyloid angiopathy (CAA), vascular cognitive impairment, and other less common conditions, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and Moya-Moya disease.[3,16–18] Despite the above reported associations, EPVSs are yet to gain widespread recognition. Notable impediments include the aforementioned heterogeneity of measurements, differences in outcomes among studied populations, and a paucity of prospective clinical trials. To help identify gaps in existing knowledge, inform the design of future research on EPVS imaging and correlations, and advance the role of EPVSs as imaging biomarkers for clinical use, we performed a literature review and qualitative analysis of the associations between the imaging features of brain EPVSs, such as size, number, and location, and the various clinical and radiological aspects of cerebrovascular disorders.

PATHOLOGICAL BASIS FOR EPVSS IN CEREBROVASCULAR DISEASE

The primary inciting factor leading to enlargement of PVSs in cerebrovascular diseases in humans is yet to be determined. On the basis of animal models, inflammation is presumed to be an important catalytic event in the physiopathological cascade resulting in PVS expansion.[19] Similarly, in humans, there is evidence that

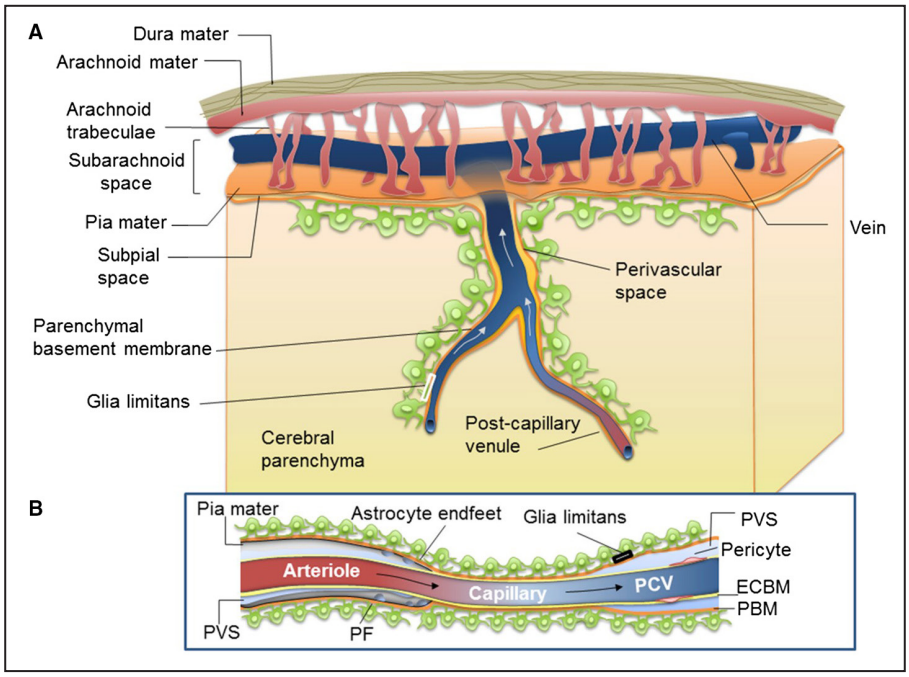

Figure. Anatomic relations within the central nervous system and microvasculature. **A**, The subarachnoid space is delimited by the arachnoid mater and the pia mater. The pia mater is composed of a single layer of fibroblasts supported by a thin fibrous tissue matrix and underlain by the subpial space. This space is separated from the cerebral parenchyma by the glia limitans. **B**, Arteries passing from the subarachnoid space into the cerebral cortex are surrounded by a perivascular sheath composed of the pial membrane, which is adherent to the glia limitans and forms the inner lining of the PVS. This pial lining becomes incomplete and then disappears at the level of capillaries. Capillaries have no PVS, because their ECBM is fused with the glia limitans (itself formed by astrocyte foot processes embedded in the parenchymal basal lamina). Postcapillary venules (PCVs) are surrounded by a PVS that is delimited by ECBM and the glia limitans; there is no intact pial membrane, but small clusters of pial cells adherent to the vessels are present. The PVS is in continuity with the subpial space (**A**). Reprinted from Kaufman-Francis et al with permission. Copyright ©2018, Elsevier. ECBM indicates endothelial basement membrane; PBM, parenchymal basement membrane; PF, pial fenestration; and PVS, perivascular space.

systemic inflammatory markers are elevated in patients with EPVSs and white matter hyperintensities (WMHs), both markers of CSVD.[20,21] Furthermore, inflammatory cells, such as macrophages, also accumulate directly in the PVSs in several conditions, such as hemorrhagic stroke, ischemic stroke, demyelination, CAA, Alzheimer disease, and traumatic brain injury.[19,22–26] Progression of perivascular inflammation results in pericyte damage and blood-brain barrier dysfunction, possibly leading to altered fluid dynamics, ineffective interstitial fluid drainage, and dilatation of the PVS. In fact, in the NOMAS (Northern Manhattan Study) and in Alzheimer's Disease Neuroimaging Initiative, we found that a higher burden of EPVSs is associated with larger white matter volume,[27] which we interpret as a sign of a physiopathological relationship between EPVSs and dysfunctional brain interstitial fluid drainage. Finally, the cumulative damage to the endothelium may lead to vessel wall alterations and subsequently impaired cerebrovascular reactivity and pulsatile bulk-flow dynamics.[28]

Mice models of ischemic stroke have demonstrated inflammatory markers and impaired clearance of by-products in the EPVSs in the immediate poststroke period, which may lead to further free-radical damage, impaired oxygen use, and stroke expansion.[29] PVSs also play a vital role in clearance of amyloid-β protein. Although most amyloid-β is cleared through the transvascular route influenced by sleep and aerobic activity, the PVS pathway is thought to account for ≈20% to 40% clearance via interstitial fluid.[22,30] Therefore, factors that impair interstitial fluid dynamics may lead to accumulation of amyloid-β, expansion of PVSs, and poorer cognitive outcomes.[31,32] As a result, targeting paths related to amyloid-β clearance, such as activation of macrophages, induction of pericytes, or promotion of interstitial clearance using focused ultrasound, have emerged as potential therapeutic options.[32]

METHODS

Using broadly applicable keywords in combination, such as "brain," "Virchow-Robin," "space," "perivascular space," "Virchow-Robin space," "PVS," and "VRS," we searched the MEDLINE, EMBASE, Web of Science, and The Cochrane Library databases, and registries, such as World Health Organization International Clinical Trials Registry Platform and Clinicaltrials.gov from inception to December 31, 2021. Gray literature was searched for additional relevant abstracts. An example of a search term used was (((brain[Title/Abstract] OR arterial[Title/Abstract] OR arteries[Title/Abstract] OR artery[Title/Abstract] OR cerebral[Title/Abstract])) AND space*[Title/Abstract]) AND (enlarged[Title/Abstract] OR dilated[Title/Abstract] OR visible[Title/Abstract]).

The objective of this review was qualitative and narrative, with a purpose of informing current literature on EPVSs in cerebrovascular disease given the high heterogeneity of methods used to study EPVSs. Consequently, we decided not to pursue a meta-analysis. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and inclusion and exclusion criteria were not applicable. In total, 4980 abstracts were retrieved after removal of duplicates. Abstracts and full texts were screened by 2 reviewers (S.R. and F.K.) for inclusion. Conflicts were addressed by the senior author (J.G.).

EPVSS AND CEREBROVASCULAR DISEASE

Transient Ischemic Attack and Acute Stroke

Transient Ischemic Attack

EPVSs in relationship to transient ischemic attack (TIA) have not been extensively studied. One prospective study compared EPVSs in patients with either transient or persistent neurological deficits attributable to ischemic stroke and found no differences in the total small-vessel disease (SVD) scores on imaging, which included EPVS scores as one of its components.[33] Hypothetically, PVSs may play a role in preventing the progression of TIA to ischemic stroke through effective clearance of inflammatory markers and timely interstitial fluid drainage. In this context, it remains to be tested whether a heavier load of EPVSs could increase the risk of stroke in the short-term after a TIA.

EPVSs and Stroke Risk

In the Lothian birth cohort (Table 1), EPVS scores computationally assessed for width and length were associated with history of stroke.[34] Similarly, the prospective 3-city population study from France reported that higher total EPVS scores were associated with a higher risk of incident ischemic stroke and intracerebral hemorrhage (ICH). The association was found significant only for EPVSs in the basal ganglia, however.[35] The OxVasc (Oxford Vascular Study) also found that basal ganglia, but not centrum semiovale, EPVSs were associated with increased risk of recurrent ischemic stroke and ICH.[36] This was replicated in another study of 1622 individuals where >20 basal ganglia EPVSs had a 1.8-fold higher risk of recurrent ischemic stroke and a 2.6-fold increased risk of ICH compared with patients with <11 or 11 to 20 basal ganglia EPVSs.[37] In NOMAS, we reported that participants in the highest tertile of EPVS scores had an increased risk of stroke and other vascular events compared with those in the mid and low tertiles.[38] Notably, EPVSs >5 mm were not associated with higher risk of vascular events in NOMAS or in another community-based study of 1204 stroke-free participants.[38,39] On the basis of these reports, there appears to be a consistent risk of increased risk of stroke in people with heavier burden of EPVSs in the basal ganglia, which we hypothesized could be partially mediated by a more intense or longer exposure to hypertension.[38]

Existing meta-analyses and systematic reviews of EPVSs are challenging to interpret. A meta-analysis exploring the association between the various components of SVD and stroke identified only 2 studies on EPVSs that fulfilled inclusion criteria.[40] A separate pooled analysis discussed a potential qualitative trend for the association between EPVSs, incident stroke, and death but could not retrieve data that sufficed for meta-analysis.[41] More recently, a third study pooled 116 studies of EPVSs and reported no relation of EPVSs with the risk of stroke, dementia, or mortality.[42] The validity of pooled analyses using heterogeneous studies is a concern, however.

Neurological Deterioration and Functional Outcomes After Stroke

Impaired glymphatic drainage and removal of inflammatory mediators after stroke may result in blood-brain barrier damage, worsening oxygen use, and necrosis, as discussed in prior sections. In a study of small subcortical ischemic strokes, moderate and high-grade basal ganglia EPVSs were associated with neurological deterioration in the first 72 hours after stroke.[43] However, another prospective study of 687 patients with ischemic stroke reported that none of the imaging makers of SVD were associated with neurological decline in the first 72 hours.[44] For more chronic poststroke outcomes, EPVSs do correlate with increased infarct size and progression of white matter disease after stroke.[45] In a study of 1096 patients with acute ischemic stroke, high-grade EPVS scores were

Table 1. Summary of the Major Studies of the Relationship Between EPVS Parameters and Ischemic Stroke and ICH

No.	Study/authors/duration	Study design	Study setting	Sample size	Association/relation studied	Results/outcomes
1	Ballerini et al (2020); Lothian birth cohort[34]	Retrospective cross-sectional	Population	533	EPVS association with vascular risk factors, WMH, and history of stroke	EPVS width and length associated with history of stroke (OR, 1.36 [95% CI, 1.08–1.71])
2	3C Dijon; Duperron et al (2019)[35]	Prospective (9.1±2.6-y follow-up)	Population	1678	Longitudinal relationship of EPVSs with risk of incident stroke, ischemic stroke, and ICH	Increasing EPVSs associated with risk of incident stroke (HR, 1.24 [95% CI, 1.06–1.45]) and ICH (HR, 3.12 [95% CI, 1.78–5.47]). Only BG-EPVSs and hippocampal EPVSs associated with risk of any stroke and ICH
3	Gutierrez et al (2017); NOMAS[38]	Prospective (9±2-y follow-up)	Population	1228	Relation of EPVSs to myocardial infarction, any stroke, and death	Highest tertile small EPVSs had higher risk of any stroke (RR, 1.79 [95% CI, 1.03–3.11]) after adjustment for confounders. No association with large EPVSs (>3 mm diameter) or anatomical subtypes of small EPVSs
4	Yilmaz et al (2019); Rotterdam study[68]	Prospective (7.2-y follow-up)	Population	1622	Association of CAA score (including EPVSs) with cognition, stroke, dementia, and mortality	Total CAA score, but not CSO-EPVS score, was not associated with higher risk of incident stroke, dementia, or death
5	Lau et al (2017); OxVasc/Hong Kong studies[36]	Prospective (total 6924-y follow-up)	Hospital (ischemic stroke/TIA)	1028	Clinical and imaging correlates, prognostic implications for stroke and death in BG and CSO-EPVS	BG-EPVSs independently associated with increased risk of recurrent ischemic stroke (maximum risk with >20 BG-EPVS: HR, 1.82 [95% CI, 1.18–2.80]; *P*=0.011) but not ICH (*P*=0.10). CSO-EPVSs not associated with recurrent stroke (*P*=0.57)
6	Lau et al (2017); OxVasc/Hong Kong studies[37]	Prospective (total 6924-y follow-up)	Hospital (ischemic stroke/TIA)	2002	Predictive value of total CSVD score (including EPVSs) for risk of recurrent stroke	No difference in risk between <11 and 11–20 BG-EPVSs. However, patients with >20 BG-EPVSs had 1.9-fold higher risk of recurrent ischemic stroke and 2.6-fold increased risk of ICH
7	Francis et al (2019)[42]	Systematic review and meta-analysis	Not applicable	36 108 (116 studies)	EPVS associations with risk factors, neurological disorders, and neuroimaging lesions	EPVSs associated with aging, hypertension, lacunes, and CMBs, but not WMHs, stroke, or cognitive impairment. Analysis limited by heterogeneity
8	Doubal et al (2010)[16]	Prospective	Hospital (ischemic stroke)	350	Comparison of EPVSs between stroke subtypes and controls	Among 129 patients with lacunar strokes and 124 patients with cortical ischemic strokes and 97 controls; total EPVSs and BG-EPVSs were associated only with lacunar subtype (*P*=0.04; *P*=0.003)

(*Continued*)

Table 1. Continued

No.	Study/authors/duration	Study design	Study setting	Sample size	Association/relation studied	Results/outcomes
9	Adachi et al (2002)[56]	Cross-sectional	Hospital (ischemic stroke)	171	Evaluate EPVS score using MRI among subtypes of ischemic stroke	High-grade EPVSs (grade ≥2) observed more frequently in lacunar compared with atherothrombotic or cardiogenic infarction (63.3% vs 24.2% vs 0%; $P<0.001$)
10	Charidimou et al (2017)[80]	Cross-sectional	Hospital (ICH)	452	Assess EPVS burden and topography in CAA and HA	Among 315 patients with CAA-ICH and 137 with HA-ICH, a CSO-EPVS–predominant pattern was more common in CAA-ICH than in HA-ICH (75.9% vs 39.4%; $P<0.0001$). BG-EPVS predominance was associated with HA-ICH and WMH volumes

BG indicates basal ganglia; CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed; CSO, centrum semiovale; CSVD, cerebral small-vessel disease; EPVS, enlarged perivascular space; HA, hypertensive arteriopathy; HR, hazard ratio; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; NOMAS, Northern Manhattan Stroke Study; OR, odds ratio; OxVasc, Oxford Vascular Study; RR, relative risk; TIA, transient ischemic attack; and WMH, white matter hyperintensity.

associated with increased all-cause mortality and fatal ischemic and hemorrhagic stroke, but the adjusted risk remained statistically significant only for fatal ischemic strokes.[46] In patients with acute ischemic stroke treated with intravenous tissue-type plasminogen activator, retrospective analyses have found that higher EPVS scores were associated with increased stroke severity (moderate to severe) and poorer poststroke outcomes measured by the National Institutes of Health Stroke Scale and the modified Rankin Scale.[47]

Functional outcomes, measured using the modified Rankin Scale grade between 3 and 6 months post-stroke, were not associated with EPVSs.[48] However, in one study of patients with stroke with low National Institutes of Health Stroke Scale scores (≤2), higher basal ganglia EPVSs were associated with poor functional measures, such as lower total stroke-specific quality-of-life score, lower mobility, depressed mood, and poor self-care.[49] In another study of 743 patients with acute ischemic stroke, EPVS scores were only associated with health-related quality of life. Of note, the cumulative SVD burden appears to have a larger effect on functional outcomes compared with individual scores, such as EPVS or WMH alone.[50]

INTRACRANIAL AND EXTRACRANIAL CALCIFICATION AND ATHEROSCLEROSIS

Atherosclerosis in the carotid vasculature may alter pulsatile hemodynamics and impair interstitial fluid drainage in the brain, resulting in EPVSs.[51–53] In patients with ischemic stroke, intracranial atherosclerotic stenosis of >50% is independently associated with >20 centrum semiovale EPVS but not basal ganglia EPVS.[36] These results were not replicated by another study, however.[54] Intracranial arterial calcifications, not a sine qua non of atherosclerosis, do not relate to EPVSs in patients with ischemic stroke or TIA, but there is a cross-sectional association between higher EPVS scores with carotid siphon calcifications in stroke-free individuals.[55] We have argued before that stiffening of the conduit arteries between the heart and the brain may relate to higher EPVS load, therefore suggesting that EPVSs may be markers of systemic arterial aging and its effect on pulsatile hemodynamics.[52] Further longitudinal studies are essential to demonstrate a relationship between EPVS burden or location and progression of luminal stenosis.

CEREBRAL SMALL-VESSEL DISEASE

Among the different ischemic stroke subtypes, lacunar stokes have carried the strongest association with EPVSs. In a prospective study of 350 participants,

total EPVS scores were associated only with the lacunar stroke subtype.[16] In another retrospective study of patients with acute ischemic stroke, high-grade EPVSs (grade ≥2) were observed more frequently in lacunar strokes compared with other stroke subtypes.[56] Community-based studies have also reported similar results, wherein individuals with silent lacunar strokes on imaging had a higher EPVS burden.[33] The association between lacunar stroke and EPVS is found consistent for bilateral hemispheres compared with just the ipsilateral side of stroke, suggesting a more widespread process of altered interstitial fluid dynamics and enlargement of PVSs in patients with lacunar strokes.[34]

With regard to associations between EPVSs and other markers of CSVD, EPVSs in both the basal ganglia and centrum semiovale were consistently associated with WMH volume and deep WMH.[5,12,35–37] There is conflicting evidence as to whether the association between EPVS and WMH varies by anatomical location, but the association appears more consistent with deep than with subcortical WMH.[37–39] Cerebral microbleeds, another marker of SVD, have been also associated with EPVSs, at both the basal ganglia and the centrum semiovale.[55,57] The association between EPVSs and other markers of SVD are likely to represent an epiphenomenon, but whether this coexistence is synergetic in the risk of vascular or cognitive outcomes remains uncertain.

CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS

CADASIL is a neurological disorder caused by a mutation in the *NOTCH3* gene, which is responsible for vascular smooth muscle homeostasis. Clinical features include subcortical infarcts, migraine headaches, psychiatric disturbances, and cognitive impairment. CADASIL represents a monogenic, early-onset variant of the CSVD.[58] As a result, EPVSs have emerged as a possible marker to study in these patients. Advanced 7-T MRI studies have shown correlation between EPVS number and WMH across all regions in patients with CADASIL compared with controls in whom EPVSs were correlated only to juxtacortical WMH.[59] Furthermore, pathological studies in CADASIL revealed that EPVS severity is associated with adjacent lacunar infarcts and myelin degradation.[59,60] EPVS burden is higher in asymptomatic patients with CADASIL compared with noncarriers. The severity of EPVSs in CADASIL is associated with advancing age and male sex, specifically for basal ganglia EPVSs.[18,60] The burden of EPVSs and the widespread white matter lesions seen in CADASIL may have a common underlying link of altered interstitial fluid drainage. Nonetheless, the clinical implications of EPVS measures in patients with CADASIL are uncertain. Some studies have shown a lack of association between EPVS severity with outcome scores, such as the Institute of Cognitive Neurology Frontal Screening, Mini-Mental State Examination, or modified Rankin Scale, but others have suggested that EPVSs may correlate with poorer cognition and higher disability.[7,41,60] Understanding the role of EPVSs in CADASIL-related neurodegeneration may offer insights into the physiopathology of this monogenic small-vessel disorder and highlight novel therapeutic pathways.

ICH AND CAA

Data supporting an association between EPVS and ICH risk are conflicting. In a study of 2002 participants with mean follow-up of 3.5 years (±2 years), there was no relationship between any EPVS score and incident ICH.[36] In another study with longer follow-up (about 9 years), increasing total and basal ganglia EPVS scores were independently associated with a 3-fold higher incident ICH.[35] In hospital-based samples, the risk of recurrent ICH associated with EPVS scores is inconclusive.[46,61]

Segregating ICH into CAA and non-CAA related, centrum semiovale EPVS >20 is more common in CAA-related ICH, independent of age.[62] In another retrospective cohort of 315 patients with CAA-related ICH and 137 with hypertensive ICH, high-grade centrum semiovale EPVSs were associated with CAA-related ICH and basal ganglia EPVSs were associated with hypertensive ICH, a finding replicated in other research.[17,49,63] In patients with spontaneous cerebellar ICH, the presence of >20 centrum semiovale EPVSs was associated with higher lobar cerebral microbleed scores, which also add evidence for possible association between CAA-type ICH and EPVSs.[64] Furthermore, there is a correlation between higher severity of centrum semiovale EPVSs with increased uptake of 11C-Pittsburgh compound B in patients with ICH who are diagnosed with “probable” CAA.[65] One autopsy study found that patients with CAA have hemosiderin-laden macrophages in their EPVSs and mononuclear cells in the white matter.[53–66]

Whether EPVSs can influence the clinical presentation of CAA has been investigated, and the results suggest that EPVSs do not influence the clinical presentation of ICH or its severity. One study noted that there were no demonstrable differences in EPVS severity (for both centrum semiovale and basal ganglia) between patients presenting with focal deficits or cognitive impairment.[63] Similarly, EPVS burden was not predictive of hematoma expansion or recurrent ICH risk in patients with CAA-related ICH.[50,67] In patients with CAA, there is no correlation between centrum semiovale

Table 2. Summary of the Major Studies of the Relationship Bet ween EPVS Parameters and VCI and Dementia

No.	Study/authors/duration	Study design	Study setting	Sample size	Association/relation studied	Results/outcomes
1	Ding et al (2017); Gene/Environment Susceptibility–Reykjavik Study[71]	Prospective (5-y follow-up)	Population	2612	Whether large EPVSs (L-PVSs) (>3 mm in diameter) on MRI associated with CSVD and cognitive decline in older individuals	Presence of L-PVSs associated with steeper decline in information processing speed and quadruple risk of vascular dementia. Persisted when adjusted for genetic and cerebrovascular risk factors
2	Zhu et al (2010)[72]	Prospective (4-y follow-up; total 6135 y)	Population	1778	Assess the association between severity of EPVSs and incident dementia and cognitive decline	Highest-degree EPVSs associated with risk of incident dementia independently, both for WM-EPVSs (HR, 9.8 [95% CI, 1.7–55.3]) and BG-EPVSs (HR, 5.8 [95% CI, 1.2–28.4]). After further adjustment, association remained for WM-EPVSs. Higher rate of cognitive decline related to high BG-EPVSs but not WM-EPVSs
3	Valdes Hernandez et al (2020); Lothian birth cohort[73]	Retrospective cross-sectional	Population	700	Possible associations of CSO-EPVS volume and count with cognitive abilities using MRI	CSO-EPVS volume was only associated with memory (B=–114.5; SE=48.35; P=0.018) and not overall cognition in linear models, adjusting for various demographic and vascular factors
4	Yilmaz et al (2018); Rotterdam study[74]	Prospective (7.2-y follow-up)	Population	1651	Association of CAA score (including EPVSs) with cognition, stroke, dementia, and mortality	Total CSVD score related to stroke, death, and dementia but not BG-EPVS scores
6	Jokinen et al 2020; LADIS study.[75]	Prospective (7-y follow-up)	Population	560	Quantify CSVD predictive value on cognitive and functional abilities	Total EPVS volume associated with overall performance and decline in processing speed, as well as decline in memory; however, in multivariable model, EPVSs were not independent predictors
7	Paradise et al (2020)[76]	Cross-sectional	Population	414	EPVS associations with cross-sectional global and domain-specific cognition	Neither BG-EPVS nor CSO-EPVS independently associated with global or domain-specific cognitive impairment
8	Banerjee et al (2017)[77]	Cross-sectional	Hospital/clinical	226 (110 patients with AD and 116 with VCI)	Study if CSO-EPVSs associated with clinically diagnosed AD and BG-EPVSs associated with subcortical VCI	In adjusted analyses, CSO-EPVSs independently associated with AD (OR, 6.26 [95% CI, 1.66–23.58]; P=0.017, compared with none/mild grade). BG-EPVSs associated with VCI and negatively predicted AD (OR, 0.03 [95% CI, 0.00–0.44]; P=0.009, compared with none/mild grade)

(*Continued*)

Table 2. Continued

No.	Study/authors/duration	Study design	Study setting	Sample size	Association/relation studied	Results/outcomes
9	Molad et al (2017) TABASCO study[78]	Prospective (1-y follow-up)	Hospital (TIA or stroke)	266	Determine if adding other SVD markers to WMH improves prediction of poststroke cognitive performances	WMH score was associated with poor poststroke cognitive performance. Adding other CSVD markers or CSVD burden score, however, did not improve prediction
10	Puy et al (2018); GRECogVASC study[79]	Prospective (6-mo follow-up)	Hospital (stroke)	356	Define imaging determinants of poststroke cognitive performance, including lesion burden and strategic locations	Strategic strokes, medial temporal atrophy, and total brain tissue volume predicted cognitive outcome. No predictive value of EPVSs, WMHVs, or CMBs

AD indicates Alzheimer disease; BG, basal ganglia; CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed; CSO, centrum semiovale; CSVD, cerebral small-vessel disease; EPVS, enlarged perivascular space; GRECogVASC, Groupe de Réflexion pour l'Evaluation Cognitive Vasculaire; HR, hazard ratio; LADIS, Leukoaraiosis and Disability Study; MRI, magnetic resonance imaging; OR, odds ratio; TABASCO, Tel-Aviv Brain Acute Stroke Cohort; TIA, transient ischemic attack; VCI, vascular cognitive impairment; WM, white matter; WMH, WM hyperintensity; and WMHV, WMH volume.

EPVSs and outcomes, such as non-ICH stroke, dementia, or mortality.[68] Total CSVD score, but not EPVS score alone, correlates with the risk of hemorrhagic transformation of ischemic strokes.[69] Nonetheless, there may be a role for EPVSs in risk stratification for anticoagulation-related ICH. For example, a study of 1386 patients with TIA or ischemic stroke on therapeutic anticoagulation for atrial fibrillation reported that basal ganglia but not centrum semiovale EPVSs were associated with risk of ICH.[70] Despite this evidence, no study to date has provided strong data that anticoagulation is contraindicated among people with EPVSs, and it should be used when indicated regardless of EPVS status.

DEMENTIA AND VASCULAR COGNITIVE IMPAIRMENT

Numerous population-based studies have investigated the association of EPVSs with prevalent or incident cognitive impairment (Table 2).[71–80] Perhaps the strongest evidence supporting a role for EPVSs in cognitive decline comes from the Gene/Environment Susceptibility–Reykjavik Study that included 2612 patients with 5-year follow-up. EPVSs were associated with steeper cognitive decline in information processing speed and >4-fold risk of vascular dementia.[71] Another community-based study of 1778 participants without dementia assessed longitudinally over 4 years showed that higher EPVS burden in either the basal ganglia or the centrum semiovale was associated with risk of incident dementia. However, only basal ganglia EPVSs were associated with a higher rate of cognitive decline.[72] With regard to other locations, hippocampal EPVSs are inversely correlated with verbal reasoning but not with overall cognitive impairment or dementia.[81] EPVSs have been also associated with cognitive dysfunction in older dementia-free men specifically in nonverbal reasoning and visuospatial functions, but this association is partially confounded by atrophy.[82] The association between EPVSs and measures of cognition and dementia is less consistent in the Rotterdam study, the LADIS (Leukoaraiosis and Disability Study), and the Lothian birth cohort.[76] A meta-analysis of 116 studies limited by heterogeneity also reported no association between EPVSs and dementia.[42] The conflicting results are partially attributable to the heterogeneous exposure measurement and various populations.

Dementia Subtypes

In a study of 110 patients with Alzheimer disease and 116 patients with vascular cognitive impairment, centrum semiovale EPVSs were associated with Alzheimer disease, and basal ganglia EPVSs were associated with vascular cognitive impairment.[77] Basal ganglia

EPVS scores were higher with vascular dementia than with Alzheimer disease, frontotemporal dementia, or healthy controls. Basal ganglia EPVSs carried a higher sensitivity of and specificity (67% and 70%, respectively) for vascular dementia compared with other dementia subtypes.[9] In a systematic review of EPVSs and dementia, 5 of 13 studies of vascular dementia reported an association with basal ganglia EPVSs. The results were ambiguous for relationships between EPVS and Alzheimer disease or the other dementia subtypes.[83] This evidence does suggest that in older individuals, EPVSs in deeper brain areas relate better to vascular dementia than to Alzheimer disease. Using the same EPVS scale as in NOMAS, we reported that increasing EPVS severity is associated with worse cognitive diagnosis in patients with Down syndrome (amyloid-β hyperproducers), which does suggest an association between amyloid accumulation and EPVSs in a clinical context less biased by older age and traditional vascular risk factors, as is in the case of late-onset Alzheimer disease.[84]

Poststroke Cognitive Performance

In patients with lacunar strokes, basal ganglia EPVSs were negatively correlated with processing speed after adjusting for confounding factors.[85] Similarly, Mini-Mental State Examination scores at 1-year poststroke were related to higher basal ganglia EPVSs.[86] Other studies, however, have not replicated an association between EPVSs and poorer poststroke cognitive performance.[87,88] In the TABASCO (Tel-Aviv Brain Acute Stroke Cohort) study of patients with TIA or stroke, only WMH but not EPVS was predictive of cognitive performance at 1 year.[78] Finally, a meta-analysis of 3575 patients, aged between 63 and 73 years, found no correlation between total EPVS burden and Mini-Mental State Examination scores, except for hippocampal EPVSs associated with decreased memory function.[89]

CONCLUSIONS

EPVSs have been extensively studied as biomarkers of various clinical aspects of neurological diseases, specifically as imaging biomarkers of SVD and of dysfunctional brain interstitial fluid drainage. Deep EPVSs localized to the basal ganglia are closely related to vascular outcomes, whereas centrum semiovale EPVSs are more often associated with dementia or CAA. These differential associations are likely related to the greater exposure of deep penetrating arteries and surrounding tissue to systemic pulsatile hemodynamics, whereas cerebral convexity diving arteries (ie, medullary arteries) are more likely related to alterations in interstitial fluid drainage. Despite the evidence reported to date, EPVSs are not routinely used to stratify the risk of vascular or cognitive outcomes in clinical practice, and the use of EPVSs remains confined to research.

Integrating EPVSs into mechanistic studies simultaneously to other markers of SVD can help understand whether there is a unique role of EPVSs in brain disease physiopathology or whether EPVSs represent only an epiphenomenon of aging and specifically of SVD. Although there is evidence that the association between EPVSs and certain vascular and cognitive outcomes is independent of other MRI markers of SVD, such as chronic lacunar infarcts, cerebral microbleeds, and WMHs, these association are not always replicated, which introduces hesitancy as of the worth of EPVS rating given the effort it takes to measure them. Furthermore, the heterogeneity in the methods to study EPVSs hinders the comparison of studies, which itself perpetuates the lack of consistency in results across various populations. Therefore, a unified, reproducible, and preferably automated method to measure EPVSs is a high priority in the field. Alternatively, integration of EPVSs in algorithms to risk stratify patients to a given treatment or intervention as part of a clinical trial could help decide whether there is value in measuring EPVSs in clinical practice.

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