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Review Article

Pericytes and Resident Perivascular Macrophages Play a Key Role in the Development of Enlarged Perivascular Spaces in Obesity, Metabolic Syndrome and Type 2 Diabetes Mellitus

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Abstract

Pericyte(s) (Pcs) and resident perivascular macrophages (rPVMΦs) are positioned perfectly in the neurovascular unit (NVU) and perivascular spaces (PVS) to facilitate metainflammation that results in brain endothelial cell activation and dysfunction and neuroinflammation. Their positions within the NVU allow intimate contact with one another between the NVU and PVS as follows: Brain endothelial cells (BECs) and the Pcs via their shared basement membrane and physical contact peg-socket junctions with N cadherins and gap junctions Cx43; Pcs and intimate contacts with rPVMΦs residing in the PVS. Additionally, rPVMΦs have intimate contact with the astrocyte endfeet (ACef) that form the outermost membrane of PVS. Importantly, ACef have intimate contact with BECs that have intimate physical contact with neuronal axons and dendrites to complete NVU coupling. The multiplicity of intimate contacts of NVU cells allow for continuous crosstalk communications to provide brain homeostasis. While each of the cells of the NVU play important roles in the development of enlarged perivascular spaces (EPVS), this review focuses on the Pcs and rPVMΦs and discusses each of the intimate contacts and their functional significance in detail with numerous illustrations and transition electron microscopic images to demonstrate their role in the development of EPVS. EPVS are known to be biomarkers for cerebral small vessel disease and impaired glymphatic system waste clearance. While the importance of EPVS in mixed dementia, vascular contributions to cognitive impairment and dementia that result in high economic and psychosocial cost to the global community are unquestionable, the focus in this manuscript is on the how the triad of obesity, metabolic syndrome, and type 2 diabetes mellitus has on the development of EPVS.

Keywords: Astrocytes; Blood-brain Barrier; Enlarged Perivascular Spaces; Glymphatic System; Microglia; MRI; Pericytes; Perivascular Macrophages; Perivascular Spaces; Small Vessel Disease

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Abbreviations

AC: Astrocyte

ACef: Astrocyte End-Feet

AGE/RAGE: Advanced Glycation End Products/Receptor For Advanced Glycation End Products

AQP4: Aquaporin-4

BBB: Blood–Brain Barrier

BEC(s): Brain Endothelial Cell(s)

BEC*act/dys*: Brain Endothelial Cell Activation/Dysfunction

BG: Basal Ganglia

BM: Basement Membrane

CAA: Cerebral Amyloid Angiopathy

CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

CBF: Cerebral Blood Flow

CCVD: Cerebrocardiovascular Disease

CBF: Cerebral Blood Flow

Cl: Capillary Lumen

CNS: Central Nervous System

CR: Capillary Rarefaction

CSF: Cerebrospinal Fluid

CSO: Centrum Semiovale

DVS: Dural Venous Sinus

EPVS: Enlarged Perivascular Spaces

GS: Glymphatic Space

HTN: Hypertension

ISF: Interstitial Fluid

ISS: Interstitial Space

LPS: Lipopolysaccharide

lpsEVexos: Lipopolysaccharide Extracellular Vesicles;

MetS: Metabolic Syndrome

MGCs: Microglia Cells

MMPs: Matrix Metalloproteinases

MRI: Magnetic Resonance Imaging

MW: Metabolic Waste

NO: Nitric Oxide

MW: Metabolic Waste

MRI: Magnetic Resonance Imaging

NVU: Neurovascular Unit

Pc: Pericyte

Pcfp: Pericyte Foot Process

PVS: Perivascular Spaces

PVS/EPVS: Perivascular Space/Enlarged Perivascular Space

rPVMΦ: Resident Perivascular Macrophages

SAS: Subarachnoid Space

sLPS: Soluble Lipopolysaccharide

rPVMΦ: Reactive Perivascular Macrophage

SVD: Small Vessel Disease

T2DM: Type 2 Diabetes Mellitus

TEM: Transmission Electron Microscopy

TIA: Transient Ischemic Attack

WMH: White Matter Hyperintensities

Introduction

Perivascular Spaces (PVS) and Enlarged Perivascular Spaces (EPVS) (PVS/EPVS) or Virchow-Robin spaces have multiple structural and functional importance. PVS/EPVS are fluid filled spaces that ensheathe the precapillary arterioles (transporting CSF) and postcapillary venules(transporting primarily interstitial fluid mixed with lesser amounts of CSF) in the brain [1-4]. Precapillary arteriole PVS are known to deliver cerebrospinal fluid (CSF), while postcapillary venules are known for the anatomical transcytosis of proinflammatory leukocytes and their clearance of interstitial fluid (ISF) and metabolic waste (MW) from the interstitial spaces (ISS) via the PVS that serve as a conduit for the glymphatic system (GS) that bathe the parenchymal neurons (Figures 1 and 2) [5, 6].

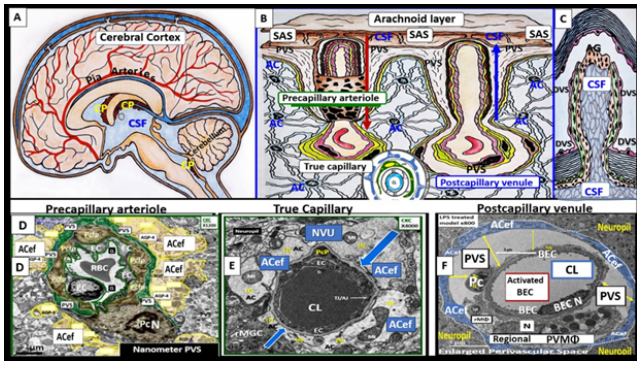

Figure 1: A collage of cerebrospinal fluid (CSF) and interstitial fluid (ISF) bathing the brain and transmission electron micrographs of precapillary arteriole, true capillary, and postcapillary venule with its perivascular spaces (PVS).

Panels A, B, and C illustrate the CSF being delivered from the subarachnoid space (SAS) throughout the central nervous system (CNS) and parenchymal neurons via the perivascular spaces that ensheathe the pia arteries and precapillary arterioles to the true capillaries where solutes and fluids are delivered and then the postcapillary venules and veins to carry the interstitial fluid (ISF) and metabolic waste to the SAS and CSF for disposal in panels B and C. **Panel D** illustrates a precapillary arteriole and note the pseudo-colored golden yellow astrocyte endfeet (ACef) that tightly abut the pseudo colored green perivascular space (PVS). **Panel E** illustrates a true capillary wherein the ACef tightly abut the basement membrane (BM) of the mural neurovascular unit (NVU) endothelial cells (EC) and pericyte (Pc) cells. **Panel F** depicts an enlarged PVS as denoted by the space demarked by yellow double arrows and note the ACef have detached and separated from the BM of the mural cells [7].

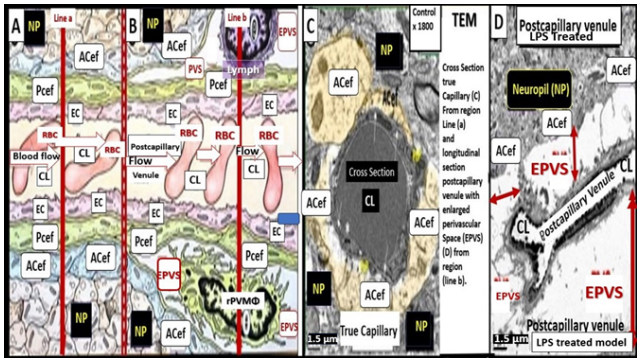

Figure 2: Illustration depicting the transition from normal capillaries with no perivascular space at the level of the true capillary to a postcapillary venule with a normal perivascular space (PVS) that transitions to a postcapillary venule with an enlarged perivascular space (EPVS) with supportive transition electron micrographs (TEMs) in panels C and D.

Panels A and B are an illustration to demonstrate the transition from a true capillary without a perivascular space in panel A that transitions to the postcapillary venule with a normal perivascular space (PSV) to the postcapillary venule with enlarged perivascular spaces (EPVS). **Panel C** demonstrates a normal control true capillary in cross section without a perivascular spacethat is responsible for the delivery of nutrients, solutes, and oxygen and note how the pseudo-colored golden yellow astrocytes (ACs) and their endfeet (ACef) tightly abut the mural cells (endothelial cells (ECs) and pericytes (Pcs). **Panel D** depicts an elongated postcapillary venule with obvious EPVS in a longitudinal section and note how the ACef have detached and separated from the NVU mural endothelial cells (ECs) and pericytes (Pcs) basement membranes (BMs) to create the EPVS. Scale bars C and D equal 1.5 µm. PVS are considered not to be enlarged if they are not visible on T-2 weighted magnetic resonance images (MRI). However, PVS are considered to be enlarged (EPVS) when they can be

identified by T-2 weighted MRIsand EPVS are approximately one-three millimeters in diameter [4, 8]. EPVS are recognized as important structural remodeling changes in various neurologic diseases and are currently known as biomarkers for cerebral small vessel disease (SVD) and vascular dementia (VaD), which are also known to be associated with lacunar stroke and white matter hyperintensities (WMH) [3,8-12]. Importantly, EPVS associate with advancing age, hypertension, lacunes, microbleeds, intracerebral hemorrhages, cerebrocardiovascular diseases with transient ischemic episodes and stroke, SVD, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADISIL), cerebral amyloid angiopathy (CAA), obesity, metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), WMH, late-onset Alzheimer's disease (LOAD), sporadic Parkinson's disease, and non-age-related multiple sclerosis [2-4, 8-10, 13-17]. Further, our global population is already one of the oldest in history andadditional aging is expected to increase in the coming years as ourglobal population continues to age [7,18,19]. Additionally, EPVS are related to extracranial atherosclerosis, cerebromacrovascular, and cerebromicrovascular disease in addition to age-related neurodegenerative diseases such as LOAD and sporadic Parkinson's disease. EPVS are located primarily in the basal ganglia (BG) and the centrum semiovale (CS0); however, they have also been identified in the hippocampus, midbrain, and the frontal cortex (Figure 3) [4, 9, 20].

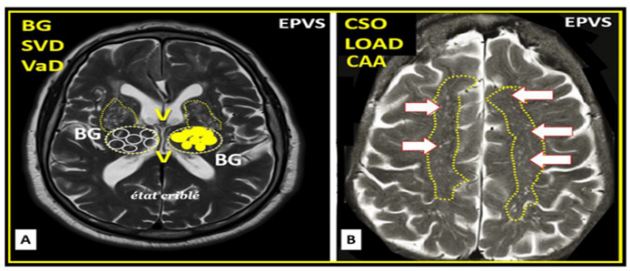

Figure 3: Magnetic resonance imaging (MRI) comparisons of basal ganglia (BG) enlarged perivascular spaces (EPVSs) to centrum semiovale (CSO) EPVSs.

Panel (A) depicts the paired EPVSs within the BG that are traced in open circles on the left and masked yellow circles on the right BG. Additionally, note the faint white spaces within the paired dashed lines just above the paired BG structures. This MRI image is from a 75 y/o male status post-stroke, recovered with small vessel disease. **Panel (B)** depicts the paired elongated oval structures outlined by yellow dashed lines to enclose multiple white enlarged perivascular spaces. Note the open white arrows outlined in red pointing to prominent EPVSs. MRI image from a 79 y/o female with history of transient ischemic attacks. Importantly,note that BG EPVSs strongly associates with cerebral small vessel disease (SVD) in **Panel (A)** and that CSO EPVSs strongly associates with late-onset Alzheimer's disease and cerebral amyloid angiopathy (CAA) in **Panel (B)**. Permission to reproduce this image by author is by CC 4.0 [20]. Notably, it has been determined that EPVS in the CSO may have a greater association with amyloid beta pathology [21], and that EPVS of the BG are more indicative of arteriolosclerosis, hypertensive arteriopathy, diabetes mellitus, hyperlipidemia, prior stroke, lacunes, deep microbleeds, and SVD [22-24]. Also, EPVS have been determined to be a marker for an increased risk of cognitive decline and dementia independent of other small vessel disease markers over a four-year period [25]. EPVS are known to exist in at least three major subtypes based on the regions of their occurance as follows:- Type I PVS/EPVS are located along lenticulostriate arteries that enter the BG sometimes referred to as État criblé (a collection of multiple radiolucent 1-5 millimeterof EPVS frequently found in the BG in T-2 weighted MRIs); type II are present along the path of perforating medullary arteries to enter cortical gray matter around high convexities that extend into the white mater and are associated with CSO regions; type III are located in the midbrain and surround the penetrating branches of the collicular and assessory collicular arteries [26]. Recently, Paradise et al., have shown that EPVS are a marker for an increased risk of cognitive decline and dementia, independent of other small vessel disease markers [27]. Further, this group has also suggested that EPVS should no longer be thought of as just an incidental finding associated with aging but also a biomarker for SVD and cognitive impairment, dementia, and a biomarker of impaired waste clearance in the brain [28]. Multiple mechanisms are thought to be involved in the development of EPVS, which include the following: (1) increased fluid and neurotoxic proteins that enter the PVS due to BBB dysfunction/disruption due to increased permeability; (2) increased fluid inflow to the PVS due to ACef dysfunction, detachment, separation and aquaporin-4 dysfunction with decreased water uptake allowing the accumulation of water in the PVS; (3) stalling or obstruction of the PVS conduit or impaired glymphatic efflux due to inflammation and the accumulation of excess leukocytes with phagocytosis and accumulation of excessive phagocytic debris, oxidative stress, and activation of increased MMPs, which result in stagnation, stalling, and/or varying degrees of PVS conduit glymphatic system obstruction of the waste removal mechanisms; (4) arteriole or venule vascular stiffening and/or spiraling of arterioles that are associated with decreased vascular pulsatility, which results in decreased fluid flow within the PVS contributing to PVS enlargement; (5) atrophy or loss of surrounding neurons and their axons [2, 3,7,9-11,15,16,28]. Further, EPVS do not develop all at once but are thought to be associated with a sequence of events and exist as an evolutionary spectrum such that they develop over time to result in SVD, neuro inflammation, impaired cognition and neurodegeneration (Figure 4) [7,29].

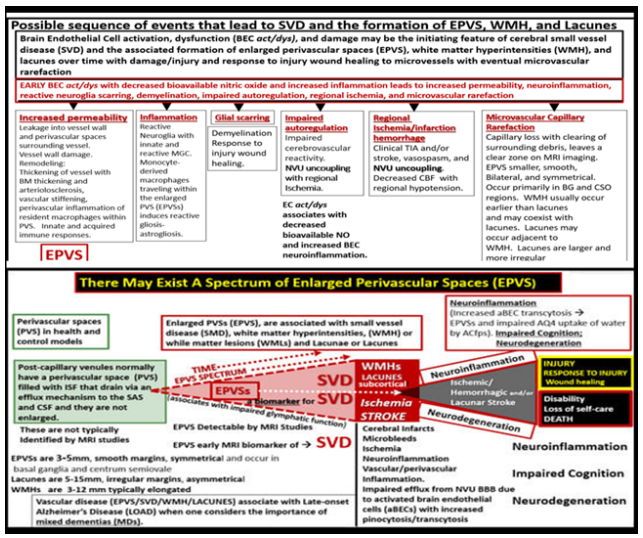

Figure 4: A probable sequence of events and a continuum of remodeling, which results in a spectrum regarding the development of enlarged perivascular spaces (EPVS) over time. There exists a sequence of remodeling changes and events in the development of enlarged perivascular spaces, white matter hyperintensities, lacunes and small vessel disease [7, 29].

The Obesity, MetS and T2DM triad is associated with the development of EPVS and may contribute to accelerated brain aging and injury [7]. Notably, the MetS is known to increase the risk for developing cerebrocardiovascular disease with both macro-and microvascular disease; arteriolosclerosis and extracranial and cranial atherosclerosis as well as T2DM [29, 30]. The MetS has multiple risk factors and variables that would contribute to EPVS and it is known that T2DM increases the risk for late-onset Alzheimer's disease (LOAD) as well as other neurodegenerative diseases including age-related Parkinson's disease (Figure 5) [29].

There are four arms to the central X in this illustration thatpoints to hyperlipidemia (lower left), hyperinsulinemia of insulin resistance (IR) (lower right), essential hypertension (upper right), and hyperglycemia (upper left). It is currently known that EPVS are a biomarker of SVD, cognitive decline and dementia, and possibly impaired glymphatic system waste removal. Importantly, visceral adipose tissue (VAT), increased triglyceride/glucose index (TG index), and

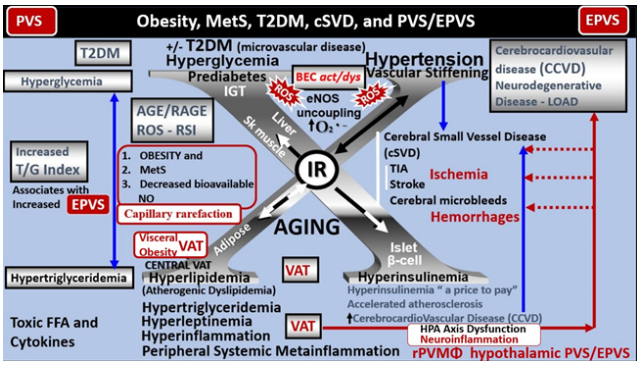

Figure 5: Metabolic syndrome (MetS), cerebral small vessel disease (SVD) and perivascular spaces (PVS)/enlarged perivascular spaces (EPVS).

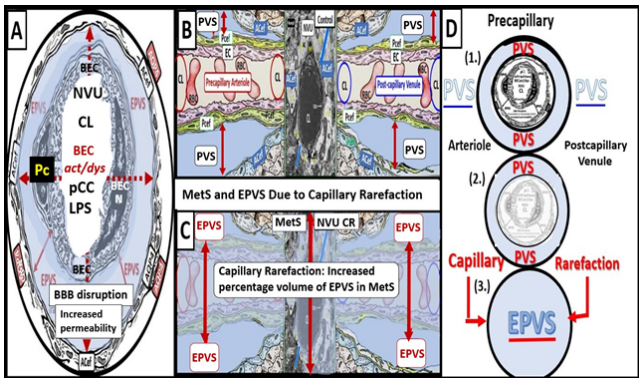

Figure 6: Cross and longitudinal sections representitive of pre- and post-capillary arterioles and venules with an encompassing surrounding perivascular space (PVS).

Panel A depicts a cross section of a capillary surrounded by a PVS (solid double red arrows) and its increase in total volume to become an enlarged perivascular space (EPVS) (dashed double red arrows), which represents capillary rarefaction. **Panel B** demonstrates a control longitudinal capillary that runs through an encompassing PVS (light blue). **Panel C** depicts capillary rarefaction in a longitudinal view and note how the volume of the PVS increases it total volume once the capillary has undergone rarefaction (double red arrows). **Panel D** depicts the progression of a normal precapillary arteriole and postcapillary venule PVS to an EPVS once the capillary has undergone rarefaction allowing for an increase total percentage volume of the PVS (1.- 3) [7].

hypertension associate with SVD. Each of these four arms is either directly or indirectly associated with EPVS and SVD. Notably, the triad of obesity, MetS, and decreased bioavailable nitric oxide (NO) are known to associate with capillary rarefaction. Also, note how metainflammation (the chronic production of sterile peripheral induced inflammation) primarily by VAT in obesity, MetS and T2DM contributes to the development ofhypothalamic pituitary axis (HPA) axis dysfunction due to neuroinflammation that is partially induced by the resident perivascular macrophage (rPVMΦ) in the hypothalamic regions and cerebrocardiovascular disease (CCVD), SVD, TIA, stroke, microbleeds, hemorrhages, and neurodegeneration (red arrows straight and dashed lines) [7,29,31] has recently demonstrated that in addition to cerebral infarcts EPVS burden was associated with diabetes independently of other neuropathologies in a cohort of 654 individuals from a community-based older adults [31]. Capillary rarefaction (CR) in the brain (loss of capillaries) has recently been found to be associated with an increase in obesity, MetS, and T2DM [7, 31-33]. Recently, Schulyatnikova and Hayden have hypothesized that capillary rarefaction may leave an empty space within the PVS that is subsequently filled with interstitial fluid [7]. This loss of capillaries within the PVS may allow for an increase in total percentage fluid volume within the PVS when the capillary undergoes rarefaction and may contribute to the development of EPVS (Figure 6) [7].

CR is known to occur in multiple clinical situations, including: aging, hypertension, obesity, MetS, T2DM, SVD, and LOAD. Also, there are multiple proposed mechanisms that may co-occur to result in CR, including: oxidative – redox stress, inflammation, BECact/dys and loss, Pc dysfunction and loss, impaired angiogenesis (increased ratio of antiangiogenic factors/proangiogenic factors), microvessel ischemia with emboli or hemorrhage, decreased microvessel shear stress, increased microvessel tortuosity, and in some cases increased transforming growth factor beta [34, 35]. While this mechanistic hypothesis for possible expansion of PVS due to CR is plausible, more research will be required for it to gain support as a mechanism for increased EPVS. Pericyte(s) (Pc) cells and brain endothelial cell(s) (BECs) are the two mural cells that are essential to form the multicellular neurovascular unit (NVU) consisting of BECs, Pcs, astrocytes and their endfeet (ACef), perivascular microglia cell(s) (PVMGCs) and resident perivascular macrophages (rPVMΦs), and neurons [36], which are important in the development of EPVS. Pcs extend their elongated pericyte foot processes (Pcfp) that encircle BECs and communicate via physical contact peg sockets and gap junctions connexins with BECs and are also in intimate association with rPVMΦ.

Pcs are uniquely positioned within the NVU and make physical and intimate connections with BECs, rPVMΦs, and ACef [3, 36]. Pcs are multifunctional and known to process signaling, integrate and coordinate signals from BECs, rPVMΦs, and neurons to complete the NVU and provide for NVU coupling to assist in increasing cerebral blood flow (CBF) in regions of increased neural activity, and signaling [36, 37]. Pcs also generate multiple functional responses critical for central nervous system functions in both health and disease. These functions include the regulation and maintenance of the blood brain barrier (BBB), BBB permeability, angiogenesis, NVU capillary hemodynamic responses, and clearance of metabolic waste including neurotoxins, hemodynamic responses including NVU coupling via ACef that connect to neurons and control microvascular cerebral blood flow (CBF) via NVU coupling, and importantly neuroinflammation [37, 38]. Notably, Pcs have been thought to act as pluripotent mesenchymal stem cells and are capable of lifting from the NVU niche and migrating to regions of CNS injury [37]. The unique structural localization of Pcs and their foot processes that are interspersed or sandwiched between the BEC BMs of the NVU and ACef and the PVS and its outermost ACef place them in pivotal position to regulate the inflammatory responses of the CNS in the immediate region of the NVU PVS in addition to the CNS neuronal parenchyma [39,40]. rPVMΦs play a key and important role in the development of EPVS. Resident perivascular macrophages (rPVMΦs)reside within the PVS andsimilar to the CNS microglial cells (MGCs), in that, both are derived from the yolk sack play an important role in the development of EPVS (Figures 1F & 7) [41, 42].

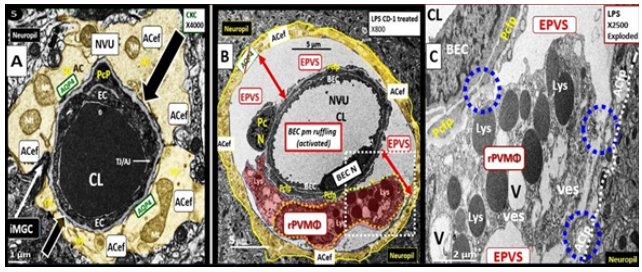

Figure 7: Enlarged perivascular space (EPVS) and resident-reactive perivascular macrophage (rPVMΦs) in a postcapillary venule compared to a true capillary.

Panel A demonstrates a normal true capillary in a 20-week-old female C57B6/J control model and note how the ACef tightly abut the shared basement membrane (open black arrows) of the brain endothelial cell (BEC) and pericyte foot process (PcP). **Panel B** depicts an EPVS with a prominent rPVMΦ (pseudo-colored red) in a 20-week-old lipopolysaccharide (LPS)-treated CD-1male model and note how the astrocyte endfeet-foot processes (ACfp) are markedly separated from the capillary mural cells (BEC and Pc) (red double arrows). **Panel C** depicts the rPVMΦs in an exploded image with intimate contact with the Pcfps basal lamina and the rPVMΦ intimate contact with basal lamina of the ACef (outermost boundary of the EPVS abluminal lining) (dashed blue circles) [29]. TEM images have consistently shown that rPVMΦs are located within the PVS between the luminal mural cells and the outermost basal lamina of the ACef or glial limitans and the brain parenchyma as depicted in (Figure 5B) [42-44]. As one reviews the literature on rPVMΦ, the term border-associated macrophages (BAMs) is frequently discussed and these BAMs are now thought to be rPVMΦ since they have been shown to reside within the PVS by TEM studies [42-44]. rPVMΦs are known to facilitate BBB integrity, promote glymphatic drainage, and exert immune function such as phagocytosis and serve as antigen presenting cells within the PVS to facilitate neuroinflammation once it is initiated since they are key components of the PVS and CNS-resident immune system [41].

The PVS As an Anatomical Crossroad and Space that Provide Multicellular Crosstalk to Facilitate the Development of EPVS

Neurological disorders and diseases are known to have heterogenous pathogenesis, with multiple overlapping contributions of vascular, immune, and neuronal mechanisms of brain injury. PVS/EPVS in the brain represent a crossroad intersection where those mechanisms interact [16], in addition to providing a conduit for the key anatomical component of the glymphatic pathway/system (GS) [5], which plays a crucial role in waste clearance of interstitial fluid that has been shown to be linked to neurodegenerative disease [16]. This neuroinflammation occurs initially in the PVS that has become enlarged (EPVS) due to the obstruction of the PVS/glymphatic system due to the accumulation of cells and cellular debris due to excessive neuroinflammation that occurs within the PVS of precapillary arterioles and postcapillary venules [16].These PVS provide a niche space for the ongoing inflammatory processes, which occur due to the extensive crosstalk between activated and dysfunctional BECs with proinflammatory leukocytes and rPVMΦ that are initially activated via peripheral metainflammation (sterile peripheral inflammation primarily produced by the extensive visceral adipose tissue) associated with obesity, MetS, and T2DM. These activated BECs undergo extensive crosstalk with adjacent Pcs that are in direct physical cell-cell contact via peg sockets, gap junction Cx43, and N-Cadherins. In turn, these reactive Pcs undergo extensive crosstalk communication with the PVS rPVMΦs and these rPVMΦ undergo extensive crosstalk communication with incoming proinflammatory leukocytes that are passed into the PVS via diapedesis through the activated BECs to eventually travel throughout the CNS [45]. These incoming proinflammatory leukocytes provide the oxidative stress and phagocytosis that activate MMP 2-9 that are capable of degrading the outer boundary of the perivascular space glia limitans to allow these now proinflammatory leukocytes to enter the CNS interstitial spaces (ISSs) to affect local, regional, and generalized neurons to instigate neuroinflammation with impaired synaptic function, neurodegeneration, and impaired cognition. Thus, the PVS and their subsequent enlargement act as the crossroad for extensive crosstalk communication between activated BECs, Pcs, rPVMΦs, incoming leukocytes, and ACef to allow leukocytes to pass into the interstitium to result in CNS neuroinflammation. Thus, PVS represent a crossroad where cerebrovascular, neuroinflammatory, and neurodegenerative mechanisms, of brain injury converge and interact (Figure 8) [16, 45].

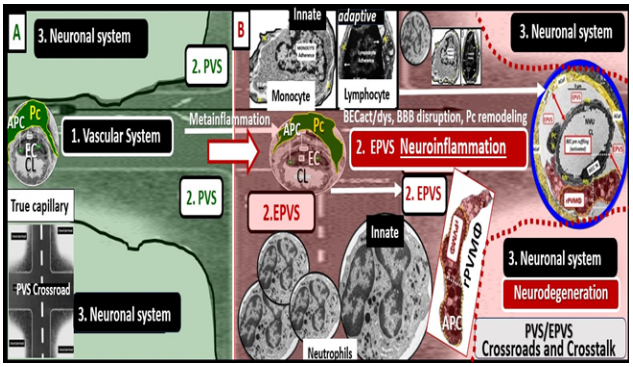

Figure 8: The perivascular spaces/enlarged perivascular spaces (PVS/EPVS) serve as an anatomical crossroad or intersection for the vascular, neuroinflammatory, and neuronal systems.

These three systems interact and allow for multiple cellular signaling crosstalk communication associated with the metainflammation of obesity, metabolic syndrome (MetS), and type 2 diabetes mellitus (T2DM) to result in impaired cognition and neurodegeneration. **Panel A** demonstrates the normal appearing PVS in control models with the green background. Note the highway PVS crossroad icon in lower left panel from which this figure was constructed. **Panel B** depicts the EPVS with its resident reactive perivascular macrophage (rPVMΦ) and leukocytes (neutrophils, monocytes, and lymphocytes) that have undergone diapedesis via paracellular or transcytotic routes via the activated BECs to enter the EPVS and comprise step 1 of the 2-step process of leukocytes entering the neuropil interstitial space (ISS). These leukocytes not only undergo cellular crosstalk with the activated BECs but also crosstalk with one another as well as the resident perivascular macrophage (rPVMΦ) within the PVS/EPVS, the pericyte (Pc), and the astrocyte endfeet (ACef) to result in EPVS, impaired cognition, and neurodegeneration. It is important to note that both the Pc and the rPVMΦ are known to be antigen presenting cell(s) (APCs). Additionally, the reactive leukocytes are capable of generating a huge amount of reactive oxygen species - oxidative stress and secretion of matrix metalloproteinases 2, 9 that are capable of degrading the outermost boundary of the PVS/EPVS ACef basal lamina or glia limitans to allow for the second-step for leukocyte entry into the neuropil interstitial spaces to result in neuroinflammation and subsequent neurodegeneration. The PVS/EPVS anatomical crossroad along with its multiple cellular crosstalk can therefore result in a self-perpetration or vicious cycle of brain injury and response to injury wound healing to result in neuroinflammation and neurodegeneration with impaired cognition. Additionally, it is important to note that the PVS forms the conduit for the glymphatic system to deliver metabolic waste and toxins from the interstitial fluid and provides the crosstalk communication necessary for neuroinflammation to develop within the PVS/EPVS. The increased neuroinflammation that occurs within the PVS/EPVS will develop considerable metabolic waste debris that will slow and cause delayed efflux to the interstitial fluid and cerebrospinal fluid to result in further dilation of the PVS/EPVS. Thus, the

vascular, neuroimmune, and neuronal systems can develop a pathological interplay, which can create a conducive environment capable of promoting a self-perpetration of brain injury mechanisms across different neurological regions of the CNS and neurological diseases, including those that are primarily thought of as neurodegenerative, neuroinflammatory or cerebrovascular diseases [16]. The PVS/EPVS provide a safe sanctuary space region to harbor the incoming proinflammatory leukocytes due to the NVU BBB disruption with increased permeability due to obesity, MetS, and T2DM as well as other possible clinical diseases. There is plenty of incoming proteinaceous waste material being taken up by the PVS. The PVS acts as a conduit space of CNS GS drainage that occurs between the ISF and the contents of postcapillary PVS efflux conduit for human and rodent models CNS metabolic toxic waste removal that is now widely accepted in the literature [5, 8, 20, 46, 47]. Thus, the postcapillary venule PVS serves as the anatomical conduit for the GS efflux of metabolic waste [48]. The accumulated leukocytes that reside within the PVS storage santuary will have plenty of opportunity to phagocytose this proteinaceous waste debris to eventually result in PVS neuroinflammation with stalling of PVS efflux waste removal of ISF flow even to the point of PVS obstruction with downstream enlargement and EPVS [5,16, 25,49,50]. Recently, Mendes et al., were able to show that in obese high-fat-diet fed mice (C57BL6) that this induced proinflammatory rPVMΦs in the hypothalamus helps to explain the HPA axis dysfunction found in obesity, MetS, and T2DM (Figures 5 & 9) [51].

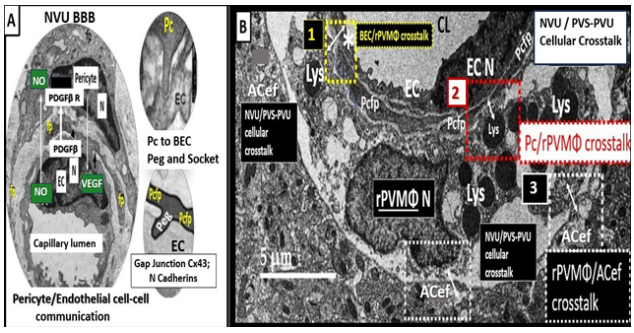

Figure 9: Perivascular spaces (PVS) and enlarged PVS (EPVS) provide a santuary space to serve as a crossroad for multicellular crosstalk between brain endothelial cell(s) (BECs), pericyte(s) (Pcs) and pericyte foot processe(s) (PCfps), resident perivascular macrophage(s) (rPVMΦs), leukocytes, and astrocyte endfeet (ACef).

Panel A demonstrates the neurovascular unit (NVU) with its blood-brain barrier/interface (BBB), as a result of the BECs tight and adherens junction(s) (TJ/AJs). The BECs and encircling Pc and its Pc foot processes (Pcfp) have a unique cell-cell direct physical contact for cell-cell communication via its peg socket morphology and phenotype along with its N-cadherinjunctions and its gap junction protein connexin 43 (Cx43). **Panel B** depicts the PVS/EPVS with its cellular contents of a rPVMΦ. Importantly note that there are three close intimate cell-cell contact regions for cellular crosstalk including 1. BEC/rPVMΦ (yellow boxed-in dashed lines and asterisk); 2. Pcfp/rPVMΦ (red boxed-in dashed lines; 3. rPVMΦ/ACef (white boxed-in dashed lines). Thus, this figure identifies the Pc and its foot processes along with the rPVMΦ as key cells residing within the PVS/EPVS – perivascular unit (PVU) to provide for this extensive crosstalk communication between NVU BECs, Pcef, rPVMΦs, and ACef.Double arrows depict this cell-cell crosstalk communication.

Reactive Juxtavascular Microglia Cells (rJVMGCs), Neuroinflammation, and Enlarged Perivascular Spaces (EPVS)

When neuroinflammation is discussed, the CNS resident immune microglia cell(s) (MGC) most often comes to mind and is discussed extensively in the literature [52-56] however, in this narrative review the focus has been primarily on the rPVMΦ that reside within the PVS by TEM studies. This is not only because PVS and EPVS are important [2, 8, 57] but also because both MGCs and PVMΦs have been rapidly gaining interest over the past decade [58]. Additionally, Xie et al., revealed that a bibliometric analysis linked brain related diseases with rPVMΦs and also pointed to the interest of reactive peripheral macrophages in visceral adipose tissue and vascular diseases in obesity, MetS, and T2DM as current hotspots in research [58]. Notably, CNS rJVMGCs could play a concurrent role along with rPVMΦs in PVS-induced neuroinflammation and enlargement [59]. For example, rJVMGCs are capable of promoting NVU BBB disruption allowing the diapedesis of leukocytes into the PVS [60] and further, neurotoxic insults are capable of inducing both rJVMGCs and reactive astrocytes (rACs) [61-63]. Also, rPVMGCs that lie outside of the PVS in the CNS parenchyma are known to be concurrently associated with ACs when peripheral cytokines/chemokines are chronically increased as in metainflammation associated with obesity, MetS, and T2DM [61-63]. Additionally, rACs and rPVMΦs would be capable of increasing CNS-derived proinflammatory cytokines/chemokines as well as reactive oxygen, nitrogen, sulfur species to result in an increased activity of the reactive species interactome (RSI), which are known to increase the secretion of matrix metalloproteinases (MMPs-2, 9) and contribute to BBB disruption [64-65]. These MMPs would be capable of contributing to the degradation of the ACef basal lamina (glia limitans) to allow the breaching of the PVS by proinflammatory leukocytes to complete the 2nd step of the 2-step process of CNS neuroinflammation [45, 59]. Notably, Zeng et al., recently demonstrated that EPVS severity was associated with the progression of tauopathy in LOAD and that rMGCs neuroinflammation mechanisms mediated this relationship of EPVS and tauopathy [66].

Current and Evolving Technologies to observe the Perivascular Spaces (PVS)

In 2019 Sepehrbandet al., examined and summarized the current and evolving technologies to observe PVS [67]. The current clinical methods now include identification and quantification of PVS asthe number of visible PVS by visual hand-counting methods or axial slices of T2-weighted images that has the highest number of PVS in the region of interest and then utilizing the Wardlaw's scale as previously demonstrated (Figure 3) [4,68, 69]. As one uses the Wardlaw's scale, the observer selects a representative axial slide for each region to be studied. If EPVS are observable in the midline or midbrain, it is automatically given a score of one, otherwise it is assigned a score of zero. When observing the BG and CSO, each EPVS and the region is rated according to five-point rating scale as follows: zero equaling no EPVS found; one equaling one to 10; two equaling 11-20; three equaling 21to 40; five equaling more than 40 EPVS. For example, earlier (Figures 3A & 3B) each have a Wardlaw's scale score of fiveby visual hand-counting methods. This five-point rating is known to have higher inter observer and test-retest reliability. However, it has been used to objectively link EPVS to neurological diseases and glymphatic dysfunction as a maker of disease [68]. This methodutilizing Wardlaw's scale is known to be laboriousand prone to errors, therefore; efforts to improve efficiency and accuracy have been made by using a wide range of automatic or semi-automatic segmentation techniques, from classical image processing approaches to deep neural network modelling that utilize complex algorithms (Box1) [70-81].

When the PVS become visible in MRI images in white matter regions such as in the BG and CSO regions they represent pathological features of brain vasculature damage, which also indicate obstruction of the CSF/ISF flow and associated impairment of waste efflux of clearance to the SAS/CSF and systemic vascular system (Figure 2) [82]. Currently, the most widely accepted and adopted technology

Current and Emerging Technologies of Quantification of Enlarged Perivascular Spaces

1. Currently in clinical practice the PVS is quantified based on the number of visible PVS on the axial slices of T2-weighted images
2. Higher Tesla (ultrahigh magnetic field strengths) such as 7 Tesla are known to have improved sensitivity and resolution to quantify both concentration and size as compared to current lower Tesla MRI.
3. The development of a higher range of automatic or semi-automatic segmentation techniques utilizing voxel algorithm and deep learning (applied machine learning) techniques, from previous classical hand-counting image processing with approaches to deep neural network modelling, such as automated morphologic segmentation of enlarged perivascular spaces at clinical field strength, Haar transform of non-local cubes, optimal 3D filtering, object-based approach for detecting small brain lesions, sequence optimization and morphology characterization of 7 Tesla, auto-context orientational information of the PVS for automatic segmentation, multiscale vessel enhancement filtering, convolutional neural network with a 3D kernel to automate the quantification of enlarged perivascular spaces, 3D regression neural network for the quantification of enlarged perivascular spaces in brain MRI
4. Quantitative voxel-based algorithm automatic may prove to be the most accurate method to quantitate enlarged perivascular spaces.
5. In the coming years author is certain that consensus will be developed for the quantification of enlarged perivascular spaces.

involve the utilization of Wardlaw's scale [4, 69]. For a more in-depth discussion of the current and evolving technologies to observe enlarged perivascular) readers are urged to read the following paper by Pham et al, [69].

Conclusion

EPVS have been previously noted for decades, but frequently overlooked and were initially thought to be of uncertain pathophysiology [9]. However, EPVS are currently emerging as important aberrant morphological findings in association with multiple clinical diseases and aging. Some have even suggested that it is now uncontested that PVS play critical roles in not only maintaining homeostasis but also priming neuroinflammation as illustrated in (Figure 8) [82, 83]. In this narrative review, the first paragraph of the introduction discusses the perivascular spaces (PVS) and enlarged perivascular spaces (EPVS) (PVS/EPVS) or Virchow-Robin spaces that have multiple structural and functional importance; the second paragraph discusses the obesity, MetS and T2DM triad that is associated with the development of EPVS that may contribute to accelerated brain aging and the injury role and the association of obesity, MetS, and T2DM in the development of EPVS; while the third paragraph discusses the key role of Pc cells in the development of EPVS; the fourth paragraph discusses the key role that rPVMΦs play in the development of EPVS. Section 2. discusses the importance of the PVS and the EPVS as a regional anatomical crossroads and spaces that provide for multicellular crosstalk to facilitate the development of EPVS as well as functioning as a repository space for leukocytes that have undergone diapedesis across the NVU BBB due to BE*act/dys*. Section 3. discusses the current and emerging technologies of quantitating EPVS. Importantly, the key roles of Pcs and rPVMΦ were explored in more depth as they relate to neuroinflammation and the development of EPVS than in most other papers that have reviewed EPVS. As our knowledge regarding the development of EPVS continues to grow and we better understand how they are important in their associated clinical disease states we will undoubtedly continue to make new findings regarding their development and progression. For example, how might we be able to slow or prevent PVS enlargement and how might EPVS associate with impaired glymphatic waste removal, impaired cognition, neuroinflammation, and neurodegeneration? While this narrative review parallels many of the referenced publications regarding PVS/EPVS and their development, the author has utilized multiple TEM images and multiple illustrations in order to aid in the understanding of not only structural remodeling but also the functional changes associated with the development of EPVS. More research in this field is necessary and it is obvious that this field is growing rapidly with many different hot spots being explored along the way, especially in regards to the postcapillary venule, which is the conduit for the glymphatic system of interstitial fluid waste efflux and removal to the CSF and systemic circulation. Additionally, there isan exponential expansion of research studies in the glymphatic pathway-system field of study, which utilizes the postcapillary venule perivascular space and itsgrowing expansion in this research field of study. M.R.H. is totally responsible for theConceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing—Original Draft Preparation, Writing—Review and Editing, Visualization, Supervision, Project Administration, and Funding Acquisition. Author has read and agreed to the published version of the manuscript.

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Data and materials will be provided upon reasonable request.

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Conflicts of Interest

Author declares no conflicts of interest.

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