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Hemodynamic Alterations in Multiple Sclerosis

Aise Seda Artis

Abstract

Multiple Sclerosis is an autoimmune disease of the central nervous system. It is a demyelinating and neurodegenerative condition, however, changes in the vasculature can occur and play a role in the pathophysiology. Cardiac and vascular risk factors contribute to the disease severity. Understanding the occurring hemodynamic changes may potentially lead to improved diagnosis, better patient management, and prevention of disease progression. This paper discusses the hemodynamic impairment in multiple sclerosis focusing on both the cerebral and cervical regions and presents an up-to-date review of the literature.

Keywords: multiple sclerosis, cerebral hemodynamics, cervical hemodynamics, perfusion, oxidant damage

1. Introduction

Multiple Sclerosis (MS) is a chronic disease of the central nervous system (CNS), today affecting approximately 2.8 million people worldwide (35.9 per 100,000 population) [1]. It leads to demyelination and diffuse neurodegeneration in both brain and spinal cord gray matter (GM) and white matter (WM) of the brain and spinal cord [2].

The natural history of the disease seems to be divided into 2 distinct phases for most of the patients with MS (PwMS): 1) initially most of them present recurring clinical symptoms followed by total or partial recovery, this form is called relapsing-remitting MS (RRMS); 2) after 10–15 years, the pattern becomes progressive in up to 50% of untreated patients. This second phase is defined as secondary progressive MS (SPMS) and determined by a slow but steady progression in neurologic deficit associated with CNS degeneration. Alternatively, 15% of PwMS can present with a progressive form at the onset, a progressive clinical decline without superimposed exacerbations, and this form is called primary progressive MS (PPMS) [3]. There is also a pre-clinical stage in which a combination of genetic and environmental factors triggers the disease [2].

MS is an autoinflammatory condition. However, changes in the vasculature can occur and contribute to pathophysiology [4]. The pathophysiology of hemodynamic impairment in MS is multifactorial and, at least partly, secondary to the downstream effects of the neuro-inflammatory cascades [2]. The incidence of vascular comorbidities was previously reported as up to 50% but continues rising in the MS population, making it important to understand their impacts on outcomes [5, 6].

Cardiovascular risk factors are known to contribute to MS disease severity. Smoking is associated with a higher lesion burden and more severe brain atrophy in

people with MS (PwMS). This relationship becomes even more prominent if there are multiple cardiovascular comorbidities [2, 7]. Comorbidity is associated with greater diagnostic delays, worse magnetic resonance imaging (MRI) outcomes, increased disability at diagnosis, and increased risk of disease progression in MS [8, 9]. There is a direct relationship between cardiovascular risk factors and clinical status as measured by the Expanded Disability Status Scale (EDSS) [10]. A large cohort study reported that hypertension and heart disease were associated with brain atrophy and obesity was associated with lesion volumes [8]. Also, high sodium intake, a regulating factor of blood pressure, seems to be linked to MS disease activity [11]. Understanding the hemodynamic changes in MS could potentially lead to better management of patients and improved diagnosis and prevention of disease progression.

2. Cervical hemodynamic changes in MS

When compared with the healthy population, PwMS show different patterns of vascular morphology in the neck, with respect to aging. The arteries supplying the CNS are possibly subject to particular atherosclerotic harm in MS [12]. The vascular cross-sectional area (CSA) in the neck is crucial to further understanding the associations between the extracranial and intracranial vascular changes.

Ranadive et al. reported significantly altered arterial function, as shown by decreased carotid artery compliance, but not structure in PwMS compared with the control matched for age, sex, height, and weight [12]. However, recent data suggests a smaller arterial cross-sectional area of the main and secondary arteries (common, internal, and external carotid arteries and vertebral artery, respectively) in PwMS. The CSA of the carotid and vertebral arteries is reduced [7]. Besides, significantly higher carotid intima-media thickness was reported in PwMS without cardiovascular disease compared to the healthy group, suggesting that PwMS have a predisposition to atherosclerosis [13]. In MS, even without the presence of cardiovascular disease carotid and vertebral arterial CSA was reduced [7]. A 5-year follow-up study checked the neck vessel CSA in PwMS and healthy controls during 5 years by 3 Tesla (3 T) MRI using 2-dimensional (2D) neck MRI angiography. At baseline, they observed no difference in CSA between the groups. The monitoring revealed a decrement in CSA of the common carotid artery – internal carotid artery, vertebral artery, and internal jugular vein (IJV), regardless of the disease phenotype. Interestingly, PwMS without the cardiovascular disease had significantly greater change than PwMS with cardiovascular disease for IJVs at all levels. Their observation of longitudinally changing IJV CSA may suggest a potential link between IJV CSA and the disease course in MS [14]. Heterogeneity of PwMS groups among the studies may contribute to explaining the difference in the results. Still, some hypertension-perfusion interactions might be considered in PwMS without cardiovascular disease when the lately lowered hypertension threshold to >130/80 mmHg in the guidelines taken into consideration.

Some cross-sectional studies revealed a greater prevalence of morphologic and hemodynamic alterations of extracranial venous drainage pathways in PwMS [15, 16]. Zamboni asserted that narrowing of the veins in the neck could be causing iron accumulation in the brain and spinal cord, triggering the inflammatory autoimmune response and proposed his hypothesis of Chronic Cerebrospinal Venous Insufficiency (CCSVI) as a cause of MS [15, 17]. The distinct abnormalities observed in the intracranial and extracranial veins in PwMS defined by Zamboni in 2009. Zamboni criteria include: 1) Reflux in the IJVs in sitting and supine posture; 2) Reflux in the deep cerebral veins (DCV); 3) High-resolution B-mode evidence

of IJV stenoses; 4) Flow not doppler-detectable in the IJVs. 5) Reverted postural control of the main cerebral venous outflow pathways [15].

CCSVI is only seen in MS patients and not in other neurodegenerative disorders or healthy individuals [15, 18]. It causes venous hypertension in the dural sinuses which can alter intracranial compliance. Subsequently, it may alter the CSF dynamics, affecting the ability of the vasculature to dissipate arterial pulsatility and provide smooth capillary blood flow that is known as the windkessel mechanism [19]. CCSVI is characterized by multiple areas of stenosis of the extracranial venous draining pathways, namely the IJVs and the azygous veins, with collateral formation. Normally the blood leaves the brain by postural and respiratory mechanisms, where the venous outflow increases during inspiration. The normal venous drainage pathway of the blood leaving the brain is via the IJV and the azygous vein (in the supine posture) and the vertebral vein (in the upright position). And for the spinal cord, the main route for venous drainage is the azygous vein [15, 18]. CCSVI can be easily assessed using doppler sonography or magnetic resonance venography.

Compared with healthy controls, PwMS exhibit reduced venous flow in IJV [16]. Haacke et al. confirmed the venous flow abnormalities in all clinical forms of MS. In their study, IJV stenosis was more prevalent in PwMS, and IJV carried significantly less flow when compared to the nonstenotic group [20]. PwMS show a higher frequency of secondary neck veins and larger cross-sectional areas when adjusted for all cardiovascular factors (including body mass index, hypertension, heart disease, smoking history, and age) [7]. Accordingly, flow in the paraspinal venous collaterals is higher in PwMS and exacerbated by venous stenosis. Collateral drainage may be a compensatory response to IJV flow reduction [16]. Both CCSVI and small IJVs (with a cross-sectional area of less than 0.4 cm^2) seem to influence or follow MS severity. However, only small IJVs are an independent factor. Thus, small IJVs with restricted outflow, which might be aspects of CCSVI different from the criteria originally described by Zamboni, emerge as a cofactor in the multifactorial pathophysiology of MS [21]. Considering the morphology of neck veins demographic factors may also be confounding between PwMS and healthy groups [7]. Notably, no significant difference in PwMS regarding IJV CSA and flow rates has also been reported [22, 23].

With CCSVI, Dr. Zamboni also proposed venous percutaneous transluminal angioplasty (so-called “liberation treatment” or “liberation therapy”) as a potential therapy for PwMS [24]. Today liberation treatment is a controversial treatment. CCSVI-like venous anomalies seem unlikely to affect cerebral blood flow (CBF) in PwMS according to some researchers [19]. Recent studies do not support the continued use of angioplasty for the extracranial jugular and/or azygous venous narrowing to improve patient-reported outcomes, chronic MS symptoms, or the disease course of MS [25–27]. But Zamboni et al. reported that venoplasty decreases new cerebral lesions at 1 year in RRMS and SPMS after the angioplasty [28]. It seems that the debate will continue until more detailed and comprehensive long-term studies are provided. Future studies should investigate CSA of the arterial and venous systems of neck vessels in more detail at disease onset, when the presence of cardiovascular risks is minimal, with a comprehensive approach.

3. Cerebral hemodynamic changes in MS

Changes in brain vasculature contribute to the pathophysiology of MS [4]. Especially the periventricular veins are vulnerable to ischemia and plaque formation due to their hydrodynamic properties. Demyelination and lesion formation is associated with the breakdown of the blood–brain barrier around postcapillary

venules, where MS lesions are commonly located [29]. MS is characterized by changes in the WM in the periventricular region and is also associated with enlarged lateral ventricles. The brain atrophy seen in MS might be primarily responsible for ventricular enlargement [19, 30]. The cerebral venous system plays an important role in the intracranial hemodynamic/cerebrospinal fluid regulatory system. This influence both the perfusion of the brain parenchyma and the dynamics of the CSF system. The generally accepted opinion is that cerebral perfusion is globally reduced in MS [19].

Cerebral perfusion is usually measured as CBF. It represents the blood volume that passes through a given volume of brain parenchyma per time unit [31]. Absolute measurements of cerebral blood volume (CBV), CBF, and mean transit time (MTT) reflect the overall perfusion of chronic lesions in PwMS. Long ago there were reports of reduced cerebral perfusion of the WM and GM of PwMS, which received little attention at the time [31–34].

Vasoreactivity reflects the ability of microvasculature to adapt to a changing microenvironment. A dynamic process called cerebral vasoregulation redistributes CBF depending on the fluctuating metabolic demands such as oxygen and glucose delivery and blood pressure variations. The neurovascular unit (NVU) broadly describes the relationship between brain cells and their blood vessels, regulating local, regional, and global perfusions. The other related terms are neurovascular coupling, cerebrovascular reactivity, and hemodynamic response function [35–37]. Both cellular and extracellular components are involved in the regulatory function of the NVU [35]. The cellular components are the neurons, perivascular astrocytes, microglia, pericytes, endothelial cells, and the basement membrane. Glial cell intermediaries facilitate the ability of neurons to adequately convey metabolic needs to cerebral vasculature for sufficient oxygen and nutrient perfusion [36]. The NVU is responsible for the maintenance of a highly selective blood-brain barrier and cerebral homeostasis, as well as the control of CBF through the cerebral metabolic rate of oxygen consumption [38]. It facilitates the relationship among neuronal activity, hemodynamic factors, and cell-to-cell signaling. Suboptimal blood delivery during neuronal activities caused by disrupted NVU coupling may eventually lead to neuronal dysfunction and degeneration in a chronic state.

The most characteristic brain tissue injury in MS is primary demyelination, with partial preservation of axons. Neural inflammation causes neurodegeneration together with demyelination; both of which are also worsened by tissue hypoxia. Inflammation further contributes to tissue hypoxia through impaired CBF and hypoperfusion which are the result of NVU dysfunction [4].

MRI is an important diagnostic tool for MS because it produces images of lesions in the brain and spinal cord. Widespread microglial activation observed in MS in areas surrounding the focal lesions is called normal-appearing WM (NAWM) [39]. Also, if on conventional T2-weighted (T2w) MRI normal-looking GM is histopathologically abnormal then this is referred to as normal-appearing GM (NAGM) [40].

Investigated absolute measures of flow and volume revealed decreased CBF in the NAWM of patients with RRMS [41]. Interestingly, another group observed elevated CBF and CBV in NAWM of RRMS patients several weeks before focal leakage of the blood–brain barrier and plaque formation [42]. In NAWM, hypoperfusion has been associated with persistent low-grade inflammation, metabolic or vascular dysfunction, or primary ischemia [43, 44]. Conversely, increased perfusion preceding focal WM lesion formation could indicate an increased inflammatory response before tissue damage in NAWM [45]. Many studies suggest that CBF is decreased in several regions of NAWM and NAGM compared to the healthy population [42, 43, 46–55]. One study reported lower CBF and higher MTT, consistent with reduced perfusion, in WM lesions compared to NAWM in

patients with early MS [44]. However another one observed increased CBV and CBF in RRMS, in patients with high inflammatory lesion load, underlining the role of global modified microcirculation prior to leakage of the blood-brain barrier in the pathophysiology of MS [56]. The perfusion alterations in RRMS seem to be independent of GM volume atrophy, which presents in all types of MS [57]. Hemodynamic changes in both WM and GM seem to occur even at the earliest stages of MS. Interestingly, a greater reduction of NAWM CBF was found in PPMS compared to RRMS [47, 49]. This finding is important because people with RRMS tend to have more brain lesions with more inflammatory cells.

Clinically isolated syndrome (CIS) refers to a single clinical attack of CNS inflammatory demyelinating symptoms that are suggestive of MS [58]. Reduced cerebral perfusion has also been observed in the NAWM of patients with CIS [50]. This is not surprising in CIS, since those patients already show evidence of NAWM [59]. But the decrement in CIS is at a lesser degree than in RRMS [50]. One of the earlier studies using DSC MRI demonstrated that acute gadolinium-enhancing lesions in PwMS have higher relative CBV when compared with their own contralateral NAWM [60]. However, possibly it is inappropriate to use NAWM as a reference by itself since it is also a pathological state [50]. On the other hand, CBF in the subcortical NAGM was not reduced in patients with CIS when compared to the healthy group [50]. Nevertheless, there is an observation of altered perfusion in the deep GM in both RRMS and CIS: In CIS all measured NAWM and deep NAGM regions had significantly higher CBV and MTT values, while averaged deep GM regions had significantly lower CBF values. In RRMS, the same regions showed lower CBF values than those of healthy volunteers and even lower CBV and CBF values compared to patients with CIS [61]. Hemodynamic changes in CIS present differently than the other forms of MS.

DSC-MRI and arterial spin-labeling studies of NAWM, cerebral cortex, subcortical GM, and deep GM point to a widespread decrease in perfusion in RRMS and progressive MS patients compared to healthy individuals [41, 49, 50, 61, 62]. The findings of a recent transcranial Doppler ultrasonography study also are consistent with the accumulating evidence of decreased cerebral perfusion in MS [4]. These results suggest that cerebral hypoperfusion, regardless of the clinical type, is an early and integral part of MS pathology [63]. The studies also suggest a continuum of reduction in tissue perfusion, beginning in the WM and spreading to GM with the disease progression [50].

4. Possible mechanisms of altered perfusion

Determining whether the cerebral hypoperfusion has primary or secondary etiology is critical in MS. For this purpose, researchers try to investigate every possible mechanism. **Table 1** summarizes the possible causes of altered perfusion in MS that are discussed briefly below.

Autonomic dysfunction resulting from demyelination.
Obliterating perivascular MS lesions.
Chronic cerebrospinal venous insufficiency (CCSVI).
Axonal injury with microglia activation caused by global inflammation.
Oxidative damage due to released toxic inflammatory mediators.

Table 1.
Possible causes of altered perfusion in MS.

Demyelination in MS may cause damage to the autonomic nervous system [64]. Autonomic receptors, both sympathetic and parasympathetic, have a significant role in dynamic cerebral autoregulation. Autonomic cardiac dysfunction is seen in up to 63% of PwMS [65, 66]. It can be present with or without symptoms and may be associated with the presence of brainstem lesions [67]. The symptoms are caused by cerebral hypoperfusion. They are typically induced by standing and quickly resolve when lying flat. The most likely cause is the central dysregulation of sympathetic and parasympathetic outflow to the cardiovascular system [68].

Another possibility would be reduced blood flow associated with obliterating perivascular MS lesions. However, as focal CBF decrease is not in a patchy pattern in MS, this idea can easily be ruled out. Microvessel thrombosis and other structural abnormalities have been observed very exceptionally within MS plaques [69]. Besides the increased CBF in active inflammatory lesions also argue against this theory [63]. Notably, compensatory functional adaptations might also account for MS-related changes in brain perfusion and activity [70].

Zamboni et al. reported a strong relationship between CCSVI and MS [15, 17, 18, 28, 71]. However, Beggs et al. propose that CCSVI-like venous anomalies seem unlikely to account for reduced CBF in PwMS [19]. The results of a phase-contrast MRI study do not support the CCSVI hypothesis that CSF flow decreases in MS patients [30]. Their results favor Beggs et al. who observed increased CSF pulsatility in the aqueduct of Sylvius, which they explain by the mechanisms increasing the hydraulic resistance of the cerebral vascular bed [19]. The results of the studies discussing angioplasty as a treatment of MS also seems in favor of the idea that CCSVI is less likely to take part in the pathophysiology of MS [25, 26].

Astrocytes actively control the blood-brain barrier and regulate CBF. In progressive MS lesions, diffuse pathology is also present in NAWM and NAGM, reflected by diffuse axonal injury with profound microglia activation within a background of a global inflammation of the entire brain and the meninges [72]. The relation between perfusion-weighted and diffusion tensor MRI features in the normal-appearing corpus callosum of patients with RRMS revealed a decreased CBF, which positively correlated with mean diffusivity but not with fractional anisotropy. This observation favors primary ischemia, rather than hypoperfusion secondary to axonal degeneration [51]. Decreased levels of N-acetylaspartate (NAA) indicate reduced axonal metabolism [73]. A positive correlation of cerebral perfusion with NAA levels was present for healthy controls, not for PwMS. The perfusion reduction was greater than would be expected from decreased axonal metabolism or axonal loss alone in MS [74]. Additionally, the excitability of primary motor cortex neurons is increased in progressive MS, which potentially escalates their metabolic demand [75]. So, reduced CBF does not seem to be secondary to axonal degeneration with reduced metabolic demands [76]. On the other hand, a hypothesis proposes that hypoperfusion is the result of neuronal dysfunction, which is the result of oxidative injury in cortical neurons or retrograde neurodegeneration due to axonal injury from demyelination [77]. There is another conflict is on the NVU coupling. Most investigators report diffusely impaired NVU coupling in PwMS [37]. However, some studies such as recent magnetoencephalography (MEG)- fMRI study suggest that NVU coupling is preserved in MS patients [78].

Accumulating evidence proposes that toxic inflammatory mediators and resulting oxidative damage play a prominent role in the pathophysiology of altered cerebral hemodynamics in MS. Iron accumulation in the extracellular space and its uptake into cells within the lesions might increase the susceptibility of the surrounding tissue to free-radical driven demyelination and neurodegeneration, which is likely to be more pronounced in progressive MS [39]. Mitochondrial damage in MS lesions could be mediated by reactive oxygen and nitric oxide (NO)

species [79]. It is evident that WM lesions represent the regions, where most current, past, and repetitive inflammatory activities occur that are associated with overproduced NO [37]. The overproduction and prolonged exposure to NO can affect the elasticity of the blood vessels and cause vascular habituation that leads to impaired perfusion, and cerebrovascular response deficit, and neurodegeneration including GM atrophy [37]. Endothelin-1 (ET-1) is a vasoconstrictor secreted by endothelial cells, which acts as the natural counterpart of the vasodilator NO. ET-1 levels elevate in both peripheral blood and cerebrospinal fluid of PwMS [80]. Reactive astrocytes in MS plaques release ET-1 in the cerebral circulation, which participates CBF reduction in MS by inducing arteriolar vasoconstriction [63]. ET-1 upregulation has been associated with reduced extra-ocular blood flow velocities [81]. Besides retinal oxygen metabolism is reportedly affected in MS by increased venular oxygen saturation and lower AV difference [82]. Oxidative stress causes calcium influx into the cytoplasm from the extracellular environment and endoplasmic reticulum or sarcoplasmic reticulum. A rise of calcium levels within astrocytes induces constriction of blood vessels and consequently reduces CBF [83]. Another possible role player is transcription factor hypoxia-inducible factor-1 α (HIF-1 α). It mediates adaptive responses to oxidative stress by nuclear translocation and regulation of gene expression. Expression of hypoxia-inducible factor-1 α and its downstream genes is also elevated in MS [69, 81]. Finally, glutathione levels are reduced in CNS of PwMS [84]. Glutathione serves as an antioxidant that aids in protecting neurons against oxidative damage. Glutathione levels are low also in the periphery [85].

5. Methods for evaluation of perfusion

Reduced cerebral perfusion in both the WM and GM of PwMS is known by single-photon emission computed tomography (SPECT) and positron emission tomography (PET) studies since the 1980s [31–34]. However, the main problem with these studies was a low spatial resolution, and eventually they received little attention at the time [63]. The topic of cerebral perfusion in MS regained interest with the development of more accurate imaging and processing techniques, allowing better visualization and differentiation between WM plaques, NAWM and NAGM. Today commonly Doppler and MRI-based techniques are used and provide better imaging [15, 17, 18, 25, 26, 86].

In the 2000s Doppler ultrasound and invasive selective venography studies helped to coin the term CCSVI [15, 17]. Today the latter is mostly replaced by magnetic resonance venography [86].

Transcranial Doppler sonography is for real-time cerebral vasomotor reactivity assessment. This technique is safe, low-cost, practical, and easy to perform in clinical practice. Lattanzi et al. measured NVU response to hypercapnia by the breath-holding index through this method. The main findings were a decrease in NVU coupling for both RRMS and SPMS groups, and greater impairment in cerebral hemodynamics in SPMS than RRMS, as suggested by lower breath-holding index in SPMS patients [4].

Arterial spin labeling is a non-invasive perfusion-weighted MRI method and uses magnetically labeled arterial blood as the endogenous tracer [87]. It characterizes oxidative stress and provides a completely non-invasive means to measure quantitative CBF within the brain [87]. It is effective in detecting decreased perfusion in GM [46, 48, 55]. A study using arterial spin labeling found an increased WM CBF in both RRMS and SPMS groups [48]. However, the authors did not distinguish NAWM from focal WM lesions [63].

Functional MRI (fMRI) measures brain activity by detecting changes associated with blood flow. This technique relies on the fact that CBF and neuronal activation are coupled, so helps to assess the NVU function. The primary form of fMRI uses the blood-oxygen-level-dependent (BOLD) contrast, which is the MRI contrast of blood deoxyhemoglobin. Turner et al. used fMRI to quantify the extent to which WM affects NVU coupling and cognitive performance [36]. NVU function is generally considered to be a proxy for underlying neural activity originating in GM. The researchers modeled it from multiple brain regions during multiple cognitive tasks. Their results support the idea that intact neural-glial-vascular communication underlies optimal neural and cognitive functioning [36].

Functional-near infrared spectroscopy (fNIRS) measures blood oxygenation changes similar to fMRI. The results of an fNIRS study in the prefrontal cortex indicate that measuring the slope coefficient of oxy- and deoxy-hemoglobin concentrations during walking is reliable for most of the included areas in PwMS [88].

Additionally, dynamic susceptibility contrast (DSC)-MRI, one of the most frequently used techniques for MRI perfusion, can be used to quantitatively assess cerebral perfusion. It can be diagnostic for the acute inflammatory phase of lesion development [89, 90]. DSC-MRI relies on the susceptibility induced signal loss on T2w sequences which results from a bolus of gadolinium-based contrast passing through a capillary bed. The most commonly calculated parameters are CBV, CBF, and MTT [91]. One research reported an increase, and another one reported a decrease in global perfusion in RRMS patients, both using DSC-MRI [44, 56]. The methodological differences in both studies seem to be a cause of this contradiction: The first researchers included newly diagnosed PwMS and used a 1.5 Tesla (T) MRI [44]. On the other hand, the second researchers divided the participants into high- and low-inflammatory groups according to the number of new contrast-enhancing lesions; and had a 3 T MRI [56]. This reflects the intricate spatiotemporal dynamics and heterogeneous disease progression that is characteristic of RRMS [92]. Of course, better imaging provided by 3 T MRI should not be ignored. Another important point is that gadolinium-enhancing areas (MS lesions) show increased CBF on DSC-MRI [42, 43, 60]. So total WM CBF may thus be overestimated when focal

Principles	Methods
X-ray based techniques	Selective venography
Nuclear imaging techniques	SPECT
	PET
USG based techniques	Doppler USG
MRI based techniques	fNIRS
	BOLD – fMRI
	MR venography
	DSC-MRI ± SAGE
	Arterial spin labeling
	Whole-brain OEF mapping
Infrared light absorption	Retinal oximetry

**Single-photon emission computed tomography (SPECT), positron emission tomography (PET), ultrasound (USG), magnetic resonance imaging (MRI), blood-oxygen-level-dependent (BOLD), functional MRI (fMRI), functional-near infrared spectroscopy (fNIRS), dynamic susceptibility contrast (DSC)-MRI, spin and gradient-echo (SAGE), oxygen extraction fraction (OEF).*

Table 2.
Principles and methods for evaluation of perfusion in MS*.

lesions were not properly excluded from perfusion measurements [63]. Recently, an advanced DSC-MRI method was used to quantitatively measure global and capillary-sized CBF, CBV, and MTT in RRMS: a combined spin- and gradient-echo (SAGE) perfusion imaging method. It showed that compared to NAWM, lesion regions-of-interest (ROIs) had significantly reduced perfusion (CBF and CBV) and increased MTT, as well as reduced WM microstructural integrity. The changes within lesion ROIs were associated with altered WM microstructural integrity. WM microstructural integrity displayed weak positive correlations in lesion ROIs with perfusion parameters [92].

Additionally, whole-brain oxygen extraction fraction mapping for measuring lesion-specific and regional oxygen extraction fraction abnormalities may serve as a useful quantitative marker of tissue oxygen utilization in MS [93].

Besides, by applying optical principles similar to those used in pulse oximetry, retinal oximetry reflects the retinal oxygen metabolism changes. And it has the potential of becoming a new biomarker in MS [82]. Above mentioned methods are listed in **Table 2**.

6. Clinical implications

Cerebrovascular hemodynamic insufficiency in MS may have clinical implications due to its contributions to MS symptomatology. Reduced CBF may contribute to focal lesion formation [63]. West et al. observed a lower cerebral metabolic rate of oxygen (CMRO₂) in PwMS compared to healthy volunteers. After controlling for demographic and disease characteristics (i.e., age, education, disability, lesion volume), CMRO₂ predicted increased fatigue and reduced cognitive performance in MS patients. PwMS with higher CMRO₂ have a reduced fractional anisotropy, a useful measure of connectivity in the brain, in NAWM [94]. When metabolic demand is increased by the activation of cerebral areas, as during cognitive tasks, blood supply may not suffice due to the reduced perfusion reserve [95]. Impaired NVU coupling increases the hazard of cerebral ischemic events. Epidemiological data showed that PwMS are at higher risk of stroke [76].

CBF in NAWM correlates with clinical disability [49]. But in GM CBF correlates with neuropsychological dysfunctions [47]. Beyond global CVR deficits and neurodegeneration found in MS, the integrity of specific functional networks may be more affected than others [37]. The evaluation of cerebral hemodynamic status may stratify individual vascular risk [4].

In the light of pathophysiological studies, clinicians try some approaches with the efforts to minimize the disease progression. There are dietary approaches like Wahls diet [96]. To overcome the oxidative stress altering hemodynamics the importance of dietary nitrate intake should not be underestimated. Dietary nitrate, derived in the diet primarily from vegetables, is converted to NO in the body. There are also therapeutical intervention trials. In order to restore CBF in RRMS, Hostenbach et al. administered ET-1 antagonist bosentan. In the study, the results showed that CBF in the patients was not different from that of the healthy controls and bosentan did not increase CBF. The authors commented that it has no effect when CBF values are within the normal range [53]. Similarly, Shahrpour et al. administered N-acetylcysteine (NAC) to RRMS and PPMS patients. Interestingly, certain brain regions experienced an increase while others experienced a decrease in CBF following the treatment. This highlights the notion that NAC does not have a uniform effect on the brain but appears to target specific regions that are affected in MS. NAC administration was associated with altered resting CBF and qualitative improvements in cognition and attention in PwMS [97].

7. Conclusion

The pathways of tissue damage in MS are heterogeneous and not completely understood. The studies exploring the relationships between cerebral hemodynamics, functional impairment, disease course, and therapeutic response may reasonably allow to improve the understanding of MS pathophysiology and translate in implications for clinical practice [4]. The NVU dysfunction and interplay between inflammatory and vascular changes seem to be the key players in the pathophysiology of MS. Altered cervical and cerebral perfusion in MS is associated with reduced brain integrity. WM and GM integrity changes lead to a higher risk of relapses, disability, and disease-modifying therapy escalation. So, understanding the hemodynamic effects is very critical to help PwMS.

There are debatable issues for cervical and cerebral hemodynamics in MS. These disagreements can at least be partially explained by the heterogeneity of inclusion criteria and methods. The variety of the tools, techniques, and used protocols cause different outcomes.

In order to avoid additional factors damaging the brain, to provide improved diagnosis, superior patient management and prevention of disease progression, to define reliable biomarkers, and to design novel therapeutic strategies, a thorough understanding of the hemodynamic changes in MS is critical. Future research especially follow-up studies with larger populations under different activity conditions would ease answering today's questions.

Conflict of interest

The author declares no conflict of interest.

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