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Review article

# Cerebral vasomotor reactivity in neurodegenerative diseases

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ABSTRACT

Small-caliber cerebral vessels change their diameters in response to alterations of key metabolite concentrations such as carbon dioxide or oxygen. This phenomenon, termed the cerebral vasomotor reactivity (CVMR), is the basis for blood flow regulation in the brain in accordance with its metabolic status. Typically, CVMR is determined as the amount of change in cerebral blood flow in response to a vasodilating stimulus, which can be measured by various neuroimaging methods or by transcranial Doppler. It has been shown that CVMR is impaired in cerebrovascular diseases, but there is also evidence of a similar dysfunction in neurodegenerative disorders. Here, we review studies that have investigated CVMR in the common neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and multiple sclerosis. Moreover, we discuss potential neurodegenerative mechanisms responsible for the impairment of CVMR.



## 1. Introduction

Cerebral blood flow (CBF) is controlled by three principle mechanisms – pressure regulation, neurogenic regulation, and metabolic regulation [1]. Pressure regulation, also referred to as the cerebral autoregulation, is a mechanism responsible for maintaining a constant CBF within a certain range of arterial blood pressure, whereas neurogenic regulation is the control of the vascular tone by both peripheral nervous system as well as central nervous system (CNS). Metabolic regulation is a mechanism responsible for keeping balance between energy supply and demand in the CNS. At the cellular level, these three mechanisms interact within a functional unit, termed the neurovascular unit (NVU), consisting of vascular cells, glial cells and perivascular nerves [2] (Fig. 1).

### 1.1. *Metabolic regulation of CBF and cerebral vasomotor reactivity*

It has been shown that CBF rises in response to an increasing arterial carbon dioxide concentration and decreasing arterial pH, whereas oxygen has the opposite effect [3]. These effects are mediated by changes in diameters of cerebral arterioles, and therefore, this phenomenon is described as the cerebral vasomotor reactivity (CVMR). It should be noted that CVMR is

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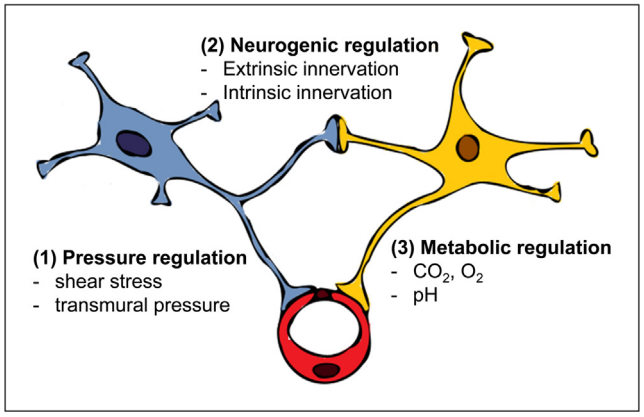


**Fig. 1 – Control of cerebral blood flow and the neurovascular unit. At the cellular level, CBF is controlled by the NVU – a tripartite unit consisting of neurons (blue), vascular cells (red), and glial cells (yellow). (1) Pressure regulation is achieved by a reflex constriction of vascular cells in response to increased flow velocity (shear stress) and increased transmural pressure. (2) Neurogenic regulation is the control of vascular tone by both autonomic neurons (extrinsic innervation) and CNS neurons/interneurons (intrinsic innervation), (3) Metabolic regulation is responsible for maintaining appropriate levels of e.g. oxygen, carbon dioxide. CBF–cerebral blood flow, CVMR, cerebral vasomotor reactivity; NVU, neurovascular unit. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)**

different from the notion of neurovascular coupling (functional hyperemia), whereby changes in CBF occur in accordance, temporally and spatially, with local brain activity.

### 1.2. *Measurement of CVMR*

In principle, CVMR is determined by measuring CBF changes following a vasoactive challenge. CBF can be determined directly by neuroimaging methods (e.g. single photon emission computed tomography – SPECT, positron emission tomography – PET, functional magnetic resonance imaging – fMRI) or indirectly through the measurement of blood flow velocity (FV) in major cerebral arteries by transcranial Doppler (TCD). This latter approach is based on the assumption that vasoactive substances exert their effects by acting on small cerebral arterioles, whereas the effect on the major cerebral arteries, in which measurements are made, is negligible [4]. Among all the stimuli used for the assessment of CVMR, $CO_2$ is regarded as the most reliable [5]. However, other vasodilating stimuli such as intravenous acetazolamide and breath-holding are also commonly used. Lastly, several CVMR indexes have been used so far. Earlier studies used a qualitative approach and classified CVMR in individuals as either present (observable increase in CBF after vasoactive challenge) or absent (no observable change in CBF). More recent studies have used quantitative indexes such as a relative increase in CBF or FV following a vasoactive challenge, which is sometimes additionally normalized per each mm Hg of the increase in end-tidal partial pressure of $CO_2$ ($ETpCO_2$) that approximates arterial $pCO_2$. Finally, in the breath-holding test, CVMR is expressed as the breath-hold index (BHI), which is a relative change in FV upon apena divided by the time of breath holding in seconds (usually 30 s).

## 2. CVMR in neurodegenerative diseases

Below, we review studies that have assessed CVMR in the common neurodegenerative diseases – Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS).

### 2.1. *Alzheimer's disease*

Alzheimer's disease (AD) is a neurodegenerative disease that accounts for approximately 70% of dementia cases [6]. Although amyloid beta deposition in the CNS is considered as the central pathological feature of AD, the importance of vascular mechanisms has also been underscored [7]. There have been numerous studies investigating CVMR in AD, and they have been reviewed elsewhere [8,9]. Therefore, they are not described here in detail but are presented in Table 1. In summary, the evidence, especially that coming from more recent studies with appropriate control groups, indicates an impaired CVMR in AD. The clinical significance of CVMR is reflected by the fact that its impairment is associated with an increased risk of both conversion from mild cognitive impairment to AD [10,11] and cognitive decline in AD [12]. However, it remains less clear whether CVMR is affected differentially in AD and vascular dementia (VD).

### 2.2. *Parkinson's disease*

Parkinson's disease (PD) is a common neurodegenerative disease resulting primarily from the degeneration of dopaminergic neurons of the substatia nigra, which leads to the development of motor symptoms such as tremor, rigidity, and bradykinesia. Moreover, non-motor symptoms such neuropsychiatric symptoms (e.g. depression, dementia, psychotic disturbances) and autonomic symptoms can be present as well [34]. Autonomic dysfunction in PD manifests for instance as orthostatic hypotension [35] and can affect CBF and CVMR as well (see Table 2) [36,37].

Two out of three studies using TCD and breath-hold as a vasoactive stimulus reported significantly impaired BHI in PD patients in comparison to healthy controls [38–40]. In contrast, studies using fMRI for the assessment of CVMR did not show significant differences between PD patients and controls [41,42]. Similarly, the change in FV induced by hyperventilation was normal in PD patients [43]. Moreover, studies without control groups also indicated that CVMR in PD patients might be normal [44,45]. Because of the inconsistency of results between studies and a low number of studies that typically enrolled small samples, no definite conclusion as to a possible CVMR impairment in PD can be made. However, it seems that CVMR is not affected by dopaminergic treatment [38,39,41,45].

**Table 1 – Studies on cerebral vasomotor reactivity in Alzheimer's disease patients.**

| Ref. | CBF measurement | Vasoactive stimulus | Number of patients | Control group | Conclusions |
|---|---|---|---|---|---|
| [13] | TCD | Rebreathing | 17 AD | Yes, $n = 17$ | CVMR decreased in AD (~40% increase in FV vs. ~60% in controls) |
| [14] | TCD | Breath-hold | 40 AD | Yes, $n = 40$ | BHI lower in AD |
| [15] | SPECT | Acetazolamide | 12 AD | Yes, $n = 9$ | CVMR significantly decreased in AD. |
| [16] | TCD | 6% $CO_2$ inhalation, hyperventilation | 60 AD; 58 VD | Yes, $n = 62$ | CVMR equally decreased in AD and VD (~60% increase in FV vs. ~80% in controls) |
| [17] | SPECT | 5% $CO_2$ inhalation | 5 AD | Yes, $n = 21$ | CVMR in gray matter preserved in AD |
| [18] | BOLD-fMRI | 5% $CO_2$ inhalation | 17 AD | Yes, $n = 17$ | CVMR impaired in the prefrontal, anterior cingulate, insular areas. |
| [19] | TCD | Acetazolamide | 9 AD; 9 VD | No | No significant differences between AD and VD |
| [20] | SPECT | Acetazolamide | 35 AD; 16 stroke | No | CVMR in AD preserved in contrast to stroke. |
| [21] | BOLD-MRI | 7% $CO_2$ inhalation | 9 AD; 7 MCI | Yes, $n = 11$ | CVMR impaired in AD and MCI, most pronounced in the occipital and parietal lobes |
| [22] | TCD | 7% $CO_2$ inhalation, hyperventialtion | 12 AD patients | Yes, $n = 24$ | CVMR decreased in AD (~40% increase in FV vs. ~80% in controls). No differences to hyperventilation. |
| [23] | SPECT | Acetazolamide | 12 AD; 11 MCI | No | CVMR in AD and MCI preserved |
| [24] | TCD and ASL-MRI | 5% $CO_2$ inhalation | 26 AD; 23 VD | No | No differences between AD and VD in TCD. CVMR lower in AD in both frontal lobes |
| [25] | SPECT | Hyperventilation | 8 AD; 9 MID | No | CVMR in AD and MID preserved; however, in AD regional CVMR decreased in temporal lobes |
| [26] | PET | 8% $CO_2$ inhalation | 5 AD | Yes, $n = 16$ | CVMR in AD preserved |
| [27] | PET | 5% $CO_2$ inhalation | 5 AD; 5 VD | Yes, $n = 5$ | CVMR normal AD in contrast to VD patients |
| [28] | TCD | Breath-hold | 10 AD; 10 MID | Yes, $n = 20$ | CVMR to hypercapnia decreased in MID but not in AD. |
| [29] | TCD | Breath-hold | 23 AD; 16 AH | Yes, $n = 25$ | BHI lower in AD and AH than in controls |
| [30] | CT | Acetazolamide | 10 AD | Yes, $n = 10$ | CVMR impaired in AD, in the frontal, parietal, and temporal cortices. |
| [31] | SPECT | Acetazolamide | 33 AD; 18 VD | No | CVMR response seen in 76% of AD patients and 18% of VD patients |
| [32] | TCD | Hyperventilation, breath-hold, rebreathing | 20 AD; 20 MID | Yes, $n = 25$ | CVMR to hypercapnia decreased in MID but not in AD. CVMR to hypocapnia equally impaired in AD and MID. |
| [33] | BOLD-fMRI | 7% $CO_2$ inhalation | 20 AD; 15 MCI | Yes, $n = 28$ | CVMR impaired in AD in all brain regions except for the insula and subcortical nuclei. |

AD, Alzheimer's disease; AH, amyloid hemorrhage; ASL-MRI, arterial spin labeled magnetic resonance imaging; BHI, breath-hold index; BOLD-fMRI, blood-oxygen-level-dependent functional magnetic resonance imaging; CBF, cerebral blood flow; CT, computed tomography; CVMR, cerebral vasomotor reactivity; FV, flow velocity; MCI, mild cognitive impairment; MID, multi-infarct dementia; PET, positron emission tomography; SPECT, single-photon emission tomography; TCD, transcranial Doppler; VD, vascular dementia.

### 2.3. *Multiple sclerosis*

MS is an inflammatory, demyelinating disease of the CNS. The role of inflammation in MS is undisputed – it is present at all stages of the disease and has been the primary target for drug development [46]. However, the contribution of neurodegenerative processes in the disease pathogenesis has been increasingly recognized, especially with respect to possible mechanisms of progression. These may include axonal degeneration, mitochondrial injury, energy failure, hypoxia, oxidative damage, iron accumulation or global cerebral hypoperfusion [47,48]. Interestingly, CVMR in MS may be impaired as well. Uzuner et al. studied 12 relapsing-remitting MS patients and 11 healthy controls [49]. A breath-hold of 15-s was used as a vasoactive stimulus, and CVMR was expressed as a percentage ratio between the maximal and minimal flow velocity recorded during the period of breath-holding, as measured by TCD in the MCA. In MS patients, measurements were made on three time points – before the first and after the last methylprednisolone infusion as well as one month after discharge. Although MS patients had lower CVMR values (46.5% prior to treatment, 48.3% after treatment, and 50.9% in

**Table 2 – Studies on cerebral vasomotor reactivity in Parkinson's disease patients.**

| Ref. | CBF measurement | Vasoactive stimulus | Number of patients | Control group | Conclusions |
|---|---|---|---|---|---|
| [38] | TCD | Breath-hold | 12 PD | Yes, $n = 12$ | No differences in BHI between PD patients and age-matched controls |
| [39] | TCD | Breath-hold | 15 PD | Yes, $n = 15$ | BHI significantly lower in PD patients than in controls |
| [40] | TCD | Breath-hold | 11 PD | Yes, $n = 11$ | BHI significantly lower in PD patients than in controls |
| [41] | BOLD-fMRI | 7% $CO_2$ inhalation | 10 PD | Yes, $n = 8$ | Whole-brain and regional CBF increased similarly in PD patients (1.62%) and controls (1.48%). |
| [42] | ASL-fMRI | Close-circuit rebreathing | 14 PD | Yes, $n = 14$ | Difference in whole-brain CBF not significant between PD patients and age-matched controls. Large variability of CVMR values. |
| [43] | TCD | Hyperventilation | 13 PD | Yes, $n = 22$ | No significant difference in FV between PD patients (~20–30%) and healthy controls (~40%) |
| [44] | TCD | Acetazolamide injection | 9 PD<br>10 MSA<br>5 PAF | No | No differences between patient groups in percentage increase in FV in MCA and VA that were within the normal range of the laboratory. |
| [45] | TCD | 8% $CO_2$ inhalation | 44 PD | No | Percentage increase in FV in MCA normalized by increase in $EtC0_2$ in mm Hg less than 5% (arbitrary lower limit value) observed in 34.1% of PD patients. Mean value of 8.4% in PD patients greater than the mean value in healthy subjects from an earlier study |

ASL-MRI, arterial spin labeled magnetic resonance imaging; BHI, breath-hold index; BOLD-fMRI, blood-oxygen-level-dependent functional magnetic resonance imaging; CBF, cerebral blood flow; MCA, middle cerebral artery; MSA, multiple system atrophy; PAF, pure autonomic failure; PD, Parkinson's disease; CVMR, cerebral vasomotor reactivity; FV, flow velocity; TCD, transcranial Doppler; VA, vertebral artery.

remission) than controls (55.7%), this difference was not statistically significant. In another study, Marshall et al. [50] assessed CVMR in 19 MS patients and an equal number of controls. They measured CBF by fMRI in a baseline condition and following 5% $CO_2$ inhalation. CVMR was expressed in percentage terms as a ratio between the relative increase in CBF per each mm Hg of end-tidal $CO_2$ change. MS patients had a significantly lower CVMR (3.56%) than healthy controls (5.08%) in the gray as well as in the white matter (6.1% vs. 4.0%, respectively). Moreover, gray matter CVMR was impaired particularly in the temporal, parietal, sublobar, and limbic regions, and correlated negatively with lesion volume and positively with gray matter volume normalized for total intracranial volume.

## 3. Mechanisms of CVMR impairment in neurodegenerative diseases

Although the cause of CVMR impairment in neurodegenerative disease is not clear, several potential factors might contribute to this phenomenon. For the purpose of clarity, we divide them into (1) vascular factors, (2) glial factors, and (3) neuronal factors – according to the three cell types comprising the NVU (Fig. 2).

### 3.1. *Vascular factors*

Vascular risk factors such as hypertension, hypercholesterolemia, smoking or obesity frequently coexist with AD, PD and MS [51–53]. Consequently, they may contribute to cerebral vessel disease, and thus, to the impairment of CVMR. Moreover, it is postulated that vascular factors might additionally aggravate the course of neurodegenerative diseases, and in clinical practice it is often difficult to distinguish whether the disease process is driven by a neurodegenerative or vascular pathology.

Amyloid beta is considered to play a key role in the pathogenesis of AD – its deposits are seen in the nervous tissue but also in the walls of cerebral vessels. Soluble amyloid beta may directly constrict cerebral arterioles [54,55], and once

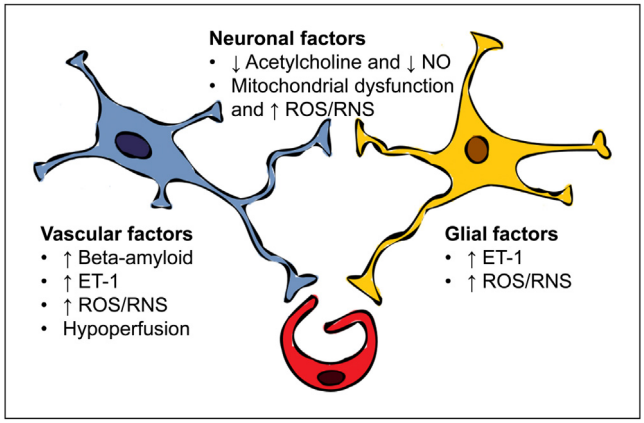


**Fig. 2 – Blood–brain barrier disruption and other possible factors causing impairment of cerebral vasomotor reactivity – description in text (Sections 3 and 4).**

deposited in the vessel wall, impairs CVMR in a mouse model of cerebral amyloid angiopathy [56] as well as in amyloid hemorrhage (AH) and AD patients [29,57]. Amyloid beta compromises the ability of cerebral endothelial cells to produce vasodilators and thus can impair not only CVMR but also other mechanisms regulating CBF such as autoregulation (inadequate blood supply during hypotension) and neurovascular coupling (inadequate blood supply during increased brain activity) [58]. In contrast, the tau protein, which has also been implicated in the pathology of AD and PD, has been recently shown to increase CVMR in transgenic mice expressing this molecule [59].

Blood–brain barrier (BBB) disruption might be another factor contributing to CVMR impairment in neurodegenerative disorders [60–62]. The hemodynamic consequences of BBB breakdown may include albumin extravasation leading to perivascular edema and subsequent cerebral hypoperfusion [2], which is a well-established feature of AD, PD and MS [48,63,64]. It has been reported that peritumoral gray-matter edema reduces both local CBF and CVMR, with improvement upon tumor resection [65]. This finding might explain how perivascular edema caused by BBB breakdown can lead to both cerebral hypoperfusion and impaired CVMR in neurodegenerative diseases. In the case of MS, one would also expect glucocorticoid treatment to improve CVMR as it might reduce perivascular edema by restoring BBB [49].

CVMR impairment could also be caused by an increase in the concentration of vasoconstrictive agents. For instance, endothelin-1 (ET-1) – a potent vasoconstrictor, is overexpressed in the cerebral vessels of AD and MS patients [66,67]. In MS, there is also evidence that ET-1 is elevated in both serum and cerebrospinal fluid [68–71]. In AD, a pro-contractile state of the cortical arterioles can also be reflected by an increased expression of the serum response factor and myocardin – nuclear transcription factors that orchestrate smooth muscle contraction [72] as well as an increased expression of thrombin in endothelial cells [73]. In MS, inflammatory mediators, such as tumor necrosis factor alpha, might also contribute to vasoconstriction [74].

### 3.2. *Glial factors*

Glial cells, and especially astrocytes that directly abut vascular cells, may influence the contractility of cerebral arterioles. Moreover, glial cells play an important role in the neurodegenerative and/or neuroinflammatory processes.

Reactive astrocytes, i.e. hypertrophied astrocytes that overexpress GFAP (glial fibrillary acidic protein) have been described in virtually all CNS disorders including AD, PD, and MS [75]. Although reactive astrocytes may exert some beneficial effects, they could also contribute to CVMR impairment through the production of ET-1 and possibly other vasoconstrictors. ET-1-expressing astrocytes have been described in AD and MS patients [71,76,77]. Interestingly, reactive astrocytes might lead to a decreased CVMR in a mouse model of Huntington's disease by promoting dysfunctional angiogenesis and reducing the number of pericytes [78].

Another way in which glial cells could contribute to the impairment of CVMR might be associated with their involvement in oxidative stress pathways [79,80]. The research of Zhang et al. [81,82] shows how oxidative stress may lead to impaired CVMR. In the tail-suspended hindlimb unweighting rat (a model of microgravity), the authors showed that acetylcholine-induced vasodilation in the basilar and common carotid arteries was reduced, which was associated with a seemingly paradoxical increase in NO arterial concentration, and a parallel increase in the superoxide radical ($O_2^{\bullet -}$) content in the arterial wall. Subsequently, the authors demonstrated that a pharmacological inhibition of the NADPH-oxidase, a major source of the superoxide radical, significantly improved the dilation of cerebral arteries and restored NO concentration to near-normal values. This shows that the vasodilating effect of NO may be inactivated in an oxidative milieu. Notably, increased levels of nitric oxide in various bodily fluids have been reported in patients with AD, PD and MS [83–86] and in AD NO levels correlated with the concentration of oxidized low-density lipoproteins, a marker of oxidative stress [84]. These findings might be explained by the fact that under pathological conditions associated with oxidative stress, NO is generated abundantly by glial cells through the inducible NO synthase (iNOS), but instead of contributing to vasodilation, NO is transformed into toxic reactive nitrogen species (RNS) [87].

Glial pathology may also cause BBB dysfunction [62], leading for instance to cerebral hypoperfusion, but also to the perivascular leakage of hemoglobin-containing red-blood cells, which might result in iron-induced ROS formation [2].

### 3.3. *Neuronal factors*

It has been shown that cholinergic projections originating from the nucleus basalis induce cerebral vasodilation directly through the release of acetylcholine and indirectly through the stimulation of NO-releasing interneurons [1]. Thus, cholinergic dysfunction could lead to a less efficient cerebral vasodilation, and consequently to an impaired CVMR. Importantly, the cholinergic system is almost invariably impaired in AD [88], and there is evidence of a cholinergic deficit in PD and MS [89,90]. Moreover, it has been shown that CVMR improves in AD and VD patients following the administration of galantamine – a cholinesterase inhibitor [91].

Finally, cerebral hypoperfusion observed in neurodegenerative diseases may lead to a state of hypoxia resulting in ROS production by neuronal mitochondria [92–95].

## 4. Conclusions

There is evidence suggesting that CVMR might be impaired in neurodegenerative diseases. In AD, most studies with age-matched control groups reported a significant impairment of CVMR, and studies reporting normal CMVR in AD often did not make direct comparisons with age-matched control groups and/or were underpowered. Due to a low number of studies in PD and MS, it is less clear whether CVMR in these diseases is significantly impaired as well. In MS, only two studies have been performed so far, but both reported a decrease in CVMR in MS patients. There is less certainty regarding CVMR in PD as the studies are largely inconsistent.

The reasons for CVMR impairment in neurodegenerative diseases are not clearly established, and it is likely that the

etiology is multifactorial and multidirectional. Conceptually, the disruption of BBB could be thought of as a starting point in a cascade of processes leading to the impairment of CVMR, although it would be difficult to prove that this event is primary in the temporal sense (Fig. 2). By causing perivascular edema and thus a mass effect, BBB breakdown could diminish both CBF and CVMR. In turn, this could lead to hypoxia and/or energy failure with resultant ROS generation by dysfunctional neuronal mitochondria and degeneration of neurons producing vasodilating neurotransmitters (acetylcholine, NO). Moreover, BBB disruption could provoke a hypercontractile state of the cerebral endothelium and the activation of glial cells expressing vasoconstrictors, such as ET-1, and generating ROS/RNS.

Although the contribution of CVMR impairment to the pathogenesis of neurodegenerative diseases is not certain, it might be suspected that a reduced cerebrovascular reserve is an additional deteriorating factor in disease progression. Therefore, it would be worthwhile to include CVMR measures in studies assessing prognostic factors and/or treatment interventions.

## Conflict of interest

None declared.

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## Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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