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Is Vasomotion in Cerebral Arteries Impaired in Alzheimer's Disease?

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Handling Associate Editor: Mauro Silvestrini

Accepted 11 February 2015

Abstract. A substantial body of evidence supports the hypothesis of a vascular component in the pathogenesis of Alzheimer's disease (AD). Cerebral hypoperfusion and blood-brain barrier dysfunction have been indicated as key elements of this pathway. Cerebral amyloid angiopathy (CAA) is a cerebrovascular disorder, frequent in AD, characterized by the accumulation of amyloid- β (A β) peptide in cerebral blood vessel walls. CAA is associated with loss of vascular integrity, resulting in impaired regulation of cerebral circulation, and increased susceptibility to cerebral ischemia, microhemorrhages, and white matter damage. Vasomotion—the spontaneous rhythmic modulation of arterial diameter, typically observed in arteries/arterioles in various vascular beds including the brain—is thought to participate in tissue perfusion and oxygen delivery regulation. Vasomotion is impaired in adverse conditions such as hypoperfusion and hypoxia. The perivascular and glymphatic pathways of A β clearance are thought to be driven by the systolic pulse. Vasomotion produces diameter changes of comparable amplitude, however at lower rates, and could contribute to these mechanisms of A β clearance. In spite of potential clinical interest, studies addressing cerebral vasomotion in the context of AD/CAA are limited. This study reviews the current literature on vasomotion, and hypothesizes potential paths implicating impaired cerebral vasomotion in AD/CAA. A β and oxidative stress cause vascular tone dysregulation through direct effects on vascular cells, and indirect effects mediated by impaired neurovascular coupling. Vascular tone dysregulation is further aggravated by cholinergic deficit and results in depressed cerebrovascular reactivity and (possibly) impaired vasomotion, aggravating regional hypoperfusion and promoting further A β and oxidative stress accumulation.

Keywords: Alzheimer's disease, cerebral amyloid angiopathy, cerebral autoregulation, endothelium, perivascular drainage, vascular smooth muscle cell, vasomotion

INTRODUCTION

Neurovascular homeostasis in the brain is maintained through the inherent ability of vascular resistance to adapt to changes in blood pressure, thereby preserving an adequate and stable cerebral blood flow (CBF) [1]. This adaptation mechanism,

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termed autoregulation, is essential as the brain has a high metabolic demand.

Cerebral autoregulation is the outcome of a complex interplay of vascular, neuronal, and metabolic components, in which the vascular tonic response to increased blood pressure (known as myogenic response [2]) plays an important role in maintaining an adequate level of tissue perfusion.

Arterial resistance, especially in the arteriolar circulation, is also modulated by spontaneous rhythmic variations in the vessel lumen resulting from smooth muscle dilatation and constriction. This intrinsic phenomenon, known as vasomotion [3–5], is unrelated to cardiac rhythm, and is observed clinically through related flow variations (flowmotion) using non-invasive technologies such as laser Doppler flowmetry.

Vasomotion has been observed *in vitro* and *in vivo* in various vascular beds including, among others, skeletal muscles, cutaneous and retinal circulation, coronary and mesenteric arteries [3, 5], and cerebral arteries [6–8].

Despite research efforts spanning over 150 years, both the underlying mechanisms and the functional implications of vasomotion remain to some extent unclear.

It has been suggested that vasomotion can improve perfusion [9, 10] and local tissue oxygenation [11, 12]. Although experimental evidence is currently limited, mathematical computational models also support the role of vasomotion in oxygen (O₂) delivery [13–15].

In the current view, vasomotion is the outcome of multiple and interacting systems, in which the inhibition of one may unveil the role of another [5], thus explaining the heterogeneous manifestation of vasomotion in different vascular beds within the same organism. This heterogeneous distribution may represent an adaptation mechanism to meet the dynamically changing local metabolic demand of the perfused tissues [6, 16, 17].

Impaired cerebral autoregulation in Alzheimer's disease and cerebral amyloid angiopathy

Alzheimer's disease

Alzheimer's disease (AD) is the most prevalent cause of dementia in the older population accounting for 65–70% of the cases [18–20]. The formation of amyloid- β (A β) plaques and neurofibrillary tangles are the hallmarks of AD [21]; however, autopsy studies also show symptoms of vascular pathology in the majority of AD cases [22–25].

The mechanisms underlying AD pathogenesis are not fully understood; however, a substantial body of evidence supports the hypothesis of a vascular contribution to pathophysiology [26–29], in which cerebral hypoperfusion and blood-brain barrier dysfunction are key elements [22, 26], aggravated by impaired cerebral microcirculation [30, 31].

Cerebral autoregulation deteriorates with age [32–34], increasing neuronal vulnerability to hypoxia and ischemia [32]. In transgenic mice overexpressing amyloid- β protein precursor, impaired endothelium-dependent vasodilatation and paradoxical vasoconstriction reduce basal CBF [35], resulting in impaired autoregulation [36]. In contrast with animal models, preliminary data from AD patients show no alterations of cerebral autoregulation [37]. These reports, however, are currently few and based on very small cohorts [38–40]. Furthermore, they rely on transcranial Doppler (TCD) techniques for noninvasive quantification of CBF (in the middle cerebral artery). These techniques measure relative velocity instead of absolute flow, under the assumption of constant arterial diameter. On the other hand, imaging techniques such as single-photon emission computed tomography (SPECT), have provided evidence of cerebrovascular deficit with reduced regional CBF in AD patients [41–44].

Cerebral amyloid angiopathy

Cerebral amyloid angiopathy (CAA), a cerebrovascular disorder characterized by the accumulation of A β peptide in the *tunica media* and *adventitia* of cerebral blood vessels, is associated with vascular smooth muscle cell degeneration and loss of vessel wall integrity [45], resulting in impaired regulation of cerebral circulation [46–50], vascular insufficiency and increased susceptibility to cerebral ischemia [51], microhemorrhages [52], and white matter damage [51].

CAA is found in elderly patients without dementia; however, its prevalence significantly increases in sporadic AD [23, 49], in which it is found in more than 60% of the cases [53]. CAA has been suggested to damage the contractile apparatus of cerebral vessels, and disrupt autoregulation [31].

Focus questions

Although vasomotion is thought to play an important role in cerebral autoregulation, specific studies in the context of AD or CAA in humans are limited—possibly owing to the experimental complexity of quantitative measurements. Furthermore, while

experimental techniques for *in vivo* measurement of vasomotion in animals are available, their application to animal models of AD or CAA remains largely unexplored.

This study reviews the current literature on vasomotion, in the attempt to address two questions:

Question I: "Is impaired vasomotion in cerebral arteries implicated in the development or progression of sporadic Alzheimer's disease?"

This question is motivated by the current view according to which vasomotion contributes to the regulation of tissue perfusion and O₂ delivery [9–12].

Vasomotion can manifest as regular, rhythmic oscillations or chaotic fluctuations [3, 54]. Chaotic patterns in vasomotion have been suggested to reflect failure of vascular tone regulation, resulting in inadequate blood supply to the tissues [17].

Increasing incidence and magnitude of vasomotion have been observed during acute conditions associated with hypoxia [55], low blood pressure and hypoperfusion [4, 56, 57], suggesting that vasomotion may play a protective role in the attempt to preserve homeostasis in acute conditions.

However, in chronic conditions such as diabetes [58–61], obesity [5, 16], and hypertension [62, 63], vasomotion appears to be depressed. Reports from longitudinal studies suggest that diabetes [64–66], untreated hypertension [67], and obesity at midlife [68–70], are associated with an increased risk of developing AD, supporting the hypothesis of an indirect link between depressed vasomotion and AD. However, the association between the above risk factors and AD remains controversial as other longitudinal studies have reported contrasting results [71–74].

Question II: "Does impaired vasomotion hinder waste product drainage in Alzheimer's disease?"

In spite of the high metabolic rate and sensitivity of brain parenchymal cells to alterations in the extracellular environment, the brain lacks lymphatic vessels for interstitial solute and fluid clearance [75], suggesting an alternative pathway should exist.

Although the underlying mechanisms remain to some extent unclear, two hypotheses on waste product clearance in the brain have been proposed.

Observations using *in vivo* two-photon imaging suggest that the cerebrospinal fluid from the subarachnoid space enters the brain parenchyma following para-arterial influx routes in the Virchow-Robin space surrounding the penetrating cerebral arteries [75, 76]. The resulting interaction with the brain interstitial fluid then acts to facilitate the clearance of interstitial solutes (including A β) via the paravascular spaces

surrounding large draining veins. This mechanism has been reported to depend on the expression of water channel aquaporin-4 in astrocytes [75]. Owing to its functional analogy to peripheral lymph vessels, this pathway has been termed "glymphatic" system [75].

A contrasting view suggests that the interstitial solutes (including A β) from the perivascular space enter the basement membranes of capillaries and drain along the basement membrane of the arterial *tunica media* toward the *leptomeningeal* arteries, in opposite direction to blood flow [77–80].

The driving force of this pathway would be the reflected wave of systolic pulsations, assisted by a "valve effect" of proteins in the basement membrane [77]. These proteins, however, have not been identified.

In spite of the different drainage pathways, the two above hypotheses share the common view of arterial pulsation as driving force. The question then arises, whether vasomotion could contribute to such force.

The rhythmic oscillations of vasomotion have comparable amplitude to those caused by the systolic pulsation, in spite of the lower rate (1–20 cycles/min [3, 4, 81–83]). In rat basilar arteries [82], the amplitude of vasomotion (percentage diameter change) was 19%, with a baseline diameter of 259 μ m.

The amplitude of systolic pulsations in the common carotid artery of the adult mouse brain is calculated to 12% according to [84, 85] (Table 1 in [84], for wild type mice; assuming a baseline diameter of 400 μ m [84, 85]).

This suggests that vasomotion could contribute to the driving force of perivascular drainage of extracellular fluids.

VASOMOTION

Mechanisms underlying vasomotion in cerebral arteries

The ongoing debate on the mechanisms underlying vasomotion reflects the inherent complexity of this phenomenon, which involves interacting processes that are difficult to target experimentally [86].

However, it is accepted that vasomotion is initiated when asynchronous oscillations (waves) in Ca²⁺ concentration ([Ca²⁺]_i) within vascular smooth muscle cells become synchronized along the vascular wall [5, 6].

A substantial body of evidence has consistently shown *in vitro* that vasomotion is associated with oscillations in the membrane potential of vascular smooth muscle cells [86–91].

The voltage-dependent cell membrane oscillator

Experimental data from rat basilar arteries support the hypothesis of a voltage-dependent membrane oscillator [6]. According to this model, the smooth muscle cell membrane undergoes cyclic depolarization and hyperpolarization stages, associated with opening and closing of Ca^{2+} -dependent chloride channels (Cl_{Ca}) and intermediate conductance potassium channels (IK_{Ca}), respectively.

Phase I: Vascular smooth muscle cell depolarization

Inositol 1,4,5-trisphosphate (IP_3), produced by phospholipase C (PLC), leads to Ca^{2+} release through IP_3 receptors from the sarcoplasmic reticulum (SR). Increased cytosolic Ca^{2+} concentration then activates Ca^{2+} -dependent chloride channels (Cl_{Ca}), depolarizing the membrane and opening voltage-dependent Ca^{2+} channel to extracellular Ca^{2+} influx [6]. This activates ryanodine receptors resulting in further Ca^{2+} release into the cytosol, in a Ca^{2+} -induced Ca^{2+} release fashion [7].

Phase II: Vascular smooth muscle cell hyperpolarization

The increased $[\text{Ca}^{2+}]_i$ opens IK_{Ca} channels resulting in membrane hyperpolarization, and subsequent closing of voltage-dependent Ca^{2+} channels and vasodilatation [7].

Following the increase in phase I, $[\text{Ca}^{2+}]_i$ decreases again as a result of two cooperating mechanisms: a decreased Ca^{2+} release by the SR (possibly caused by transient refractoriness to IP_3) and the active removal of Ca^{2+} from the cytosol, through SR and plasmalemmal Ca^{2+} -ATPases [86].

The loss of activation of ryanodine-sensitive stores then causes IK_{Ca} channels to close, completing the cycle [7].

Role of the endothelium in vasomotion

The oscillating membrane potential of vascular smooth muscle cells synchronizes $[\text{Ca}^{2+}]_i$ oscillations of adjacent cells through endothelium-mediated electrical coupling, via myoendothelial gap junctions [6–8]. As membrane potential oscillations in endothelial and smooth muscle cells were found to precede the rhythmic contraction of the vessel wall, it was suggested that the endothelium might initiate the synchronized vasomotion [7].

A substantial body of evidence from *in vitro* studies suggests that, in cerebral arteries, endothelial nitric oxide (NO) plays a role in the regulation of vasomo-

tion. In particular, inhibition of NO-synthesis has been consistently reported to promote vasomotion [8, 17, 92–95]. In [92], NO-synthase inhibitor *N* ω -nitro-L-arginine (L-NA) induced cyclic variations of cortical CBF in anesthetized rats. Consistent results were obtained in [17] by blocking basal NO release with L-NA. Exposure to NO inhibitor N-nitro-L-arginine methyl ester also evoked vasomotion [8, 93, 94].

In non-cerebral vascular beds, the role of the endothelium is less clear, with different and sometimes conflicting results. For example, removal of the endothelium or blockade of NO production prevented vasomotion in the hamster aorta [96], rat mesenteric arteries [88, 90, 97], rabbit mesenteric [98, 99], and coronary arteries [99], and also in the human cutaneous circulation [100], whereas vasomotion was initiated upon inhibition of endothelial NO in the hamster cheek pouch [101], and rat mesenteric artery [102]. Other studies have reported the absence of any endothelium-mediated effects on vasomotion in the rat thoracic aorta [103], rabbit mesenteric arteries [98], and pig coronary arteries [104].

Neurovascular coupling in vascular tone regulation and vasomotion

Astrocytes and the regulation of vascular tone

Mounting evidence from *in vitro* studies on animal brain slices suggest that astrocytes may participate in cerebral vascular tone regulation [105].

Astrocytes have indeed been shown to synthesize and release vasoactive agents such as NO, prostaglandins, epoxyeicosatrienoic acids (EETs), glutamate, adenosine and adenosine triphosphate (ATP) [106, 107], which are potential mediators of vascular tone regulation. The hypothesis of astrocyte involvement is further supported by the anatomy, as astrocytes are ideally situated in apposition to cerebral arterioles and capillaries, which would facilitate the relay of vasoactive signals [105].

Although studies on brain slices are limited by the inherent absence of cerebral perfusion, which implies the lack of myogenic and shear stress-induced modulation of vascular tone [108, 109], they provide evidence that Ca^{2+} -related events in perivascular astrocytes can influence vascular tone.

Conflicting results were reported by the early studies regarding the vascular response to astrocytic Ca^{2+} elevations such as induced by neuronal stimulation, metabotropic glutamate receptor (mGluR) stimulation, or direct Ca^{2+} uncaging—a technique based on local release of Ca^{2+} from an inert molecule exposed to UV photons [110, 111].

In [112], vascular constrictions were observed when uncaging-evoked Ca^{2+} waves propagated to the astrocyte end-feet and caused large increases in $[\text{Ca}^{2+}]_i$. The authors postulated that increased $[\text{Ca}^{2+}]_i$ in the astrocyte end-feet could activate phospholipase A_2 and increase arachidonic acid (AA) formation. AA would then diffuse to smooth muscle cells where it would be converted to 20-hydroxyeicosatetraenoic acid by CYP4A, a cytochrome P450 (CYP450) enzyme subtype, causing vasoconstriction. Contrasting results, however, have been reported by other studies in which vasodilatation rather than vasoconstriction was observed [113–115], suggesting that the build-up of AA in astrocytes could increase the production of prostaglandins and EETs, causing parenchymal arterioles to dilate [116].

Subsequent studies have reconciled these conflicting findings, suggesting that the polarity of vascular responses (vasoconstriction versus vasodilatation) could depend on basal conditions such as resting arteriolar tone [117], O_2 concentration levels [118], and NO availability [119]. The level of astrocytic increase of $[\text{Ca}^{2+}]_i$ following stimulation has also been suggested to play a role [120].

In [117], astrocytic stimulation by mGluR agonist trans-1-aminocyclopentane-1,3-dicarboxylic acid (t-ACPD) induced vasoconstriction in arterioles with moderate basal tone (diameter greater than 70% of maximum), and vasodilatation in arterioles with higher basal tone. In [118], t-ACPD stimulation caused arteriolar dilatation in conditions of low O_2 concentration (20%) and arteriolar constriction at high O_2 concentration (95%). Vasodilatation under low O_2 was shown to depend on enhanced lactate release by activated astrocytes and increased extracellular levels of the vasodilating agent prostaglandin E_2 . The authors also observed increased extracellular levels of adenosine in low O_2 and suggested this might act upon A_2A receptors in smooth muscle cells to reduce Ca^{2+} channel activity and inhibit contraction.

In [119], astrocyte-induced vasoconstriction was attributed to NO interactions with AA metabolites due to NO-mediated inhibition of CYP450 and the subsequent decrease in the formation of vasodilating EET.

In [120], the level of astrocyte end-feet Ca^{2+} determined the polarity of arteriolar response, with increasing values shifting the vascular tone response from vasodilatation to vasoconstriction. The response was attributed to the activation of Ca^{2+} -activated large conductance K^+ channels (BK) by the increased Ca^{2+} concentration, which caused extracellular K^+ increase. This, in turn caused vasodilatation at physiological

concentration levels (3 mM), and vasoconstriction at higher concentrations (8 mM).

Astrocytes mediate functional hyperemia and suppression of vasomotion

Astrocytes have been proposed to mediate vasodilatation of parenchymal arterioles in response to increased neuronal activity. This mechanism, termed 'functional hyperemia', increases O_2 and glucose supply to the active neurons in a timely and spatially localized manner [106, 116].

In [106], increased neuronal activity by electrical stimulation, increased astrocytic $[\text{Ca}^{2+}]_i$, and evoked Ca^{2+} waves travelling from the soma towards the end-foot. The increased Ca^{2+} in astrocytes was rapidly signaled to the surrounding parenchymal arterioles, which had been pre-constricted with thromboxane A_2 (TXA_2) agonist U46619, where it suppressed $[\text{Ca}^{2+}]_i$ oscillations and vasomotion. Consistent with the above, the same study also found that the activation of astrocytic glutamate receptors, which is known to increase $[\text{Ca}^{2+}]_i$ in cortical astrocytes [121], had similar effects. Consistent findings have been reported also in [122] and [123] using similar preparations.

Furthermore, in [123] epoxygenase inhibitor miconazole caused arteriolar vasoconstriction and increased vasomotion oscillation frequency, suggesting that EETs may act as mediators of neuronal-activity-related dilatation of parenchymal arterioles and dampening of vasomotion.

CAA and vasomotion

In CAA, $\text{A}\beta$ interacts predominantly with vascular smooth muscle cells in the *tunica media* causing structural alterations such as the disruption of actin in the cytoskeleton, and apoptosis [124–126]. The loss of vascular smooth muscle cells with disease progression weakens the vascular wall [127–129], increasing the susceptibility to abnormal vasodilatation and hemorrhage [126, 130, 131].

$\text{A}\beta$ deposition also affects the luminal area of arterial vessels. However, experimental data are conflicting as both increase [127, 129] and decrease [128] of the internal lumen have been reported. In the former case, which is also supported by transgenic mouse studies [130], vessel dilation could reduce the vascular reactivity to vasodilatory stimuli such as ischemia [126, 132] or hypercapnia [133] (see section on cerebrovascular reactivity). In the latter case, vasoconstriction could result in hypoperfusion downstream of the narrowing of the vascular lumen [126].

However, while the experimental evidence described above can be seen as the long-term outcome, in the short-term other processes could take place, with detrimental effects on vasomotion at an early stage.

Indeed, vascular smooth muscle cells treated with A β ₁₋₄₀—the most frequent form of A β in sporadic CAA—exhibit higher inflammatory response to interleukin-1 β [134]. This cytokine is expressed by endothelial cells exposed to A β ₁₋₄₀ [135]. As endothelial cells are adjacent to smooth muscle cells, the above finding suggests that A β could mediate the inflammatory response of smooth muscle cells, leading to the loss of contractile function through the disruption of α -actin in the cytoskeleton [134].

Findings from *in vitro* studies on neuronal cells suggest that the detrimental effects of A β could also impair intracellular Ca²⁺ dynamics as well as the membrane potential [136, 137], resulting in the loss of synchronization of cytosolic Ca²⁺ waves, a prerequisite of vasomotion according to the membrane oscillator model [6].

The effect of oxidative stress

Oxidative stress has been implicated in AD and CAA from the early stages of the disease [24, 49, 138–140]. As this condition is associated with mitochondrial dysfunction [138, 141, 142], which results in ATP deficiency, it seems plausible that in AD/CAA, ATP-dependent transport might be impaired not only in neurons but also in vascular smooth muscle cells, resulting in altered Ca²⁺ homeostasis and disruption of vasomotion.

Vascular tortuosity and vasomotion

The long path of arterioles supplying the deep white matter tends to become tortuous with aging [33, 143, 144]. Tortuosity manifests in the form of turns and curls requiring increased perfusion pressure to maintain stable CBF [33]. It has been suggested that decreased pulsations in tortuous vessels may impede interstitial fluid flow, reducing A β clearance in perivascular spaces [143]. Although this suggests a potential implication of increased tortuosity in AD, existing reports are inconclusive [144, 145].

In tortuous arterial vessels, vasomotion could act as a protective mechanism by cooperating with the systolic pulse in the attempt to compensate the dispersion of kinetic energy of blood flow caused by turns and curls, and preserve adequate CBF.

Disturbed blood flow such as occurring at turns and loops of tortuous vessels is known to reduce the wall shear stress exerted by blood flow [146–148]. On the other hand, reduced wall shear stress is associated with reduced endothelial NO production [149], a condition which has been shown *in vitro* to promote vasomotion [8, 17, 92–95]. This further supports the hypothesis of a potential protective role of vasomotion in the presence of tortuous arteriolar paths. However, given the intrinsic difficulty in measuring vasomotion in conditions of tortuous blood flow *in vivo*, this hypothesis has not been tested.

Temporal variability of vasomotion

The changes in vessel diameter observed in vasomotion are identified as “rhythms”, whereas the magnitude of the diameter oscillations is referred to as “amplitude” of vasomotion.

The rhythms of vasomotion exhibit different characteristics in different tissues of the body, and are characterized by different temporal patterns.

The rhythms in vasomotion can be highly regular—nearly following a periodic sinusoidal wave (see for example [6, 8, 86, 150])—or characterized by higher complexity [3, 54, 151]. With increasing complexity, these rhythms tend to lose their periodic nature and approach a chaotic behavior, which is thought to reflect the limit beyond which vasomotion fails [17].

In [152], vasomotion was studied as a function of arteriolar diameter. Arterioles with baseline diameter in the range 50–100 μ m showed rhythmic oscillations at rates of 2–3 cycles/min, and magnitude of 10–20%. Rate and magnitude were found to increase with decreasing vessel diameter, exhibiting oscillation rates of 10–25 cycles/min in terminal arterioles.

Vasomotion is also dependent on the intravascular pressure. In both isolated pressurized rat cerebral arteries and *in vivo* measurements from rat basilar artery, the amplitude of vasomotion has been shown to decrease (and frequency to increase) with increasing pressure [62, 82]. This finding supports the idea of vasomotion as a protective mechanism, which potentiates cerebral autoregulation in the lower blood pressure range, a condition in which maintaining adequate cerebral perfusion becomes critical [5].

A neurogenic component of vasomotion, manifesting at low frequencies (between 20 and 40–60 mHz, approximately corresponding to 1–4 cycles/min) has also been reported [16, 153].

Cerebrovascular reactivity and vasomotion

In normal conditions, resistance vessels in the vascular system dilate or constrict in response to exogenous stimuli. This can be seen as the ability of blood flow regulation to respond to hemodynamic challenges beyond the resting conditions. This phenomenon is distinct from the vascular response to changes in blood pressure (autoregulation) [154].

Hypercapnic stimuli such as breath holding [155], increased inspiratory concentration of carbon dioxide [156], and acetazolamide administration [157], induce a hyperemic response which causes resistance vessels to dilate [158]. This response is thought to be mediated by increased pH, activation of K^+ channels endothelial hyperpolarization and subsequent $[Ca^{2+}]_i$ decrease in vascular smooth muscle cells, and increased NO synthesis by endothelial cells or neurons [154].

When cerebral vessels are already dilated to compensate for a pathological reduction in cerebral perfusion pressure, the above vasodilating stimuli may become ineffective. The ability of blood vessels to dilate further in response to a dilatory stimulus (or, conversely, constrict in response to vasoconstrictor stimuli) is referred to as cerebrovascular “reactivity” (CVR) or “reserve” [157, 154] (also termed “cerebral vasomotor reactivity”). The vasodilatory reserve has been studied more extensively than the vasoconstrictor reserve, as noninvasive capnic stimuli evoke the former with greater magnitude [154].

Measuring CVR can help identify patients with reduced cerebral perfusion pressure, such as caused by occlusive lesions of the brain-supplying arteries [157, 159, 160]. CVR in middle cerebral arteries has been reported to predict cerebral ischemia (stroke and transient ischemic attack) in patients with carotid occlusion [160–162] and asymptomatic carotid stenosis [160]. Reduced CVR has also been observed in AD patients [163, 164] and has been associated with cognitive decline [165].

Impaired cerebral vasoreactivity, namely the inability of dilated vessels to dilate further in response to vasodilatory stimuli, could also reduce or suppress vasomotion. Indeed, in conditions of pronounced vasodilatation such as observed in functional hyperemia [106] or the administration of nitroglycerin [82], vasomotion is suppressed. Furthermore, depressed CVR occurring in conditions of chronically low perfusion pressure may be accompanied by impaired vasomotion as an indirect effect of the insufficient O_2 supply which alters the metabolism of vascular cells, impairing intracellular Ca^{2+} dynamics [166].

In light of the above, the observation of impaired vasoreactivity in CAA [133, 167, 168] suggests a potential indirect implication of CAA in vasomotion disruption.

Evaluation of cerebrovascular reactivity in AD by Doppler ultrasonography

CVR can be indirectly and noninvasively assessed by TCD. This method is used to measure changes in blood flow velocity in selected cerebral arteries (e.g., the middle or the posterior cerebral artery) as surrogate of the changes in CBF [157, 160]. Assuming that the vessel diameter remains nearly constant during the administration of the hypercapnic stimulus, the change in blood flow velocity measured by TCD reflects the change in CBF in response to the stimulus. Using this technique, observations of impaired autoregulation and vascular reactivity in transgenic mouse models of CAA have been confirmed in AD patients [158, 163–165, 169] and extended to vascular dementia [170]. Bär and colleagues [158] have shown that a possible cause of CVR impairment in AD might be cholinergic deficiency (a condition which has been reported in AD [171–173]), as the administration of galantamine (a substance with acetylcholinesterase inhibitor properties) increased CVR in their cohort. As vasomotion has been suggested to contain a neurogenic component, cholinergic deficiency might also affect (dampen) vasomotion, due to the cholinergic intrinsic innervation of parenchymal cerebral arteries.

A reduced CVR has also been shown to predict a worse Mini-Mental State Examination score at 12 months follow-up in AD patients with severe internal carotid artery stenosis [174], suggesting that impaired vasoregulation may be indicative of faster progression of cognitive decline in AD. Buratti and colleagues [175] found CVR depression in AD patients to be associated with the presence of obstructive sleep apnea.

CVR has also been reported to be reduced in CAA patients with a history of CAA-related hemorrhages [169].

Evaluation of cerebrovascular reactivity in AD by SPECT

Imaging of regional CBF with SPECT has been used in the quantitative assessment of cerebrovascular deficits [154] in various conditions including AD [41–44, 176–180]. Owing to the associated costs and complexity, this technique has been used in a limited number of studies compared to TCD, in the assessment of CVR. Vascular activation in response to acetazolamide (hypercapnic stimulus) has been investigated in

AD patients [177–179]. However, in [177] and [179], direct comparisons between AD patients and a control group were not reported, preventing the inference of CVR impairment in AD. In [178], CVR was reduced in AD patients compared with controls, and CVR correlated with Mini-Mental State Examination score in the AD group. Pavics and colleagues [180] assessed the ability of CVR response to acetazolamide in discriminating AD from vascular dementia by SPECT analysis of regional CBF. The majority (73%) of AD patients ($n=33$) showed no CVR alteration compared to pre-injection baseline. However, comparative results with respect to the control group were not reported.

In summary, SPECT studies have not shown substantial evidence of CVR impairment in AD [154].

Experimental approaches for measuring vasomotion: Challenges and future perspective

Due to the intrinsic difficulty in measuring vasomotion, most of the data are based either on *in vitro* experiments of isolated arteries, or *in vivo* experiments on anesthetized animals (typically rat, hamster, or rabbit).

While *in vitro* approaches provide for the most precise measurement of the arteriole diameter changes which underpin vasomotion, insights are limited because of the lack of natural perfusion and non-physiological neurochemical environment. The use of anesthesia within *in vivo* studies is also problematic because of the complex and varied effects of anesthetic agents upon physiological, cerebrovascular, and neurovascular function [181].

Furthermore, as the measurement of vasomotion in the strict sense (i.e., modulation of the vessel diameter) requires complex experimental settings, many studies rely on flowmotion (i.e., modulation of blood flow velocity) as a surrogate measure. Although the two quantities are related, they are distinct as blood flow velocity can change without significant changes in vessel diameter.

The advances in optical techniques have now introduced a new perspective for noninvasive hemodynamic measurements *in vivo*, and in awake state [181, 182]. Advanced spectroscopic techniques (the reader is referred to [183, 184] for review) provide quantitative measurements of dynamic changes not only of vessel diameter, but also of blood volume, blood flow, and tissue oxygenation. Multi-photon microscopy methods can additionally be used to probe the specific cellular drivers of vasomotion and the mechanisms by which structural or biochemical changes can impact upon

vasomotion as well as other aspects of cerebrovascular or neurovascular function [182, 185]. Important advances in the understanding of the role of vasomotion may now arise as these techniques are applied to study vasomotion in the increasingly wide range of animal models of AD and/or CAA.

In light of the literature reviewed in this study, some specific hypotheses could be tested using these models and *in vivo* quantitative imaging techniques:

H1) Vasomotion is present in tortuous vascular beds. The magnitude of vasomotion oscillations exhibits an inverse-U shaped relationship with respect to the degree of tortuosity.

H2) Vasomotion oscillations are driven differentially according to cell type. Cellular resolution *in-vivo* microscopy techniques could be used to better delineate the endothelial, neurogenic or myogenic contributors to concurrently measured vasomotion oscillations.

H3) Depressed cerebrovascular reactivity is associated with reduced vasomotion (both magnitude and frequency of oscillations). Cerebrovascular reactivity could be measured (and manipulated) *in vivo* and relationships to specific sources of vasomotion characterized.

H4) Vasomotion is depressed in diabetes and in hypertension. Multimodal imaging methods (such as optical spectroscopy and multiphoton imaging) could be applied to investigate vasomotion oscillations in animal models of these conditions.

IMPAIRED CEREBRAL VASOMOTION IN AD

Possible pathways affecting vasomotion in AD/CAA (Question 1)

The available data suggest that impaired vasomotion may be implicated in the development or progression of AD/CAA. Different pathways can be hypothesized, as illustrated in Fig. 1.

Path A: ET-1-induced vasoconstriction depresses vasomotion

Endothelin-1 (ET-1) is a potent vasoconstrictor produced predominantly by vascular endothelial cells [186]. ET-1 is generated from its inactive precursor through cleavage by endothelin converting enzyme (ECE)-1 or ECE-2 [187]. The former is expressed in endothelial cells, in neurons and astrocytes [188], and in smooth muscle cells [189].

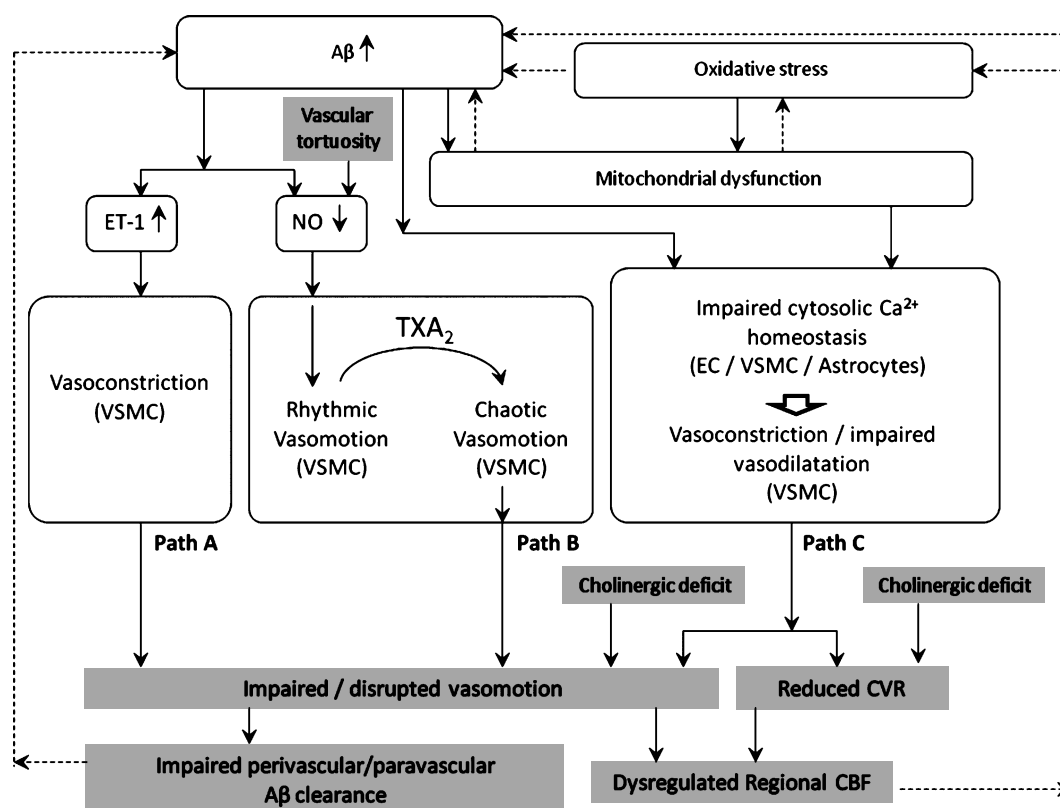


Fig. 1. Hypothetic pathways of impaired vasomotion *Path A*: A β upregulates ET-1 causing vasoconstriction and cessation of vasomotion. *Path B*: A β reduces endothelial NO synthesis. According to most studies, this promotes vasomotion (protective). However, exposure to the vasoconstrictor thromboxane (TXA₂) could increase vascular susceptibility to chaotic vasomotion. *Path C*: A β induces ER stress in endothelial cells and astrocytes, resulting in impaired calcium (Ca²⁺) homeostasis. A β also interacts with vascular smooth muscle cells dysregulating vascular tone. Mitochondrial dysfunction disrupts Ca²⁺ homeostasis by reducing ATP production and impairing ATP-mediated transport. Cholinergic deficit aggravates CVR depression and vasomotion, resulting in regional CBF dysregulation, which in turn leads to hypoperfusion and subsequent oxidative stress and A β accumulation. Dotted lines indicate “feed-back” loops triggering vicious circles. Gray (white) rectangles indicate status (process). CBF, cerebral blood flow; CVR, cerebrovascular reactivity; EC, endothelial cell; ER, endoplasmic reticulum; ET-1, endothelin-1; NO, nitric oxide; VSMC, vascular smooth muscle cells.

Substantial evidence suggests that the upregulation of ET-1 observed in AD, both in the cerebral cortex [186, 190] and in cerebral blood vessels [191, 192], is caused by the accumulation of A β [186, 187, 192–194].

ET-1 causes contraction of vascular smooth muscle cells by multiple signaling pathways [195], including, among others, the PLC/IP₃ cascade. IP₃ in turn stimulates endoplasmic reticulum (ER) release of Ca²⁺, and protein kinase C activation, ultimately resulting in myosin light chain phosphatase inhibition and consequent cell contraction.

The vasoconstriction caused by upregulated ET-1 could attenuate the amplitude of vasomotion [196] or inhibit it. This is consistent with a mathematical model of vasomotion [197] in which smooth muscle cells exhibited synchronous [Ca²⁺]_i oscillations and

vasomotion at intermediate [Ca²⁺]_i, shifting to tonic contractions and vasomotion suppression at greater [Ca²⁺]_i.

Path B: Reduced endothelial NO production may promote rhythmic vasomotion (protective) or chaotic vasomotion (detrimental)

A β -endothelium interaction causes decreased NO production [198, 199]. According to most experimental evidence, NO inhibition promotes vasomotion [8, 17, 92–95], which could be interpreted as a protective effect potentiating cerebral perfusion and O₂ delivery.

However, administration of the thromboxane TXA₂ analog U46619 has been shown to elicit irregular/chaotic vasomotion in middle cerebral arteries pre-conditioned with L-NA-induced NO blockade

[17]. As TXA₂ production (by activated platelets) is enhanced in AD [200], and L-NA mimics the effect of Aβ-induced endothelial NO synthesis inhibition, the above report suggests a plausible pathway for vasomotion disruption in AD.

Endothelial NO synthesis could also be reduced in tortuous vessels as a consequence of reduced shear-stress [149] caused by disturbed blood flow [146–148].

Path C: Altered Ca²⁺ homeostasis dysregulates vasomotion

Multiple factors can influence and impair intracellular Ca²⁺ homeostasis in the vascular wall and astrocytes. Aβ accumulation, mitochondrial dysfunction and oxidative stress have both individual and combined effects on Ca²⁺ homeostasis.

Aβ has been shown to interact with the ER in the endothelial cytosol. Incubation of rat brain endothelial cells with Aβ₁₋₄₀ increased ER stress-induced unfolded protein response, transfer of Ca²⁺ from ER to mitochondria [201], and affected cytosolic Ca²⁺ homeostasis [202].

Mitochondrial dysfunction

Intracellular Ca²⁺ dynamics are also susceptible to mitochondrial dysfunction and damage, a condition that has been consistently reported in regions of cerebrovascular lesions of the AD brain [142, 203–207], in endothelial and parenchymal cells. Mitochondrial dysfunction depletes cellular ATP [208], impairing ATP-dependent transport such as the sodium (Na⁺/K⁺-ATPase) and the calcium (Ca²⁺-ATPase) pump [26, 209], and ATP-binding cassette (ABC) transporters [26]. Of note, the latter include Aβ transporters which are responsible for Aβ clearance from the brain parenchyma [210, 211], in particular multidrug resistance-associated protein 1 (ABCC1) [212, 213] and ABC subfamily B member 1 (ABCB1) [214–216].

As mitochondrial dysfunction may itself result from Aβ cytotoxic effects [141, 217–220], a detrimental bidirectional link exists between Aβ accumulation and mitochondrial dysfunction/damage.

Mitochondrial dysfunction is further exacerbated by oxidative stress subsequent to chronic cerebral hypoperfusion [142, 207, 221].

Membrane potential-related dysregulation of vascular tone

Impaired ATPase pump function in mitochondrial dysfunction results in dysregulation of membrane potential and consequent further alteration of intracellular Ca²⁺ dynamics, which in turn affects

endothelial NO synthase activity [222], and NO-mediated vasodilatation.

A further element of membrane potential dysregulation is the effect of oxidative stress on K⁺ channels in vascular smooth muscle cells. These channels play an important role in the regulation of the membrane potential and the contractile tone of arterial smooth muscle cells [223]. Among the different types of K⁺ channels, the ATP-dependent K⁺ channels (K_{ATP}) have consistently been found to mediate vasodilatation [224–227], and their function has been shown to decrease in pathological conditions such as diabetes [228] and ischemia [229].

A substantial body of evidence suggests that oxidative stress modulates the vascular vasomotor function through K⁺ channel activity [230]. In vascular smooth muscle cells of the brain, the activity of K_{ATP} appears to be selectively modulated by different reactive oxygen species, such as superoxide, hydrogen peroxide, and peroxynitrite [230]. As oxidative stress manifests early in the development of AD/CAA [24, 49, 138–140], it is plausible that K⁺ channel activity and vasodilatation are also impaired from the early stages, potentially altering the rhythmic contractions of vasomotion.

Astrocyte-related dysregulation of vascular tone

Astrocytes are thought to participate in the regulation of vascular tone. Aβ has been shown to alter Ca²⁺ homeostasis and signaling in astrocytes [231–238], potentially affecting neurovascular coupling and vascular tone regulation, in AD/CAA.

Exposure to exogenous Aβ has been reported to affect astrocytic Ca²⁺ dynamics giving rise to fast [Ca²⁺]_i transients and oscillations [239]. Aβ also increased the expression of key components of Ca²⁺ signaling such as the glutamate receptor mGluR5 and IP₃ receptor-1 [240] leading to increased [Ca²⁺]_i. Aβ-induced [Ca²⁺]_i elevation has also been attributed to Ca²⁺-influx pathways [234, 235] and ER stress [233]. Consistent results showing Ca²⁺ elevation in astrocytes exposed to Aβ have been reported also in other studies [232, 237, 238].

Other cytotoxic effects of Aβ have been observed in astrocytes *in vitro*, which could disrupt neurovascular coupling. Exposure of cultured rat hippocampal astrocytes to oligomeric Aβ₁₋₄₂, reduced the production of the potent vasodilator EET [241]. Aβ also induced mitochondrial dysfunction and oxidative stress in a Ca²⁺-dependent manner [235, 236]. Injection of Aβ₁₋₄₂ into mouse neocortical pyramidal cells blocked BK channels [242]. In cultured hippocampal astrocytes, exogenous Aβ₁₋₄₀ enhanced the expression

of the non-selective cation channel TRPV4, resulting in increased $[Ca^{2+}]_i$ [243].

Taken together these data suggest that the cytotoxic effects of A β may locally de-couple neuronal activity (metabolic demand) from CBF (metabolic supply), with detrimental effects on neuronal function.

Indeed, A β may induce astrocyte-mediated dysregulation of local CBF by impairing vasodilatation (due to reduced EET production) and/or enhancing vasoconstriction (due to increased production of reactive oxygen species, or inhibition of astrocytic BK channels). These indirect effects on vascular tone regulation could add to the direct effects of A β on vascular smooth muscle cells [125, 134] and endothelial cells [140, 186, 192, 207], resulting in the alteration of Ca^{2+} oscillations in smooth muscle cells, which are essential to vasomotion.

Impaired CVR and vasomotion mediate cholinergic deficit-induced dysregulation of regional CBF

Cholinergic deficit has been shown in AD [154, 171–173] and implicated in CVR impairment. As the frequency spectrum of vasomotion has been suggested to contain a neurogenic component in the low frequency range [16, 153], it is plausible that the cholinergic deficit depresses not only vascular reactivity but also vasomotion (in the slow oscillations range). Both effects would then aggravate regional disruption of CBF.

Impaired vasomotion as a potential mediator of detrimental vicious circles precipitating neurovascular damage

The dysregulation of ABC transporters caused by mitochondrial dysfunction impairs A β clearance from the perivascular space [26, 244], resulting in A β accumulation [245]. This in turn causes mitochondrial dysfunction [141, 217–220] in a detrimental vicious circle. A similar bidirectional relationship exists between oxidative stress and mitochondrial dysfunction [141], which further sustains this loop.

Hypoperfusion is yet another recognized cause of oxidative stress [221] and further A β accumulation [22]. We postulate that impaired vasomotion (either low amplitude or chaotic) might contribute to this vicious exacerbation of neurovascular damage, by two independent pathways: by reducing peripheral perfusion, and by reducing the driving force to perivascular drainage, thus facilitating further parenchymal and perivascular accumulation of A β .

Vasomotion and the perivascular/glymphatic clearance of A β (Question 2)

In the current view, vasomotion in cerebral arteries manifests in the form of synchronous contractions of the vessel wall [6–8]. However, some evidence from *in vivo* studies on vasomotion in rat cerebral arteries [82] and hamster skin fold [246], suggests that vasomotion may also propagate longitudinally along the blood vessel wall, following either directions with respect to blood flow (either upstream or downstream).

The perivascular pathway proposed by Weller and colleagues [77–79] suggests that interstitial solutes (including A β) enter the basement membranes of blood-brain barrier capillaries and drain along the basement membrane of the arterial *tunica media*, in opposite direction to blood flow.

Based on the evidence that vasomotion can propagate upstream along the vessel wall, the rhythmic oscillations of vasomotion could contribute to the driving force of the perivascular drainage in the path described by Weller and colleagues.

Furthermore, the rhythmic oscillations of the arterial wall can also be viewed as a source of pressure waves exerted on the surrounding fluid in the paravascular space. According to the power-law attenuation of longitudinally propagating waves [247], higher frequency waves reach shorter distances than lower frequency waves. Thus, the oscillations produced by vasomotion, which are lower in frequency than those induced by the systolic pulse, could facilitate the propulsion of cerebrospinal fluid from the perivascular space into the brain parenchyma, allowing deeper penetration into the latter.

In this view, the impairment of vasomotion would decrease the efficiency of both the perivascular and glymphatic clearance of A β , facilitating the accumulation of the toxic peptide. This, in turn, would cause further endothelial dysfunction [198], oxidative stress [248], and decreased NO production [198]. These conditions could further dampen vasomotion [17] (Fig. 1), in a detrimental vicious circle which would accelerate neurovascular damage.

CONCLUDING REMARKS

This study has reviewed the current literature on cerebral vasomotion and identified potential pathways of vasomotion impairment in AD/CAA (Fig. 1).

A β cytotoxicity affects Ca^{2+} homeostasis in the neurovascular unit, resulting in vascular tone dysregulation. A β also reduces endothelial NO synthesis and

upregulates the potent vasoconstrictor ET-1. Impaired vasodilatation and paradoxical vasoconstriction may cooperate in the disruption of vasomotion, resulting in weakened autoregulation, chronic hypoperfusion, and reduced driving force to the perivascular/glymphatic clearance of A β . These effects in turn facilitate A β accumulation in a detrimental vicious circle.

As vascular dysfunction is thought to occur years or even decades ahead of the clinical manifestation of AD, quantitative measurements of cerebral vasomotion could predict microvascular dysfunction at an early stage of the disease, and contribute to assess the efficiency of therapeutic interventions. Detailed physiological measurements in animal models as well as advances in computational modeling approaches will be important components of future research.

ACKNOWLEDGMENTS

The present study was conducted as part of the Project VPH-DARE@IT funded by the European Union Seventh Framework Programme (FP7/2007 - 2013) under grant agreement no. 601055.

Authors' disclosures available online (<http://j-alz.com/manuscript-disclosures/14-2976r1>).

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