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## Alzheimer's Disease and Vascular Aging:

### JACC Focus Seminar

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### Abstract

Alzheimer's disease, the leading cause of dementia in the elderly, is a neurodegenerative condition characterized by accumulation of amyloid plaques and neurofibrillary tangles in the brain. However, age-related vascular changes accompany or even precede the development of Alzheimer's pathology, raising the possibility that they may have a pathogenic role. This review provides an appraisal of the alterations in cerebral and systemic vasculature, the heart, and hemostasis that occur in Alzheimer's disease and their relationships to cognitive impairment. Although the molecular pathogenesis of these alterations remains to be defined, amyloid- $\beta$  is a likely contributor in the brain as in the heart. Collectively, the evidence suggests that vascular pathology is a likely pathogenic contributor to age-related dementia, including Alzheimer's disease, inextricably linked to disease onset and progression. Consequently, the contribution of vascular factors should be considered in preventive, diagnostic, and therapeutic approaches to address one of the major health challenges of our time.

### Keywords

atherosclerosis; blood-brain barrier; cerebral blood flow; dementia; hypertension; vascular dysfunction

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Vascular aging, defined as age-related changes in the vasculature, has a deleterious impact on the brain, an organ that critically depends on its blood supply for structural and functional integrity (1). Vascular aging may also play a role in Alzheimer's disease (AD), the leading cause of cognitive impairment in the elderly. AD is a progressive disorder that affects 10% of the population age >65 years, and, due to the lack of disease-modifying treatments, it has risen to be the fifth leading cause of death worldwide (2,3). The classical neuropathologic hallmarks of AD are amyloid- $\beta$  (A $\beta$ ) plaques and intraneuronal aggregates of hyperphosphorylated tau (neurofibrillary tangles) (3). However, recent community-based autopsy studies have shown that vascular alterations are present in >50% of cases of clinically diagnosed AD, highlighting a still under-appreciated contributory role of age-related vascular factors in the mechanisms of AD (4). This review will address the vascular

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changes taking place in AD, focusing mainly on the effects of A $\beta$ , at the molecular, cellular, and systems levels and their potential involvement in the disease process (Central Illustration). We will also briefly examine the impact that systemic vascular aging may exert on the clinical expression and progression of AD. Finally, we will highlight unresolved issues that require further investigation in an attempt to identify new approaches to mitigate the heavy toll of age-related dementia on global health.

## **AD-ASSOCIATED VASCULAR ALTERATIONS IN THE BRAIN**

### **MORPHOLOGICAL ALTERATIONS ACROSS THE CEREBRAL VASCULATURE.**

**Intracranial atherosclerosis.**—Atherosclerosis, a key feature of vascular aging, is a leading contributor to death and disability worldwide (5). When atherosclerosis develops in cerebral vessels, the brain's oxygen and energy supply may be compromised because of hypoperfusion, resulting in deleterious neurological consequences. Surprisingly, cerebrovascular atherosclerosis has been identified as a prominent pathological feature of AD. Roher et al. (6) demonstrated that patients with AD exhibit substantial atherosclerosis in the arteries of the circle of Willis at the base of the brain, the lesions being more severe and more stenotic than in age-matched control individuals. Leptomeningeal arteries also exhibited extensive atherosclerotic lesions, the severity of which correlated with tangle and plaque load (7). Although some studies found no association (8), the link between intracranial atherosclerosis and AD has been validated in larger cohorts and seems to be more specific for AD than for other neurodegenerative diseases (9). Moreover, in a substantial cohort, Arvanitakis et al. (10) found that large (atherosclerosis) and small (arteriolosclerosis) cerebral vessel pathology were associated with lower cognitive performance and increased risk for AD. The link between atherosclerosis and AD development not only pertains to intracranial vessels but extends to extracranial arteries as well. For example, the prevalence of AD increases 3-fold in individuals with severe carotid and femoral atherosclerosis, an effect dramatically enhanced in apolipoprotein E4 (ApoE4) carriers (11), the strongest genetic risk factor for sporadic AD (12). In addition, coronary artery calcifications are linked to higher odds of dementia in elderly individuals (13). The mechanisms of the association between atherosclerosis and AD may involve impaired A $\beta$  clearance, nonresolving inflammation, and vascular effects of ApoE4 (14,15). Another possibility is that in severe atherosclerosis, hypoperfusion and hypoxia enhance A $\beta$  production, which, in turn, promotes the formation of atherosclerotic lesions through inflammation, vascular oxidative stress, and endothelial dysfunction (14,15). Indeed, A $\beta$  is present in atherosclerotic plaques (16), and, although the specific involvement of A $\beta$  in cardiovascular aging has not been established, the possibility that this peptide promotes atherosclerotic plaque formation or even rupture by exacerbating vascular inflammation and thrombosis cannot be ruled out at this time and needs further exploration.

**String vessels and capillary rarefaction.**—Aging leads to reduced cerebral microvascular density, a process known as vascular rarefaction (17). In advanced AD, this process is exacerbated, and autopsy studies have shown a large number of string (ghost) vessels, consisting of remnants of micro-vessels that become acellular and collapse (18). These microvascular alterations occur in 90% of AD brains and are exacerbated in ApoE4

carriers and in the presence of amyloid plaques (19). Multiple factors may contribute to vascular rarefaction in AD, including A $\beta$  toxicity to vascular cells (20) and vascular risk factors such as hypertension (21).

**Cerebral amyloid angiopathy.**—Amyloid deposition into the walls of cerebral arteries and capillaries gives rise to the so-called cerebral amyloid angiopathy (CAA) (22). CAA occurs in 85% to 95% of patients with AD, has a significant impact on vessel health, and is an important contributor to cerebrovascular pathology in AD. CAA starts with A $\beta$  deposits in the adventitia and media of the arteries and in the basement membrane of capillaries, probably due to impaired A $\beta$  clearance (1,23). In more advanced cases, this vascular accumulation of A $\beta$  progresses until vascular cells degenerate. CAA, therefore, weakens the vessel wall, reduces resting cerebral blood flow (CBF) and cerebrovascular reactivity, compromises the integrity of the blood-brain-barrier (BBB), and leads to microinfarcts and microbleeds, factors that contribute to cognitive impairment (22).

### THE BBB.

The BBB is a unique property of the cerebral circulation that controls the homeostasis of the cerebral microenvironment by tightly regulating the molecular and cellular exchange between blood and brain (24). Central to the barrier function of the cerebral microvasculature are key features of cerebral endothelial cells that are sealed by specialized intercellular junctions (e.g., tight junctions), have limited vesicular transport, and express a multitude of molecular transporters that regulate the exchange of solutes between blood and brain (24,25). Although endothelial cells are the main gatekeepers, the permeability of the BBB is regulated in concert with other cells of the neurovascular unit, such as pericytes, astrocytes, and perivascular cells (25). The BBB is disrupted in aging and AD; in AD, the disruption occurs early in the disease course, raising the possibility that it may play a role in the mechanisms underlying cognitive impairment (24). The BBB disruption is associated with endothelial and pericyte degeneration, together with alterations of the basement membrane and astrocytic end-feet, allowing infiltration of blood-borne cells and circulating factors and disrupting A $\beta$  clearance (24). Some of the most significant changes in the neurovascular unit and BBB are described in Table 1. These alterations induced by the pathogenic factors driving AD likely work in concert with the BBB dysfunction that occurs in normal aging (24), resulting in a synergistic or additive amplification of their harmful effects on the brain.

### CEREBROVASCULAR DYSFUNCTION IN AD.

Alterations in CBF have long been described in AD (26,27). CBF decreases are found in brain regions involved in cognition and affected by AD pathology, such as the hippocampus, entorhinal cortex, amygdala, and anterior cingulum, and are observed in the preclinical stages of the disease (27,28). Although these changes in CBF could be secondary to reductions in neuronal activity, which is tightly coupled to CBF (1), the data raise the prospect that vascular insufficiency could be an early contributor to the disease process (26). In support of this possibility, experimental data suggest that A $\beta$  has powerful vasoactive effects (27). Thus, Thomas et al. (29) showed that A $\beta$  induces endothelial dysfunction and damage in the rat aorta through reactive oxygen species (ROS). The first demonstration that

$A\beta$  alters cerebral endothelial function in vivo was provided by Zhang et al. (30), who showed that the increase in CBF produced by application of the endothelium-dependent vasodilator acetylcholine to the cerebral cortex is profoundly attenuated in AD mice, even before the development of amyloid deposits or cognitive dysfunction. It was then shown that the endothelial dysfunction is also secondary to vascular oxidative stress in vivo and, as such, could be reversed by ROS scavengers (31). Studies using recombinant peptides demonstrated that  $A\beta_{40}$ , but not  $A\beta_{42}$ , induces vasoconstriction in the cerebral arterioles, an effect also observed in isolated pressurized vessels in vitro, attesting to a direct effect on cerebral vessels (32–34). Accordingly, resting CBF is reduced in young AD mice (35), an effect in part related to capillary micro-occlusions (capillary stalling) by white cells (36).  $A\beta$  was also shown to alter cerebrovascular autoregulation and the increase in CBF produced by neural activity (neurovascular coupling) (37–39), major neurovascular regulatory mechanisms. These investigations, collectively, provided evidence that  $A\beta$  reduces resting cerebral perfusion and disrupts all key regulatory mechanisms of the cerebral circulation, effects that occurs before other pathological changes and precede cognitive impairment.

Later investigations focused on the cellular and molecular mechanisms of the vascular dysfunction. Park et al. (40) demonstrated that the cerebrovascular effects of  $A\beta$  are mediated by ROS derived from the enzyme nicotinamide-adenine dinucleotide phosphate oxidase and that genetic deletion of the Nox2 subunit of this enzyme fully rescued the vascular and cognitive dysfunction in AD mice without affecting amyloid plaque load.  $A\beta$ -generated ROS mediate vascular dysfunction by leading to activation of transient receptor potential melastatin-2 channels, which induce  $Ca^{2+}$  overload in cerebral endothelial cells (41). Furthermore, the deleterious neurovascular and cognitive effects of  $A\beta$  required engagement of the innate immunity receptor CD36 (42) localized to perivascular macrophages (43).

In summary, these observations suggest that vascular dysfunction is an early manifestation of  $A\beta$  accumulation, which, in conjunction with structural alterations to the cerebral microvasculature, may contribute to the disease process. This conclusion, predominantly based on basic science studies, has received support from a study in the Alzheimer Disease Neuroimaging Initiative (44), which showed that vascular dysfunction is the earliest biomarker of the disease.

## **AD, VASCULAR RISK FACTORS, AND VASCULAR ALTERATIONS OUTSIDE THE BRAIN**

### **LARGE ARTERY STIFFENING.**

Arterial stiffness is one of the consequences of vascular aging and related diseases, chronic hypertension in particular. The cerebral microcirculation is particularly vulnerable to high pulsatile forces, and arterial stiffness is considered a risk factor for cerebrovascular disease and dementia (21). A decade ago, a link between aortic stiffness and worse cognitive function was described in the Rotterdam study (45) and confirmed in different cohorts (46). An association has also been detected before patients develop dementia. For example, a correlation between higher aortic stiffness and mild cognitive impairment was found in a

large study of participants without dementia (47). Interestingly, individuals without dementia with higher arterial stiffness at baseline developed memory decline (48), and young healthy adults with elevated aortic stiffness showed reduced white and grey matter integrity in areas typically involved in AD (49). Cerebrovascular stiffness may have a profound effect on the brain by decreasing CBF, and arterial stiffness has been proposed to be a robust predictor of cognitive decline (21,50). Although the exact mechanism by which arterial stiffness affects cognition is not fully understood, an intriguing association between systemic arterial stiffness and brain A $\beta$  accumulation has been found in elderly adults without dementia (51), suggesting a link between subclinical vascular disease and A $\beta$  retention. Indeed, the altered pulsatility due to arterial stiffness may impede proper A $\beta$  clearance through the BBB as well as the perivascular and paravascular (glymphatic) pathways. However, it remains unclear whether arterial stiffness promotes A $\beta$  deposition or vice versa, and the involvement in such interaction in cognitive deterioration needs further exploration.

### **HYPERTENSION.**

Long known to be a cause of vascular cognitive impairment, hypertension has also been recently linked to AD. Thus, midlife hypertension is a risk factor for late-life dementia, including AD (21). Furthermore, clinical-pathological studies have shown that hypertension promotes the neurodegenerative pathology underlying AD, that is, amyloid plaques and neurofibrillary tangles (52). Hypertension is well known to damage cerebral blood vessels both structurally and functionally, effects mediated mainly by vascular oxidative stress (53). Thus, hypertension leads to changes in the vascular wall (hypertrophy and remodeling), promotes atherosclerosis, and produces focal microvascular alterations in penetrating arterioles arising from the basal ganglia and vascularizing the subcortical and periventricular white matter (arteriolosclerosis and lipohyalinosis), resulting in white matter damage, microhemorrhages, and microinfarcts (1,53). Functionally, hypertension reduces resting CBF, increases the permeability of the BBB, and alters all of the major factors regulating the cerebral circulation: endothelial vasomotor function, neurovascular coupling, and autoregulation (53). Less well understood are the biological bases of the relationship between hypertension and AD pathology. There is evidence that hypertension promotes amyloid accumulation in animal models as in humans (54,55), an effect that may result from increased cleavage of the amyloid precursor protein (55). However, hypertension could also promote amyloid accumulation by producing vascular damage and reduced vascular amyloid clearance (53). Recent evidence implicating perivascular macrophages in the vascular oxidative stress induced by hypertension support this hypothesis (56) because A $\beta$  is cleared in part through the perivascular space, alterations of which are linked to cognitive impairment (1,23). Preliminary data from the SPRINT-MIND (Systolic Blood Pressure Intervention) study suggest that strict blood pressure control may be beneficial to cognitive function (57). However, further studies are required to define the most effective blood pressures targets, to test for class-specific effects of antihypertensive drugs, and to define the specific contribution of hypertension to AD pathology.

### **CARDIAC ABNORMALITIES.**

Diseases of the heart are well known to be associated with cognitive dysfunction, as exemplified by the term *cardiogenic dementia* coined in the 1970s. Intriguingly, genetic

factors typically associated with AD, such as ApoE4 and presenilin mutations, have also been linked to heart failure and dilated cardiomyopathy, indicating a potential genetic association between AD and cardiovascular diseases (58). In addition, misfolded proteins play a central role not only in neurodegenerative diseases, such as AD, Parkinson's disease, and Huntington's disease, but also in cardiac hypertrophy and cardiomyopathy (59). Although the proteins that form the aggregates may differ in nature, increasing evidence points to A $\beta$  as a partner in crime in some of the proteinopathies affecting both heart and brain. For example, compromised diastolic function (60) along with A $\beta$ 40 and A $\beta$ 42 aggregates (61) have been reported in the myocardium of patients with AD, suggesting the presence of cardiac amyloidosis in the absence of overt cardiovascular disease. Whether this type of amyloidosis is due to deposits of cardiac A $\beta$  or to its interaction with other amyloidogenic peptides, such as transthyretin, remains to be established. Moreover, plasma A $\beta$ 40 is linked to cardiovascular events and arterial aging in patients with coronary heart disease (62) and, intriguingly, in those with subclinical cardiovascular disease as well (63). The relationship between heart function and AD remains to be fully elucidated, but the possibility that A $\beta$  may promote cardiac dysfunction in AD deserves further inquiry.

### PROCOAGULANT STATE.

Increasing evidence points to significant A $\beta$ -driven alterations of the coagulation cascade in AD, favoring a procoagulant state (64,65). A $\beta$ 42 binds to fibrinogen (66) and fibrin (67) and induces structural changes in fibrin clots affecting thrombosis and fibrinolysis (66–68). In AD, due to the damage to the BBB, fibrin(ogen) extravasates into the brain parenchyma and, as demonstrated in animal models, results in pericyte degeneration, amyloid accumulation, microglial activation, synaptic dysfunction, dendritic spine loss, and neuronal death (68–71). On these bases, a causative role for fibrin(ogen) in AD pathology has been proposed (65). Moreover, A $\beta$ 40 and A $\beta$ 42 activate coagulation proteins, such as factor XII (72) and factor XIIIa (73), and clotting abnormalities strongly correlate with cognitive function in patients with AD (74). Collectively, this evidence indicates that A $\beta$  interacts closely with different coagulation factors, promoting a prothrombotic and proinflammatory milieu (64). This hypothesis is further supported by experimental studies demonstrating that normalizing this procoagulant state halts disease progression. Experiments in mouse models showed that: 1) blocking the interaction between A $\beta$  and fibrinogen normalizes thrombosis, reduces CAA, and improves cognition (75); and 2) depleting factor XII reduces fibrin(ogen) deposition and ameliorates neuroinflammation, neurodegeneration, and cognitive dysfunction (76). Less is known about the effect of anticoagulation in patients with dementia. In patients with atrial fibrillation, anticoagulation decreases dementia risk, but the mechanisms are unclear and may be related to reduced cerebral embolization (77). Anticoagulants proved to be beneficial in mouse models of amyloid accumulation (78), but they have not moved forward into the AD therapeutic pipeline, probably because of concerns about risk of bleeding. The introduction of direct oral anticoagulants with decreased risk of intracranial bleeding may change this perception. Cortes-Canteli et al. (79) recently showed that long-term treatment with one of these agents in a mouse model prevents cerebral fibrin deposition; preserves CBF and BBB integrity; and ameliorates cognitive deficits, amyloid burden, and neuroinflammation (79).



## VASCULAR INTERVENTION FOR AD PRIMARY PREVENTION

AD starts decades before cognitive impairment develops (80), so early diagnosis and primary prevention are of the utmost importance to decrease disease burden. Increasing evidence indicates that a high cognitive reserve, a healthy lifestyle, and the control of modifiable cardiovascular risk factors may reduce the risk of developing dementia, including AD (81). Furthermore, interventions that promote cardiometabolic health, such as physical activity, caloric restriction, or a Mediterranean diet, may also contribute to reducing the risk of dementia (82). Based on data from existing meta-analyses, it is estimated that a third of AD cases are attributable to modifiable cardiovascular risk factors (83), suggesting that management of these factors would reduce the anticipated impact of AD, especially if interventions are carried out in midlife. Recent epidemiological evidence from multiple independent patient cohorts points to a decrease in the incidence of AD, which has been attributed to better control of vascular risk factors (84). Indeed, the randomized controlled trial FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) confirmed the positive effect of a multidomain lifestyle intervention on cognitive decline prevention. After a 2-year intervention (nutritional counseling, social stimulation, physical/cognitive training, and management of vascular risk factors), at-risk elderly individuals in the intervention group had a decreased risk of cognitive decline (85) and maintenance of activities of daily living (86). Other similar multidomain intervention studies also showed promising results, encouraging the recent launch of large-scale AD prevention trials, the results of which will reinforce effective prevention strategies (87). Single-domain interventions were not as successful, and, thus, it might be desirable to contemporaneously target several modifiable factors rather than just one (87). In the case of ApoE4 carriers, the control of these modifiable factors is even more critical because it may partially counteract the high susceptibility that this genotype confers to developing dementia and even delay its onset (88).

## CONCLUSIONS AND FUTURE DIRECTIONS

In this review, we have presented evidence that vascular aging may be exacerbated by AD pathology, thereby contributing to the vascular dysfunction present in AD (Central Illustration). These vascular changes include functional and structural alterations across the entire cerebrovascular tree, from large artery atherosclerosis and CAA to small vessel disease and BBB impairment. These alterations, in concert with the deleterious effects of A $\beta$  vasoactivity, reduce cerebral perfusion and impair the ability of the cerebral circulation to supply energy substrates and oxygen to active brain regions. Moreover, emerging evidence raises the possibility that vascular alterations outside the brain may also play a role in AD. Hypertension and systemic atherosclerosis, together with large artery stiffening and a procoagulant state in AD, may cause damage to the cerebral vasculature and further contribute to alterations in CBF, to which the brain is particularly susceptible. Plasma A $\beta$  levels increase during preclinical AD and then diminish as the disease progresses (89). As discussed in this review, the rise in plasma A $\beta$  during the early phases of AD may affect the cardiovascular system in a wide variety of ways and potentially influence the disease process and its clinical manifestations.

The brain and heart are vitally interconnected by neurovascular and humoral pathways, and more efforts should be directed at investigating the relationships between cardiovascular diseases and brain pathologies leading to cognitive dysfunction. For example, little is known about the impact of cardiac function and the vasculature on neurodegenerative pathologies underlying cognitive impairment, which, in addition to plaques and tangles, also include Lewy bodies, TAR DNA-binding protein (TDP)-43 proteinopathy, hippocampal sclerosis, etc. (9). In addition, although providing nutritional flow is a major role of the cerebral vasculature, neurovascular functions independent of blood flow delivery, such as trophic interactions, proteostasis, and neuroimmune trafficking (1), also need to be explored. For example, a high-salt diet in mice induces a deficit in cerebral endothelial nitric oxide, which leads to dementia independently of cerebral perfusion but through tau phosphorylation and aggregation (90). Rapid advances in cardiac, vascular, and neurovascular biology, coupled with single-cell genomic, proteomic, and metabolomic approaches, provide the unprecedented opportunity to dissect the cellular crosstalk underling the relationships between the brain and vasculature in health and disease. The new findings resulting from these efforts would provide new clues on how to best prevent and treat patients with AD and related dementias. In the absence of disease-modifying treatments, reducing the incidence of dementia by controlling vascular risk factors in middle age remains an attractive and feasible preventive strategy, even if effective therapeutic options become available.

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## ABBREVIATIONS AND ACRONYMS

<b>A<math>\beta</math></b>	amyloid- $\beta$
<b>AD</b>	Alzheimer’s disease
<b>ApoE</b>	apolipoprotein E
<b>BBB</b>	blood-brain barrier
<b>CAA</b>	cerebral amyloid angiopathy
<b>CBF</b>	cerebral blood flow
<b>ROS</b>	reactive oxygen species



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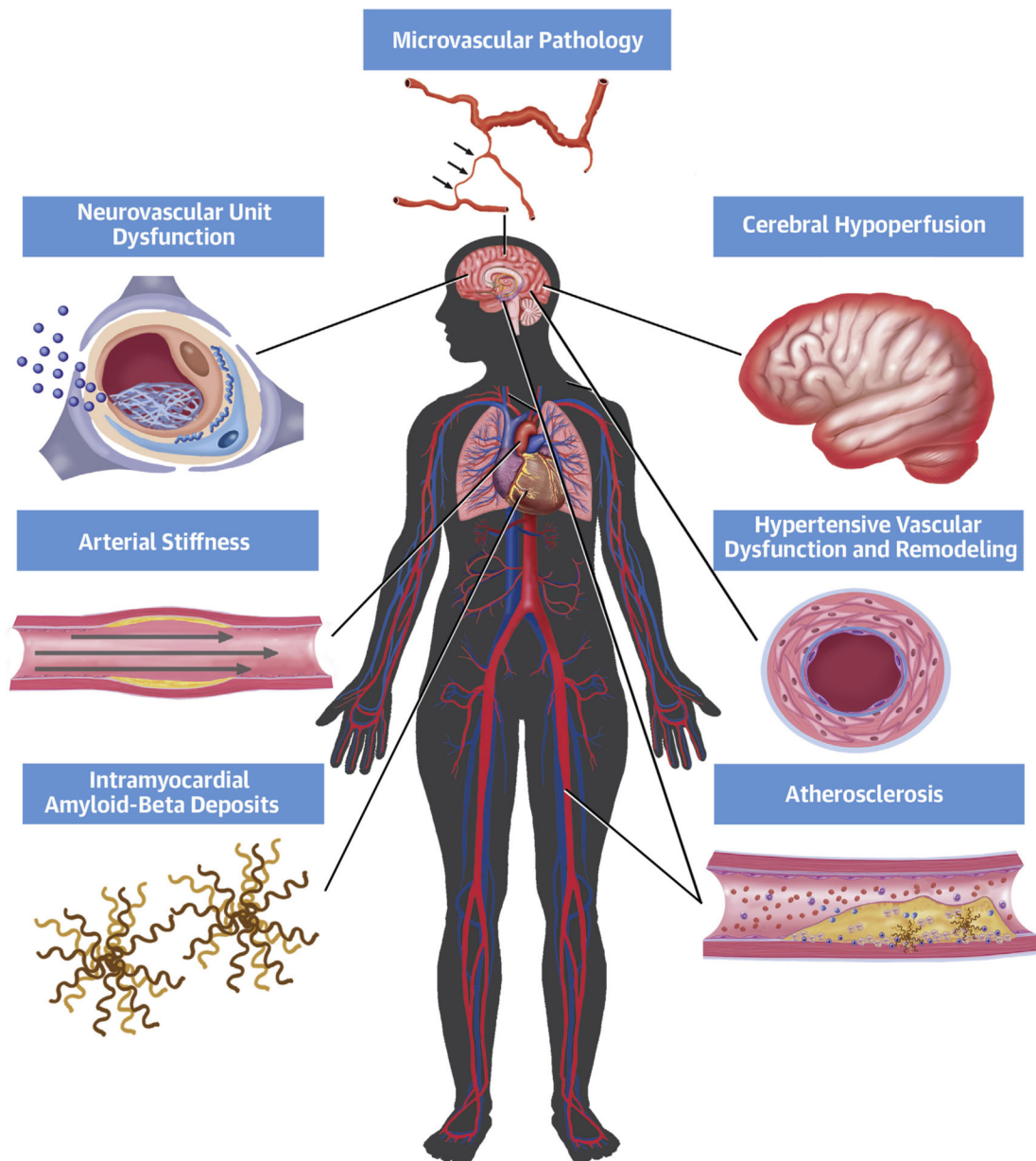
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**HIGHLIGHTS**

- AD is the major cause of age-related dementia and the fifth leading cause of death worldwide.
- Alterations in cerebral and systemic vessels and in the heart often coexist with AD pathology.
- The resulting cerebrovascular insufficiency may contribute to the onset and progression of cognitive dysfunction.
- Control of vascular risk factors may mitigate the impact of AD and related dementias.










**CENTRAL ILLUSTRATION. Alzheimer’s Disease-Associated Vascular Alterations Inside and Outside the Brain**

Age-related vascular changes across the cerebral vasculature and outside the brain are exacerbated in Alzheimer’s disease. Intracranial and extracranial atherosclerosis, reduced cerebral microvascular density, cerebral amyloid angiopathy, and neurovascular unit dysfunction, together with large artery stiffening and hypertensive vascular remodeling, changes in heart function, and a procoagulant state, contribute to important reductions in cerebrovascular blood flow. Amyloid- $\beta$  may play a contributory role in these vascular changes.

TABLE 1

Cellular Pathobiology of the Neurovascular Unit in Alzheimer’s Disease

Capillary Neurovascular Unit	Function	Alterations in Alzheimer’s Disease
	<ul style="list-style-type: none"> <li>Maintains homeostasis of the brain microenvironment.</li> <li>Regulates blood-brain molecular exchange through specialized transport systems.</li> <li>Development and maintenance depend on the interaction between endothelium, pericytes, and astrocytes.</li> </ul>	<ul style="list-style-type: none"> <li>Increased BBB permeability.</li> <li>Extravasation of neurotoxic blood-derived proteins/cells leading to inflammation oxidative stress and synaptic dysfunction.</li> <li>Disruption of Aβ clearance.</li> </ul>
	<ul style="list-style-type: none"> <li>Key cellular component of the BBB with specialized intercellular junctions and limited transcytosis.</li> <li>Regulate blood-brain exchange through molecular transporters.</li> <li>Regulate vasomotor function through vasodilators (e.g., nitric oxide) and vasoconstrictors (e.g. endothelin).</li> <li>Contribute to synaptic plasticity via nitric oxide.</li> </ul>	<ul style="list-style-type: none"> <li>Endothelial vasomotor dysfunction.</li> <li>Decreased levels of glucose transporters/impaired glucose transport.</li> <li>Disruption of endothelial junctions and increased endothelial bulk flow transcytosis.</li> </ul>
	<ul style="list-style-type: none"> <li>Mural cells in capillaries involved in BBB development and maintenance.</li> <li>Control of endothelial junctions and transcytosis.</li> <li>Involved in angiogenesis and immune cell filtration.</li> <li>Role in correct polarization of astrocyte end-feet and endothelial gene expression.</li> </ul>	<ul style="list-style-type: none"> <li>Pericyte degeneration causing BBB dysfunction and neuronal damage.</li> <li>Pericyte markers detected in cerebrospinal fluid early in patients with dementia.</li> <li>Pericyte damage may impair Aβ clearance.</li> <li>Possible involvement in vascular effects of Aβ.</li> </ul>
	<ul style="list-style-type: none"> <li>Ensheath ~98% of brain capillaries.</li> <li>Provide support and functional link for neuron-vessel communication and neurovascular coupling.</li> <li>Involved in interstitial fluid flow and exchange.</li> </ul>	<ul style="list-style-type: none"> <li>Astrocyte depolarization and detachment of end-feet.</li> <li>Loss of expression of the water channel aquaporin 4, affecting Aβ clearance.</li> </ul>
	<ul style="list-style-type: none"> <li>ECM proteins confer a physical scaffolding to the cells of the BBB.</li> <li>Basement membrane proteins enable astrocytic end-feet and endothelial cell polarization.</li> <li>ECM may participate in protein clearance through perivascular and intramural interstitial flow.</li> </ul>	<ul style="list-style-type: none"> <li>Thickening, fragmentation, and degeneration of the basement membrane.</li> <li>Alterations in content, structure, and organization of ECM proteins.</li> </ul>

Aβ = amyloid-β; BBB = blood-brain barrier; ECM = extracellular matrix.