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Review

Microvascular Perfusion Imaging in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the leading cause of dementia worldwide and significantly impacts the essential functions of daily life and social activities. Research on AD has found that its pathogenesis is related to the extracellular accumulation of amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles in the cortical and limbic areas of the human brain, as well as cerebrovascular factors. The detection of Aβ or tau can be performed using various probes and methodologies. However, these modalities are expensive to implement and often require invasive procedures, limiting accessibility on a large scale. While magnetic resonance imaging (MRI) and computed tomography (CT) are generally used for morphological and structural brain imaging, they show wide variability in their accuracy for the clinical diagnosis of AD. Several novel imaging modalities have emerged as alternatives that can accurately and vividly display the changes in blood flow and metabolism in each brain area and enable physicians and researchers to gain insights into the generation and progression of the cerebro-microvascular pathologies of AD. In this review, we summarize the current knowledge on microvascular perfusion imaging modalities and their application in AD, including MRI (dynamic susceptibility contrast-MRI, arterial spin labeling-MRI), CT (cerebral CT perfusion imaging), emission computed tomography (positron emission tomography (PET), single-photon emission computed tomography (SPECT)), transcranial doppler ultrasonography (TCD), and retinal microvascular imaging (optical coherence tomography imaging, computer-assisted methods for evaluating retinal vasculature).

Keywords: Alzheimer's disease; perfusion imaging; MRI; CT; PET

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder, and is often characterized by progressive cognitive decline and memory loss, which seriously affect the essential functions of daily life and regular social activities. AD is the leading cause of dementia in the world, affecting an estimated 50 million people worldwide, with a projected tripling of prevalence by 2050 due to an aging population [1–4]. The care required for AD patients represents a considerable healthcare cost, which is predicted to increase further. AD imposes a tremendous public health burden, not only on the patients, the caregivers, and physicians, but also on society in general [5]. Early diagnosis of AD and timely medical intervention are fundamental for reducing the risk of progression to advanced dementia, slowing down the process, and also allowing significant cost savings to Medicare [6–8].

Multiple mechanisms have been reported to contribute to the pathogenesis of AD, including the extracellular accumulation of amyloid beta (Aβ) plaques and tau proteins, as well as cerebrovascular factors [9–13]. The processing of amyloid precursor protein and dysfunction of Aβ clearance mechanisms contribute to the accumulation of Aβ plaques, which can initiate downstream tau tangle formation and neuronal dysfunction [14]. Although some studies have shown a positive association between Aβ accumulation and increased cerebral blood flow (CBF) in certain brain areas [15], recent research has demonstrated that reduced CBF may be an early indicator of AD [16]. In particular, Aβ can cause constriction of capillaries, potentially reducing CBF in AD [17]. Reduced CBF may also initiate the amyloid cascade or amplify Aβ production [14,16]. Accumulating evidence indicates that cerebrospinal fluid tau proteins are associated with lower CBF in patients with mild cognitive impairment (MCI) and AD dementia [18]. The accumulation of hyperphosphorylated tau protein and neurofibrillary tangles can lead to neuronal death and alterations in the microvascular system [19–21]. Consequently, cerebral blood perfusion alterations and microvascular system dysfunction can impair Aβ and tau clearance from tissue, leading to structural brain atrophy and cognitive decline [22]. The complex interplays between Aβ accumulation, tau pathology, and cerebrovascular factors highlight the need for a multifactorial approach to the development of effective diagnosis and therapies for AD.

Etiological research suggests that measurement of cerebral perfusion and amyloid may hold the most promise for detecting preclinical AD [23,24]. Recent studies report a strong correlation between cerebral perfusion and disease progression, indicating that CBF is a helpful parameter in the preclinical stage of AD [25–27]. Magnetic resonance imaging (MRI) and computed tomography (CT) are gen-

erally used for morphological and structural brain imaging, but they show wide variability in accuracy when used for the clinical diagnosis of AD [28]. Numerous imaging modalities have been developed and used to visualize vascularization, and these can accurately and vividly display changes in blood flow and metabolism in each brain area. In this narrative review, we summarize the currently available microvascular perfusion imaging methods applied in AD with the aim of exploring the complexities of cerebral blood flow alterations and the potential of microvascular perfusion imaging technology to shed light on the underlying mechanisms and clinical implications of CBF changes.

2. Methods

This narrative review focuses on the existing literature concerning microvascular perfusion imaging in AD. A systematic search was conducted across multiple databases including PubMed, CNKI, Web of Science, Cochrane Library, and Wanfang. The search used a combination of keywords encompassing modalities such as "Magnetic resonance imaging (MRI)", "Dynamic susceptibility contrast (DSC)", "Arterial spin labeling (ASL)", "Computed tomography (CT)", "Computed tomography perfusion imaging (CTPI)", "Emission computed tomography (ECT)", "Transcranial Doppler ultrasonography (TCD)", "Retinal microvascular imaging", "Optical coherence tomography (OCT)", and "Computer-assisted program measures retinal microvascular". This combination was further constrained by the terms "Alzheimer's disease" or "Dementia". Articles were deemed eligible if they furnished evidence for both (1) quantitative analysis of microcirculatory perfusion in relation to AD, and (2) a comparison between AD and healthy controls or MCI in terms of microcirculatory perfusion. The search encompassed literature published up to February 2023. The inclusion criteria were collectively assessed by all three authors to ascertain relevance, culminating in the selection of 22 articles for inclusion in this narrative review.

3. Results of the Literature Search

3.1 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) relies on the behavior of atomic nuclei, particularly hydrogen nuclei (protons), which are abundant in the human body. When these protons are exposed to radiofrequency pulses, the protons absorb energy and temporarily move away from their equilibrium state. After the radiofrequency pulse is turned off, the excited protons start to relax back to their equilibrium state. T1 relaxation refers to the time constant of longitudinal magnetization recovery. Different tissues exhibit distinct T1 relaxation times due to variations in molecular interactions, composition, and physical properties. T2 relaxation refers to the time over which the transverse magnetization of nuclear spins dephases and decays after an initial radiofrequency pulse, while T2* relaxation refers to the decay of transverse magnetization seen with gradient-echo (GRE) sequences. Different tissues possess distinct T1 or T2 relaxation times, influenced by molecular interactions, tissue composition, and structural properties. T1-weighted and T2-weighted imaging create contrast through the distinct relaxation behaviors of nuclear spins in different tissues to generate image contrasts that are sensitive to different tissue properties. T2*-weighted imaging can detect the smallest changes in uniformity in the magnetic field and can improve the rate of small lesion detection.

3.1.1 Arterial Spin Labeling

Arterial spin labeling (ASL)-MRI is a noninvasive procedure based on the difference in spin magnetization between mobile and static protons. ASL-MRI uses the water protons of arterial blood as an endogenous perfusion tracer. Before flowing into the imaging area, the proximal arterial blood containing water protons is labeled, and a control image of the imaging area without labeled arterial blood is obtained. The labeled water protons flowing into the imaging plane with the bloodstream within a certain delay time (post-labeling delay time, PLD) mix with the unlabeled water protons in the tissue, leading to changes in the local tissue T1, thereby generating blood flow-dependent image contrast, which can be calculated by subtracting the labeled images from the control images. The remaining signals are linear measurements proportional to cerebral blood flow perfusion. Then, qualitative and quantitative analysis can be obtained from the CBF perfusion information. The PLD time is the delay time of blood flow from the labeled area to the tissue of the imaging area, and ASL can be performed with single or multiple PLDs. Single PLD sequences are typically used in clinical practice, and estimate CBF with a simplified model, which is a potential source of error. In contrast, multi-PLD ASL can more accurately estimate CBF by also estimating the arterial transit time (ATT).

ASL implementations fall into three categories according to their different labeling methods: continuous ASL (CASL), pulsed ASL (PASL), and pseudo-continuous ASL (pCASL). The latter combines the advantages of CASL and PASL and achieves the long pulse effect of CASL by switching the gradient field and combining multiple short pulses while providing an improved signal-to-noise ratio and labeling efficiency. ASL uses fast spin echo, propeller technology, three-dimensional volume acquisition technology, and/or spiral center oversampling technology, which can significantly improve the signal-to-noise ratio and the image quality by reducing the interference of motion artifacts and magnetic sensitivity artifacts. Delayed scanning is another important technique for analyzing ASL, facilitating the collection of blood flow information from veins, perfusion imaging, and brain structure. The characteristics of ASL in microvascular perfusion imaging are summarized in Table 1 (Ref. [29–37]) and Table 2 .

Table 1. Major measurements and quantitative models or methods of microvascular perfusion imaging modalities in Alzheimer's Disease.

Imaging modality	Measurement	Quantitative model or method
DSC	Cerebral blood flow, Cerebral blood volume, Mean transit time, Time to peak	Gamma-variate model, Tofts model [29]
ASL	Cerebral blood flow, Cerebral blood volume, Mean transit time, Time to peak	Buxton's general kinetic model [29]
CTPI	Cerebral blood flow, Cerebral blood volume, Mean transit time, Time to peak	Central volume principle model, deconvolution method [30]
PET	Cerebral blood flow, Cerebral blood volume, Mean transit time, Time to peak	Autoradiographic method, Simplified reference tissue model [31,32]
SPECT	Cerebral blood flow, Cerebral blood volume, Mean transit time, Time to peak	Patlak graphical analysis method [33,34]
TCD	Blood flow velocity, Pulsatility index, Lindegaard ratio, Breath-holding index	Doppler Effect Model [35]
OCTA	Vessel Area Density, Vessel Diameter Index, Blood flow rate	Speckle variance method [36]
RVAS	Retinal vascular caliber, Retinal vascular fractal dimension, Retinal vascular tortuosity, Retinal vascular branching angle	Knudtson-Parr-Hubbard formula [37]

DSC, dynamic susceptibility contrast; ASL, arterial spin labeling; CTPI, cerebral computed tomography perfusion imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography; TCD, transcranial doppler ultrasonography; OCTA, optical coherence tomography angiography; RVAS, retinal vessels assessment system.

A study by Ding *et al.* [38] investigated CBF changes in healthy controls, patients with AD, and patients with amnestic MCI. They found decreased CBF in the bilateral temporo-parieto-occipital cortices and left limbic lobe relative to the healthy controls. In comparison with healthy controls, patients with amnestic MCI showed hyper-perfusion regions in the right temporal subgyral and bilateral frontal lobes, and hypoperfusion regions in the bilateral inferior temporal cortex, left occipital lobe, and right middle temporal cortex [38]. A recent report found that patients with MCI and AD had significantly lower quantified perfusion in the posterior cingulate and lingual gyri, but no solid positive correlations were observed between perfusion and gray matter volumes in the regions of interest, except for temporal neocortex [39]. However, the results of Zhang *et al.* [40] revealed significant differences between AD and controls, as well as between MCI and AD; patients with AD had lower mean CBF in gray matter than did the other groups. With a focus on cognition, learning, and memory-associated brain regions, such areas as the frontal and temporal lobes have shown hypoperfusion in both MCI and AD, suggesting that disrupted perfusion is a disease manifestation throughout the preclinical or dementia phase of AD. Although areas of hyperperfusion are relevant in the progression of AD, hyperperfusion might lead to lower oxygen extraction in the presence of relatively mild to moderate capillary dysfunction, requiring suppression of blood flow to optimize metabolism. The mechanism of perfusion changes in AD needs further exploration and validation in human studies. ASL is an appealing alternative because it can provide helpful perfusion information for further pathologic and neuropsychological studies in AD.

3.1.2 Dynamic Susceptibility Contrast

Dynamic susceptibility contrast (DSC)-MRI involves tracking an exogenous paramagnetic contrast medium (gadolinium-based compounds) as it passes through a given capillary bed. The bolus of gadolinium-based contrast medium with a high magnetic moment significantly decreases brain signal intensity on T2- or T2*-weighted images. These signal changes are rapidly measured with spin echo or gradient echo echo-planar sequences. The intravascular compartmentalization of the contrast-induced local magnetic field gradients results in the magnetic susceptibility effect, which dominates the T1 relaxation enhancement due to the direct interaction of intravascular protons with the coordination sphere of the gadolinium-based complexes. To evaluate the changes in contrast medium concentration occurring in each imaging voxel, a kinetic model based on the indicator dilution theory is applied to the signal reduction resulting from the first throughflow of the contrast medium bolus on T2- or T2*-weighted images. The time-signal intensity curve of the tissue can be obtained for a region of interest, which allows the estimation of quantitative hemodynamic information, including cerebral blood volume, CBF, and mean transit time. The main disadvantage of DSC-MRI is that it requires an exogenous tracer, such as a gadolinium chelate, which may increase the risk of a rare but fatal multisystem disease (i.e., nephrogenic systemic fibrosis) in patients with renal failure. The characteristics of DSC in microvascular perfusion imaging are summarized in Tables 1,2.

In a study by Eskildsen *et al.* [41], DSC-MRI was used to compare cerebral microcirculation in patients with AD or MCI with that in age-matched healthy controls. AD

Table 2. Characteristics of modalities used for microvascular perfusion imaging in Alzheimer's Disease.

	ASL	DSC	CTPI	PET	SPECT	TCD	OCTA	RVAS
Spatial resolution	High	High	High	Low	Low	Low	High	High
Contrast agent or radiotracer	No Required	Contrast agent	No Required	Radiotracer	Radiotracer	No Required	No Required	No Required
Invasive	No	No	No	No	No	No	No	No
Availability	Wide	Wide	Wide	Limited	Limited	Wide	Limited	Limited
Temporal resolution	Vary	High	Limited	Limited	Limited	High	High	High
Sensitivity	Limited	High	Limited	High	Limited	High	Limited	Limited
Quantification	Yes	Challenge	Yes	Yes	Yes	Yes	Yes	Yes
Whole-brain coverage	Limited	Limited	Yes	Yes	Yes	Limited	Limited	Limited
Acquisition time	Long	Vary	Fast	Vary	Long	Fast	Fast	Fast
Radiation exposure	No	No	Yes	Yes	Yes	No	No	No
Real-time imaging	No	No	No	No	No	Yes	Yes	Yes

DSC, dynamic susceptibility contrast; ASL, arterial spin labeling; CTPI, cerebral computed tomography perfusion imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography; TCD, transcranial doppler ultrasonography; OCTA, optical coherence tomography angiography; RVAS, retinal vessels assessment system.

or MCI patients showed widespread hypoperfusion and increased relative capillary transit time heterogeneity. Furthermore, the patients' relative capillary transit time heterogeneity was positively correlated with white matter hyperintensities and symptom severity in large parts of the temporal, parietal, and frontal cortices [41]. The diagnostic sensitivity of CBF for identifying perfusion abnormalities when using DSC-MRI was also investigated in MCI patients who progressed to AD, patients with mild AD, and healthy controls [42]. The study found decreased CBF perfusion in the parietal lobes of the progressed-to-AD patients and a negative association between cortical thickness and CBF in the right parahippocampal gyrus. Cerebral blood volume alterations were only present in the AD patients, while CBF abnormalities were already present in the MCI patients. Thus, CBF changes appear before cerebral blood volume changes in AD development. Disturbed capillary flow patterns already exist in the preclinical phase of AD, and these may affect the neurovascular coupling through which arterioles adjust the local CBF. Such a bidirectional longitudinal relationship between reduced CBF and brain atrophy would explain the inconsistencies in results, including the negative association between CBF and cortical thickness [42], as well as the cerebral hypoperfusion associated with brain atrophy [43].

3.2 CT Perfusion Imaging

CT refers to a computerized X-ray imaging procedure in which a narrow beam of X-rays is quickly rotated around the body, producing signals that are processed by a computer to generate tomographic cross-sectional images of the body that contain more detailed information than conventional X-rays. The computer can then digitally stack the successive images together to form a three-dimensional image of the body, allowing for easier identification and location of basic structures and possible abnormalities.

By acquiring dynamic and repeated scans of an area of interest following intravenous bolus injection of iodine contrast agent, the density of the contrast agent change can be recorded. Physicians and scientists can obtain time-density curve and blood perfusion information from the brain tissue through mathematical modeling calculations. The parameters include cerebral blood volume, CBF, time to peak, mean transit time, and capillary permeability. In contrast to the time-consuming nature of perfusion assessment through MRI, CT perfusion imaging (CTPI) offers a swift alternative suitable for patients with poor coordination. CTPI has a high spatial and temporal resolution, extensive scanning range, and high post-processing and data acquisition efficiency. CTPI can obtain images of morphological structure and vascular images at the same time. However, the use of CTPI is limited because of adverse reactions such as nephrotoxicity and allergic reactions to iodine contrast agents. In recent years, the emergence of low-dose multislice spiral CT and volume CT has effectively reduced the radiation dose for the broad application of CTPI. The characteristics of CTPI in microvascular perfusion imaging are summarized in Tables 1,2.

Tang *et al.* [44] used CTPI to evaluate perfusion abnormalities in AD. AD patients showed lower cerebral blood volume and CBF values in the temporal cortex, bilateral frontal cortex, hippocampus, and basal ganglia compared to healthy control, while the mean transit time and transit time peak values of these brain areas were lower in the healthy control than in the AD. The incidence of AD significantly correlated with the mean transit time perfusion parameter of the right temporal cortex, left frontal cortex, right hippocampus, and right basal ganglia [44]. These results indicate that brain CTPI is a valuable tool for detecting microcirculation abnormalities and provides new evidence for microcirculation disturbance and ischemia in AD.

3.3 Emission Computed Tomography

Emission computed tomography (ECT) is a functional imaging modality that uses radiolabeled biologically-active compounds (radiotracers) to visualize and measure physiological activities, including metabolic processes, blood flow, regional chemical composition, and absorption. Radiotracers emit either positrons or gamma rays when they decay in transport through the blood-brain barrier.

Positron emission tomography (PET) is based on the emission of positrons as radionuclides decay. In PET, the emitted positron interacts with an electron and both particles annihilate simultaneously to form two gamma-ray photons in opposite directions with high energy. Then, both gamma rays travel a few millimeters through tissue and can be detected by the sensors of the PET scanner. Reconstruction algorithms use these rays of coincidence to determine the location of the source. The PET tracers most commonly used for the measurement of CBF are 11C, 15O, and 18F. The characteristics of PET in microvascular perfusion imaging are summarized in Tables 1,2.

Unlike PET, single-photon emission computed tomography (SPECT) uses a bolus injection of radionuclides in the form a radioligand that emits a single gamma ray generated either directly or indirectly as a result of the decay. The SPECT detector attempts to record the gamma rays, and a back projection reconstruction algorithm determines the location of the decay events. The accumulation and distribution of radionuclides in brain tissue are directly proportional to cerebral blood flow. SPECT tracers for cerebral blood perfusion imaging include technetium 99m-hexamethylpropyleneamine oxime (99 mTc-HMPAO), technetium 99m-ethyl cysteinate dimer (99 mTc-ECD), 133Xe, 123I-iomazenil, and N-isopropyl-(iodine-123) p-iodoamphetamine (123I-IMP). The characteristics of SPECT in microvascular perfusion imaging are summarized in Tables 1,2.

Several studies have used ECT to investigate perfusion and functional changes in AD and MCI. For instance, Ishii *et al*. [45] used PET with oxygen-15-labeled gases as tracers to clarify the medial temporal perfusion and functional changes in mild-to-moderate AD. AD patients showed significantly decreased mean CBF in the parietal and lateral temporal cortices compared to healthy control. The medial temporal oxygen metabolism and CBF of patients with AD correlated with certain nonverbal memory test scores and cognitive impairment scales [45]. Staffen *et al*. [46] investigated the diagnostic validity of SPECT with 99 mTc-HMPAO in patients with MCI and AD. They reported reduced cerebral perfusion in AD in all evaluated cortical areas (temporal, parietal, and frontal lobes). In patients with MCI, cerebral perfusion was decreased in these measured brain areas, except for the left parietal and frontal cortex [46]. The same group also examined regional cerebral perfusion detected by SPECT with 99 mTc-HMPAO in MCI and AD patients. MCI patients showed hypoperfusion in the parietal and temporal lobes of both hemispheres and the posterior part of the cingulate gyrus of the right hemisphere. AD patients showed significant hypoperfusion in the global forebrain [47]. Habert *et al*. [48] improved the diagnosis of early AD by using SPECT with 99 mTc-ECD in patients with MCI who progressed to AD (MCI-AD group) or remained stable (MCI-stable group). Their study showed that right parietal and hippocampal perfusion was significantly lower in the MCI-AD group compared with the MCI-stable group [48]. Pappatà *et al*. [49] used SPECT with 99 mTc-HMPAO in subjects with amnestic MCI and elderly healthy controls, and performed both voxel-based and region-of-interest analysis to measure cerebral perfusion. Voxel-based analysis and region of interest analysis revealed hypoperfusion of the precuneus and the posterior cingulate cortex in MCI and MCI progressed-to-AD patients [49]. These results suggest that perfusion is impaired in MCI and AD. Hypoperfusion, as detected by ECT, is associated with clinical, functional, and cognitive decline, and may help identify candidates for future AD treatment trials.

3.4 Transcranial Doppler Ultrasonography

Doppler Ultrasonography is based on the principle of the Doppler frequency shift. The ultrasound wave from the probe is transmitted and reflected by red blood corpuscles moving within vessels. The frequency difference between transmitted and reflected waves is proportional to the speed of the moving red blood corpuscles. The Doppler signal represents a mixture of different Doppler shifts resulting from the laminar flow in the blood vessel, and thus represents a spectrum display of the velocity distribution of red blood cells on the monitor. Then, spectral analysis can be used to obtain measurements of blood flow parameters, including breath-holding index (BHI), blood flow velocity, end-diastolic velocity, peak systolic velocity, pulsatility index, time-averaged mean maximum velocity, and systolic upstroke or acceleration time.

Transcranial Doppler (TCD) transmits waves through the skull and detects blood flow within the cerebral vessels. In most transcranial doppler instruments, the time-averaged mean maximum velocity as a function of time is a continuous trace of peak velocities that can be automatically calculated and displayed. The main advantages of TCD are that it is non-invasive, does not require ionizing radiation, uses a contrast agent that is excreted rapidly, and is repeatable and quickly performed. Assessed by ultrasound, extracranial carotid artery stenosis is a risk factor for Alzheimer's disease [50]. Carotid artery disease changes the brain structure associated with dementia [51]. Studies have shown that abnormal internal carotid artery is associated with white matter hyperintensities, which are associated with the risk of progression to MCI when cerebrospinal fluid measures of neurodegeneration are low [52]. Ultrasonography can ex-

plain the relationship between carotid artery stenosis, cerebral small vessel function, and AD-related brain structural and cognitive alterations.

BHI is a commonly used method for TCD-based assessment of cerebrovascular reactivity. It is calculated based on the mean flow velocities of the middle cerebral artery. Silvestrini *et al*. [53] investigated the contribution of alterations in cerebral hemodynamics to the evolution of cognitive impairment by measuring the breath-holding index with TCD ultrasonography in patients with AD. They reported that unfavorable evolution of cognitive function was associated with the breath-holding index, and multiple logistic regression also suggested that the breath-holding index was the only significant predictor of cognitive decline [53]. Puls *et al*. [54] performed transcranial color-coded duplex ultrasound examinations to determine microvascular disease related to the integrity of brain microcirculation. They demonstrated that patients with vascular dementia had significantly longer cerebral transit times (cTT) than those with AD; cTT is significantly associated with cognitive impairment in vascular dementia patients, rather than in AD patients. These findings suggest that cTT may be a valuable tool to reveal small vessel disease in patients with dementia.

3.5 Peripheral Microcirculation Testing

3.5.1 Retinal Microvascular Imaging

The retina shares prominent similarities with the brain regarding embryological origin, anatomical features, and physiological properties. Many researchers consider the retina to be an extension of the central nervous system. It offers a unique perspective for studying cerebral microcirculation, and may improve the understanding of cerebrovascular pathophysiology processes, diagnosis, and risk assessment of dementia in the brain. Retinal microcirculatory alterations can be visualized quickly and assessed noninvasively by retinal photographic techniques, such as optical coherence tomography (OCT) and the retinal vessels assessment system with computer-assisted imaging software.

3.5.1.1 Optical Coherence Tomography. OCT imaging uses a non-invasive method to irradiate the tissue or specimen with weak coherent light and measure the time delay of the reflected light and the longitudinal internal structure of the tissue. The original OCT imaging adopted the principle of the time domain, but the mechanical motion of the reference arm limited the imaging rate, and the axial resolution was 10 µm. The low imaging speed was considered too slow to favor angiographic imaging. The highly structuralized system of eyes also caused poor blood vessel depiction because of light scattering. With the emergence of frequency domain OCT, the scanning speed has increased to 6800 times per second per scan. OCT has a higher axial resolution, which provides conditions suitable for the emergence of ocular vascular imaging (optical coherence tomography angiography, OCTA). OCTA detects the movement of blood cells in the vascular cavity by measuring the shift in the amplitude of the reflected OCT signal. It has generally been used for vascular imaging of the retina, choroid, and optic nerve. Physicians can measure the margins and areas of new blood vessels and capillaries more accurately.

Split-spectrum amplitude correction angiography is a commonly used algorithm in octal devices. It decomposes eight images into different spectral bands to increase the number of available images. Each new image has a horizontally balanced axial resolution, thereby reducing the sensitivity to axial eye movements caused by the pulsation of posterior blood flow. The appropriately weakened axial signal increases the coherence range, reflecting the signal from moving particles such as blood cells. Because each spectral band contains different spot patterns and independent blood flow information, the exponentially enhanced blood flow signal can provide high-speed and high-definition OCTA images when it integrates spectrally decorrelated images from multiple spectral bands. At present, OCTA is used not only for diagnosing the posterior segment of the optical system, but also as an aid in the evaluation of the anterior segment of it. The characteristics of OCTA in microvascular perfusion imaging are summarized in Tables 1,2.

Jiang *et al*. [55] determined the retinal blood flow rate and blood flow velocity of pre-capillary arterioles and post-capillary venules using OCTA in cognitively normal controls, comparing them with patients with MCI and AD. The macular blood flow rate and blood flow velocity in arterioles and venules of the AD group were significantly lower than in cognitively normal controls. Similarly, the blood flow rates of MCI and AD group were lower than the blood flow rates of the control group in both arterioles and venules. The thicknesses of the ganglion cell-inner plexiform layer in patients with AD and MCI were significantly lower than in controls. These findings suggest that in the neurovascular-hemodynamic system, impairment of the blood flow rate and ganglion cell-inner plexiform layer may play a critical role in AD progression.

3.5.1.2 Retinal Vessels Assessment System. The retinal vessels assessment system includes: (i) an intravital microscope focused on the bulbar conjunctival vessels, which appear as sharp black tubes; (ii) a charge-coupled device video camera for on-screen videorecording and visualization of the bulbar conjunctival vessels; and (iii) a fiber-optics light source focused on the vessels of the bulbar conjunctiva for illumination [56]. The well-resolved frames of video sequences are selected and captured, and are then used to identify morphometric microvascular abnormalities. With the help of customized or public-domain imaging software, researchers can quantitatively measure vascular parameters from retinal photographs.

Notably, software named Singapore I Vessel Assessment improved the post-processing of retinal photographs.

Singapore I Vessel Assessment can automatically identify the vessel type and optic disc and calculate retinal vascular parameters. The specified measurement area is standardized and defined with reference to the center of the optic disc, and the visible vessels coursing through this area can be measured. According to the revised Knudtson-Parr-Hubbard formula, the retinal arteriolar and venular calibers can be estimated as the equivalences to the central retinal artery and vein, respectively. The characteristics of the retinal vessels assessment system in microvascular perfusion imaging are summarized in Tables 1,2.

Smith *et al*. [56] used the retinal vessels assessment system in a real-time non-invasive *in vivo* study of vasculopathy and hemorheological perturbations in AD subjects. They found that the severity indices (SI) of conjunctival microcirculation and whole blood viscosity were significantly higher in AD subjects than in controls, with the SI being computed based on the presence of microvascular abnormalities commonly found in vascular disease. In addition, there is a strong correlation between SI and whole-blood viscosity in AD [56]. Williams *et al*. [37] evaluated retinal microvascular parameters in cognitively normal controls and AD patients. They demonstrated that AD patients had significantly lower arteriolar and venular fractal dimensions but less tortuous retinal arterioles. Multivariate logistic regression revealed that AD patients were more susceptible to having lower venular fractal dimension and lower arteriolar tortuosity after adjustment [37]. These findings suggest that patients with AD have retinal hemorheological abnormalities and vasculopathy may represent similar pathophysiological events within the cerebral microvasculature of patients with AD.

3.5.2 Other Methods

Various methods for peripheral microcirculation testing have contributed to the emerging understanding that microvascular dysfunction may extend beyond the brain, potentially manifesting systemically. These approaches include machine learning applied to functional thermal imaging, laser Doppler flowmetry for skin test response measurement, and second-derivative finger photoplethysmography. These techniques represent different avenues for investigating microcirculatory dysfunction beyond cerebral confines in AD.

Perpetuini *et al*. [57] used functional thermal imaging and machine learning methodologies to examine peripheral microcirculation impairments in individuals with AD, comparing them with age-matched healthy controls during resting states. Their findings highlighted microvascular pattern alterations in early-stage AD pathology, suggesting the integration of functional thermal imaging as a supportive tool for early AD diagnosis. Khalil *et al*. [58] conducted a comparative investigation of peripheral endothelial vascular responses in individuals with early clinically-confirmed AD and controls with normal cognition. Their study revealed an 84% reduction in peripheral endothelial vascular responses among the AD patients. This simple skin test may serve as a diagnostic adjunct for individuals displaying mild cognitive symptoms or early clinical indications of AD. Iwamoto *et al*. [59] used second-derivative finger photoplethysmography to investigate hemodynamic indices in healthy controls and AD individuals with or without severe periventricular lucency. Their research indicated that peripheral impedance exhibited no significant disparity between AD patients and healthy controls.

While peripheral microcirculation testing endeavors to ascertain whether such alterations transcend cerebral confines, the complex relationship between peripheral and cerebral microcirculation remains incompletely elucidated. The multifaceted influence of various factors on peripheral microcirculation poses challenges for isolating AD-specific changes; observed changes may not be direct reflections of cerebral alterations. To foster uniformity and comparability across studies, the establishment of standardized protocols for testing and interpretation is imperative.

4. Directions for Future Research

The assessment of cerebral blood flow in AD using microvascular perfusion imaging technology can reflect microvascular pathogenesis and clinical diagnosis. However, there is yet to be a definitive answer to which imaging method is the best. Multiple factors play influential roles in the choice of imaging modalities for evaluating cerebral blood flow, such as the feasibility and reliability of the technology, imaging speed, financial cost, and patient comfort. There are several promising future research directions that could further enhance our understanding of microvascular perfusion alterations in AD and their clinical implications: (1) investigating the underlying mechanisms that drive the biphasic response of CBF in AD could shed light on disease progression; (2) conducting longitudinal studies that track microvascular perfusion changes over time in individual AD patients would help discern the trajectory of CBF alterations, and their association with cognitive decline and disease progression; and (3) integrating CBF imaging data with other AD biomarkers, such as amyloid and tau protein levels, could offer a comprehensive view of disease progression, which might enhance diagnostic accuracy and aid in understanding the relationship between microvascular perfusion alterations and neurodegenerative processes.

5. Conclusion

The studies reviewed above suggest that hyperperfusion and hypoperfusion are both exhibited in the development and progression of AD, while hypoperfusion leads to structural changes in brain areas that are associated with cognitive impairments and dementia. Inconsistencies across studies may be attributable to methodological differences, such as CBF measurement methods, patient demographics (such as age and vascular risk burden),

diagnostic criteria for AD, disease severity, or misclassification of MCI and AD. Furthermore, there are differences in how CBF correlates with the local metabolic environment during different phases of disease development and progression, and these may explain the biphasic response. The capillary dysfunction hypothesis of AD developed by Ostergaard may offer a possible explanation for this paradox [60]. Specifically, increases in the heterogeneity of capillary blood flow patterns occur in early AD and require increases in CBF to maintain adequate brain oxygenation, while progressive increases in heterogeneity with disease progression result in low tissue oxygen that involves suppression of CBF to maintain tissue metabolism. Thus, both hyperperfusion and hypoperfusion are found in the CBF biphasic response. However, the compensatory mechanisms for cerebral hypoperfusion warrant future human studies.

Abbreviations

AD, Alzheimer's disease; Aβ, amyloid beta; MRI, magnetic resonance imaging; CT, computed tomography; DSC, dynamic susceptibility contrast; ASL, arterial spin labeling; CTPI, cerebral CT perfusion imaging; OCT, optical coherence tomography; CBF, cerebral blood flow.

Author Contributions

Conception and design, supervision, investigation, methodology, drafting, reviewing and editing, funding acquisition: YS; investigation, methodology, reviewing and editing: HX, ZZ. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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