Original Research Article

Cerebrovascular Function in Aging and Dementia: A Systematic Review of Transcranial Doppler Studies

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Key Words

Aging · Dementia · Alzheimer's disease · Transcranial Doppler studies · Cerebrovascular function

Abstract

Background/Aim: The contribution of cerebrovascular dysfunction to the manifestation of dementia and cognitive decline in late life is gaining increased attention. We aimed to systematically review evidence for associations between dementia or aging and cerebrovascular function as measured using transcranial Doppler (TCD) examination. ***Methods:*** A total of 1,172 articles were retrieved from PsychInfo and PubMed searches, and 34 relevant articles were identified using a variety of TCD methods. ***Results:*** The pulsatility index (vessel resistance), spontaneous emboli and cerebrovascular reactivity to hyper-/hypocapnia appeared good discriminators of dementia. Aging was associated with a slowing in blood flow velocity. ***Conclusion:*** TCD ultrasonography is inexpensive, portable and well tolerated by aged and demented subjects. The technique stands to make a valuable contribution to the knowledge regarding the underlying functional biology of age-related cognitive change and dementia.

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Introduction

Aging and dementia are associated with changes in cerebrovascular structure and function which contribute to associated cognitive and functional declines [1–3]. Recent autopsy studies have stressed the important role of vascular pathologies in the manifestation of late-

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onset dementia [4–6]. Further, systematic reviews and meta-analyses have highlighted the importance of vascular risk factors (e.g. hypertension and stroke) on dementia onset and progression [7–10]. Research investigating functional cerebrovascular contributions to cognitive performance in age-related decline and dementias such as Alzheimer's disease (AD) and vascular dementia (VaD) have generally reported reduced cerebral perfusion [11, 12]. These studies have employed techniques such as functional magnetic resonance imaging, positron emission tomography or single-photon emission computed tomography. However, these techniques are expensive, and there are feasibility issues which are particularly problematic for older populations, including the need for individuals to be sufficiently mobile to attend a research facility, lie still for a prolonged duration and have no metal implants.

Transcranial Doppler (TCD) ultrasonography is a non-invasive, inexpensive and portable technique with high temporal resolution, allowing continuous and bilateral recording of cerebral blood flow velocity through the major arteries (e.g. medial, anterior, posterior and basilar). Measurements can be taken at rest, during hypercapnia or hypocapnia (to assess cerebrovascular reactivity), or during cognitive tasks. TCD data collected during cognitive operations is commonly referred to as functional TCD (fTCD) and is the assessment of blood flow velocity change in response to a specific cognitive stimulus or mental operation. Resultant graphs displaying blood flow velocity versus time are known as evoked-flows and are generated in a similar manner to event-related potentials (ERPs) derived from electroencephalogram data where multiple trials are averaged relative to the presentation of cognitive stimuli [13]. Pioneered in the 1980s [14], there has been a recent resurgence in the use of the TCD technology, particularly in the aging and dementia fields.

Haemodynamic abnormalities may be critical markers of dementia and cognitive decline in elderly individuals. Chronic cerebral hypoperfusion could affect cellular health within the brain and the development of neurodegenerative pathologies [15, 16]. TCD methods have much to provide the assessment of functional cerebrovascular contributions to cognitive impairment in dementia and aging and may help in the differentiation of dementia from normal aging and between the subtypes such as AD and VaD. This paper aims to systematically review previous research assessing dementia [including mild cognitive impairment (MCI), an intermediate state between normal aging and dementia] and aging using TCD techniques, and, in doing so, summarise key protocols, metrics and consistent findings to point to areas of future research.

Search Strategy and Selection Criteria

The PubMed and PsychInfo databases were searched on March 19, 2012, using the search terms: ('transcranial doppler') AND (dementia OR age OR ageing OR aging OR Alzheim* OR 'mild cognitive impairment'). A total of 1,172 articles were retrieved. Titles and abstracts were read by at least two of the authors. Articles were retained if they collected TCD data at rest, hyper-/hypocapnia or during a cognitive task from any cerebral artery accessible via TCD [the anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA) or basilar artery] and assessed dementia (differences between subtypes or with normal aging; or changes associated with clinical progression) or aging in those over 50 years of age. Articles were included if they assessed general late-onset dementia (i.e. without subtype classification) or AD and VaD (and its historical counterpart multi-infarct dementia) subtypes. Articles were excluded if they were not written in English or were case reports. Articles with TCD as an outcome in a clinical trial of a pharmaceutical compound were also excluded unless they presented baseline (i.e. prior to drug administration schedule) comparison data (e.g. with a healthy control or another subtype of dementia).

Fig. 1. Illustration of two cardiac cycles as measured via TCD. Key resting TCD metrics and the calculation of derivatives are shown. MVCC = Mean flow velocity over one cardiac cycle; RI = resistance index; SV = systolic velocity; DV = diastolic velocity; PI = pulsatility index.
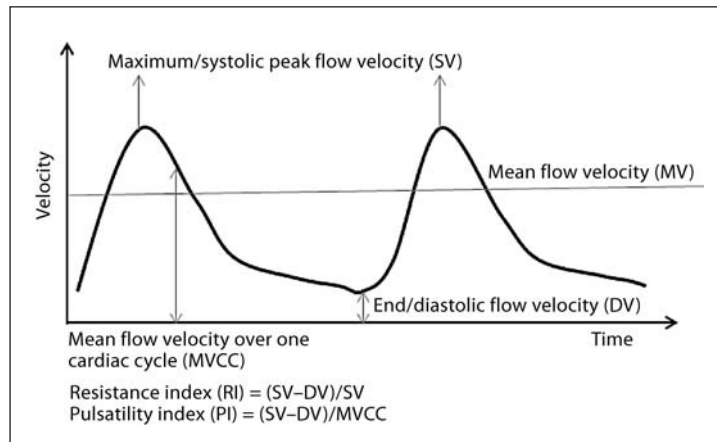
Data Extraction

Details from each included study are summarised in table 1 and include: study sample (including sex, age and diagnoses), TCD protocol, vessel(s) investigated, TCD metrics analysed and key findings.

The calculation of common resting TCD metrics employed are summarised in figure 1, including systolic peak flow velocity, end diastolic velocity, mean flow velocity (MV) and the pulsatility index and resistance index. Cerebrovascular reactivity to hypocapnia (reduced CO_2 in blood) or hypercapnia (increased CO_2 in blood) was calculated as the difference between mean flow velocity during hypo-/hypercapnia and resting mean flow velocity, divided by resting mean flow velocity [i.e. (MV during capnia – resting MV)/resting MV]. The periods of time where resting or hypo-/hypercapnia mean flow velocities were measured varied between studies. The breath-holding index (BHI) was also commonly used to assess velocity changes in response to hypercapnia which was calculated as the difference between mean flow velocity at the end of a breath hold (usually at least 30 s) and resting mean flow velocity, divided by resting mean flow velocity [i.e. (MV at end of breath hold – resting MV)/resting MV].

Results

Thirty-four articles were selected for review: 29 assessed TCD measures during rest, 13 during hyper-/hypocapnia and 4 employed fTCD (cognitive) techniques (some articles presented multiple assessments). The vast majority of articles assessed differences between demented and non-demented groups rather than age-related changes (over 50 years). There was only one population-based sample used, the Rotterdam Study [15, 17], which comprised over 1,700 individuals. The remaining studies employed clinic or convenience recruited samples. All studies are summarised in table 1.

Resting TCD Measures
A number of TCD metrics were employed to assess cerebral blood flow at rest including mean flow velocity, systolic velocity, diastolic velocity, the pulsatility index and other resistance measures, and the flow asymmetry index (i.e. the difference between right and left arteries at rest). The majority of papers assessed the MCA or PCA. Other vessels investigated

Table 1. Summary of the articles using resting, cerebrovascular reactivity and functional/cognitive TCD measures to investigate aging (over 50 years) or dementia

Article	Participants	Vessel	TCD protocol (resting/ vasoreactivity/ fTCD)	Metrics	Major findings
Purandare et al. [47], 2012	Male and female; n = 144: 84 with AD and 60 with VaD (mean age 75 ± 7 years); some drop-outs over 24 months, with n = 99 in final testing wave	Bilateral MCA	Resting	Presence of spontaneous emboli	Spontaneous cerebral emboli detected in 43% of AD and 45% of VaD cases; presence of emboli was significantly associated with cognitive and functional decline over 2 years, as well as a larger increase in psychiatric symptoms
Anzola et al. [39], 2011	Male and female; n = 15 with MCI (mean age 72 ± 9 years) and n = 28 controls (mean age 67 ± 10 years)	Right MCA	Resting	MV	No differences between groups
			CVR: room air + 7% CO_2 gas	MV	No differences between groups
Silvestrini et al. [48], 2011	Male and female; n = 41 with AD + severe right carotid artery stenosis (median age 71 years, range 65–78) and n = 57 with AD + severe left carotid artery stenosis (median age 70 years, range 65–78); TCD not collected in control group (with AD and no stenosis)	Ipsilateral to stenosis (vessel not reported)	CVR: breath hold	BHI	Those with stenosis were more likely to develop severe dementia over 12 months, and this was related to BHI ipsilateral to stenosis
Roher et al. [29], 2011	Male and female; n = 42 with AD (mean age 80 ± 7 years), n = 11 with MCI (mean age 80 ± 5 years) and n = 50 controls (mean age 79 ± 6 years)	Bilateral segments (8) of circle of Willis	Resting	PI and MV	Generally, PI higher and MV lower in AD as compared to control group; no significant differences involving MCI group unless restricting to only amnestic MCI
Kong et al. [30], 2011	Male and female; n = 30 with AD (mean age 71 ± 2 years), n = 34 with VaD (mean age 72 ± 3 years) and n = 40 controls (mean age 71 ± 3 years)	Bilateral MCA	Resting	MV	Decreased MV in demented (AD and VaD) groups as compared to controls; no differences between dementia subtypes
Gucuyener et al. [35], 2010	Male and female; n = 13 with 'pseudodementia'/severe depression (mean age 65 ± 6 years), n = 11 with AD (mean age 66 ± 6 years) and n = 10 controls (mean age 64 ± 6 years)	PCA	Resting	MV	MV significantly lower in AD and pseudodementia group as compared to controls
			fTCD: visual stimulation with shapes, with target image needing to be identified	Relative change in MV [(stimulation – rest)/rest]	Relative MV only lower in AD group as compared to controls
Gur et al. [21], 2010	Male and female; n = 37 with first-ever acute ischemic stroke within 72 h of onset: n = 20 did not progress to dementia 3–6 months after stroke (mean age 70 ± 7 years) and n = 17 did progress to dementia 3–6 months after stroke (mean age 66 ± 5 years)	Bilateral MCA	Resting	MV	No significant differences in MV between demented and non-demented groups
			CVR: following acetazolamide injection	CVR	No significant differences in CVR between demented and non-demented groups
van Beek et al. [22], 2010	Male and female; n = 21 with AD (mean age 73 ± 6 years) and n = 20 controls (mean age 75 ± 3 years)	Bilateral MCA	Resting; pre-cholinesterase inhibitor use and 10 weeks after treatment	MV and resistance (mean BP/MV)	Cerebrovascular resistance increased in AD group as compared to controls, unchanged by cholinesterase inhibitor use
van Beek et al. [20], 2010	Male and female; n = 21 with AD (mean age 72 ± 6 years) and n = 20 controls (mean age 75 ± 3 years); several participants were excluded for some measures	Bilateral MCA	Resting	MV and resistance (mean BP/MV)	No group differences in resting MV; increased cerebrovascular resistance in AD
Lee et al. [27], 2007	Male and female; n = 17 with AD (mean age 67 ± 6 years) and n = 17 control (mean age 67 ± 6 years)	Bilateral MCA	Resting	MV and PI	No group differences
			CVR: via rebreathing	MV	CVR significantly decreased in AD group as compared to controls
Likitjaroen et al. [37], 2009	Male and female; n = 9 diagnosed with AD (median age 75 years, range 68–83) and n = 9 with VaD (median age 66 years, range 52–86)	Unilateral MCA	Resting	Baseline end DV, mid SV and peak SV before and after compound	No significant differences between AD and VaD groups
			CVR: following acetazolamide injection	As above	No significant differences between AD and VaD groups
Menendez-Gonzalez et al. [49], 2009	Male and female; n = 23 with AD and n = 25 controls with age around 74 years	Bilateral MCA and PCA	CVR: breath hold	BHI	AD group had significantly lower BHI than controls for all vessels

Table 1 (continued)

Article	Participants	Vessel	TCD protocol (resting/ vasoreactivity/ fTCD)	Metrics	Major findings
Stefani et al. [31], 2009	Male and female; n = 40 diagnosed with AD (mean age 71 ± 6 years) and n = 40 controls (mean age 69 ± 8 years)	Bilateral MCA	Resting	MV and PI	MV significantly lower in AD group as compared to controls; PI displayed opposite effect (higher in AD group)
			CVR: breath hold	BHI	BHI significantly lower in AD group as compared to controls; BHI correlated with cognition (MMSE); no differences between AD without white matter abnormalities, as compared to AD with white matter abnormalities
Claassen et al. [40], 2009	Male and female; n = 9 with mild AD (mean age 68 ± 6 years) and n = 8 controls (mean age 65 ± 4 years)	Unilateral MCA	Resting	MV and RI	Resting velocity was lower in AD group but failed to reach conventional significance levels in small sample, not explained by brain atrophy; RI was higher in AD group
Purandare et al. [42], 2008, a review of relevant articles using the same cohort [43, 44, 46]	Male and female; n = 85 with AD (mean age 75 ± 8 years), n = 85 with VaD (mean age 78 ± 6 years) and n = 150 matched non-demented controls (some drop-outs over follow-up and recruitment of new patients)	Bilateral or unilateral MCA	Resting	Presence of spontaneous emboli	Spontaneous cerebral emboli significantly associated with dementia, adjusting for vascular risk factors; detected in 40% of AD and 37% of VaD cases, compared to 12% in controls; presence of emboli associated with depression in dementia; presence of emboli associated with worse cognitive decline in controls over 6 months but not over 2.5 years
Vicenzini et al. [32], 2007	Male and female; n = 118 with dementia (60 with AD (mean age 69 ± 3 years) and 58 VaD (mean age 71 ± 2 years)) and n = 62 matched controls (mean age 69 ± 3 years)	Bilateral MCA	Resting	MV and PI	Those with dementia (AD or VaD) showed lower flow velocities and higher PIs
			CVR: CO_2 mixture inhalation (6%) for hypercapnia followed by hyperventilation for hypocapnia	MV	Those with dementia (AD or VaD) showed lower total vasomotor ranges (i.e. taking into account hypercapnia and hypocapnia) as compared to those without dementia
Roher et al. [23], 2006	Male and female; n = 21 with AD (mean age 79 ± 6 years) and n = 26 controls (mean age 81 ± 6 years)	Bilateral segments (8) of circle of Willis; resting	Resting	MV and PI	AD group had higher PIs (6/16 segments), most notably for anterior segments
Rosengarten et al. [53], 2006	Male and female; n = 8 with AD (mean age 74 ± 4 years) and n = 16 controls (mean age 69 ± 7 years)	Bilateral PCA and MCA	fTCD: visual perception	SV at rest, gain, attenuation (stiffness of vascular system), natural frequency and rate time	AD group displayed a significantly reduced response to visual task as compared to controls
Silvestrini et al. [51], 2006	Male and female; n = 53 with AD (mean age 70 ± 6 years)	Bilateral MC	CVR: breath hold	BHI	BHI significantly predicted cognitive decline over a 12-month period – the lower the BHI the worse the prognosis
Asil and Uzuner [26], 2005	Male and female; n = 15 with AD (mean age 70 years), n = 12 with VaD (mean age 58 years) and n = 9 healthy controls (mean age 58 years)	Bilateral PCA	Resting	MV	No significant differences in MV between groups
			fTCD: visual perception	Relative increase from baseline to activation in MV for each task	Response similar between healthy controls and those with AD, but attenuated in those with VaD
Ruitenberg et al. [15], 2005	Male and female; n = 1,730 (mean age 71 ± 6 years), of whom n = 14 had dementia (13 with AD, 1 with VaD); population-based sample (Rotterdam Study)	Bilateral MCA	Resting	MV	Those with dementia had lower MV
			CVR: CO_2 mixture (5%)	CVR	CVR did not differ between demented and non-demented persons; in non-demented group, lower cerebral blood flow velocity was associated with (1) preceding cognitive impairment and (2) smaller hippocampal and amygdala volumes; lower CVR was associated with preceding cognitive decline
Purandare et al. [45], 2005	Male and female; n = 24 with AD and n = 17 with VaD (overall mean age 72 ± 7 years), n = 16 controls (mean age 72 ± 6)	Bilateral MCA	Resting	Presence of spontaneous emboli	Emboli detected in 17% of AD cases, 41% of VaD cases and in 7% of controls (1/16); presence of emboli was significantly associated with VaD
Bakker et al. [17], 2004	Male and female; n = 1,720 (mean age 71 ± 6 years); population-based sample (Rotterdam Study)	Bilateral MCA	Resting	DV, SV and PI	MV, DV and SV declined significantly with age, while PI increased significantly with age
			CVR: CO_2 mixture (5%)	MV	CVR significantly decreased with age

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Table 1 (continued)

Article	Participants	Vessel	TCD protocol (resting/ vasoreactivity/ fTCD)	Metrics	Major findings
Matteis et al. [52], 1998	Male and female; n = 10 with AD (mean age 62 ± 9 years), n = 10 with multi-infarct dementia (mean age 68 ± 8 years) and n = 20 controls (mean age 63 ± 12 years)	MCA	CVR: breath hold	BHI	Significantly lower in multi-infarct group compared to AD and controls
			fTCD: verbal and visual discrimination	Relative increase from baseline to activation in MV for each task	No group differences in average velocity responses; however, only the control group showed lateralised responses (left for verbal, right for visual)
Sattel et al. [18], 1996	Male and female; n = 46 with AD (median age 80 years, range 67–92) and n = 44 with multi-infarct dementia (median age 79 years, range 69–90)	Bilateral MCA, PCA and ACA, and basilar	Resting	MV and PI	PI of all arteries was higher in the multi-infarct group as compared to AD; age positively correlated with PI (of basilar)
Franceschi et al. [33], 1995	Male and female; n = 17 with AD (mean age 66 ± 7 years) and n = 20 healthy controls (mean age 63 ± 8 years)	Bilateral MCA	Resting	MV and flow asymmetry index	Velocities slower and displayed more asymmetry in AD group as compared to controls
Biedert et al. [24], 1995	Male and female; n = 23 with AD, n = 19 with multi-infarct dementia and n = 36 controls, all between 60 and 69 years	Bilateral MCA and basilar	Resting	MV and PI	Multi-infarct dementia group displayed higher PIs than AD group (no significant differences with controls)
Heun et al. [19], 1994	Male and female; n = 24 with AD and no evidence of cardio-/cerebrovascular disease (mean age 75 ± 10 years)	Bilateral ACA, MCA and PCA	Resting	Resting MV, SV, DV and RI	Left MCA SV and DV correlated negatively with age; left MCA SV, DV and MV correlated positively with MMSE score (along with some other cognitive measures, but associations not as consistent)
Biedert et al. [28], 1993	Male and female; n = 32 with dementia (23 with AD and 19 with multi-infarct dementia) and n = 36 controls, all between 60 and 69 years	Bilateral MCA and basilar	Resting	MV, SV and PI	MCA and basilar PI increased in multi-infarct dementia group as compared to AD group (no significant differences from controls); no significant group differences for MV and SV
Ries et al. [38], 1993	Male and female; n = 17 with multi-infarct dementia (mean age 69 ± 9 years), n = 24 with AD (mean age 66 ± 9 years) and n = 64 controls (mean age 61 ± 11 years)	Bilateral MCA (in 6 individuals, this was unilateral)	Resting	SV, DV and MV	MV and DV lower in multi-infarct dementia group compared to other groups
Caamano et al. [34], 1993	Male and female; n = 12 with AD (mean age 64 ± 7 years), n = 12 with multi-infarct dementia (mean age 57 ± 8 years) and n = 12 controls (mean age 57 ± 8 years)	Bilateral MCA and basilar	Resting	MV, SV, DV and PI	Demented groups displayed reduced bilateral MCA MV, SV and DV; the multi-infarct group also displayed increased PIs in MCAs; results from the basilar were weak; no significant differences between dementia groups
Bressi et al. [41], 1992	Male and female; n = 23 with AD (mean age 64 ± 9 years) and n = 10 controls (mean age 62 ± 7 years)	Bilateral ACA, MCA and PCA	Resting	SV, MV, DV, PI and laterality index	Velocities (MV, SV and DV) were slower in the MCA in AD group as compared to controls; no group differences for ACA or PCA, or for PI; MCA velocities correlated with some neuropsychological test scores (one significant for ACA)
Provinciali et al. [36], 1990	Male and female; n = 20 with AD (mean age 68 ± 5 years), n = 20 with multi-infarct dementia (mean age 65 ± 7 years) and n = 25 controls	Bilateral MCA	Resting	PI and MV	PIs higher in both dementia groups; MV slower in multi-infarct group as compared to controls
			CVR: hyperventilation/ hypocapnia, breath hold/ hypercapnia and close-circuit rebreathing	MV (highest % increase in MV between rest and hypercapnia/ hypocapnia)	Hypocapnia-induced velocity decrease lower in demented groups as compared to controls; hypercapnia-included changes in velocity only lower in multi-infarct group as compared to controls
Foerstl et al. [25], 1989	Male and female; n = 18 with dementia, of whom 9 with AD and 9 with multi-infarct dementia; n = 14 controls	MCA and basilar (unclear if uni- or bilateral)	Resting	PI and MV	PI increased in multi-infarct dementia group as compared to controls

Clinic or convenience samples unless otherwise stated.

BP = Blood pressure; CVR = cerebrovascular reactivity; DV = diastolic velocity; MMSE = Mini-Mental State Examination; PI = pulsatility index; RI = resistance index; SV = systolic velocity; MV = mean flow velocity.

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included the ACA and the basilar artery. Most papers assessed differences between those with and without dementia or dementia progression. However, some age associations in late life were reported: the pulsatility index increased with age [17, 18], while mean, diastolic and systolic flow velocities decreased with age in AD [19] and in the general population [17].

Most studies reported no significant differences in resting mean flow velocities between demented and control groups [20–28], or, lower mean flow velocities in demented groups including AD [29–35], VaD or multi-infarct dementia [30, 32, 34, 36], regardless of subtype [15]. Mean flow velocity measures in AD and VaD groups appeared similar [18, 24, 30, 32, 34, 36, 37], although this was not always the case. Ries et al. [38] reported that the multi-infarct dementia group displayed slower mean and diastolic flow velocities compared to both control and AD groups. Few studies reported flow velocities other than the mean; however, Caamaño et al. [34] reported that individuals with AD and multi-infarct dementia displayed reduced systolic and diastolic (as well as mean) flow velocities compared to healthy controls. The two articles which examined a MCI group assessed mean flow velocity and reported no differences between the MCI group and the control group [29, 39], unless restricting to amnestic MCI [29]. One study reported that mean flow velocities were more asymmetric in an AD group as compared to healthy controls [33]. In non-demented controls, lower mean flow velocities were associated with preceding cognitive impairment and smaller hippocampal and amygdala volumes [15].

The pulsatility index was the most commonly employed measure of vessel resistance and was found to be increased in AD [23, 29, 31, 32, 36, 40] and VaD or multi-infarct dementia patients [25, 32, 36] as compared to healthy controls, although this was not the case in three papers [24, 28, 41]. There were many reports that those with VaD or multi-infarct dementia displayed higher pulsatility indexes than those with AD [18, 24, 28, 34], although there were three reports of non-significant differences between subtypes [25, 32, 36]. There appeared to be no significant difference in the pulsatility index between a MCI group and controls [29]. Employing a different calculation of resistance, van Beek et al. [20] reported increased cerebrovascular resistance in an AD group.

A series of papers by Purandare and colleagues [42–47] assessed the significance of spontaneous emboli as detected during resting TCD to dementia and its progression and symptoms. In an article published in 2005, they reported the presence of emboli to be associated with VaD [45]. In a summary of a sequence of studies using the same large cohort [reviewed in 42], the group went on to report emboli to be associated with both VaD (37% of cases) and AD (40% of cases), as compared to controls (12% of cases). Further, they showed that the presence of emboli was associated with depression symptomatology in dementia and worse cognitive decline over 6 months in controls (i.e. non-demented cases at baseline). Recently, the group has reported emboli to be associated with more rapid cognitive and functional decline in AD and VaD, as well as with an increased number of psychiatric symptoms over a 24-month period [47].

Cerebrovascular Reactivity TCD Measures (i.e. during Hypo- or Hypercapnia)

The BHI was commonly employed to assess the effects of hypercapnia [31, 48–50], along with the administration of gasses with varying %CO_2 [15, 32, 39] or a pharmaceutical compound [21, 37], and closed-circuit rebreathing [27]. In a large population-based sample, cerebrovascular response to hypercapnia was found to significantly decrease with age [17]. Two papers reported that the BHI was lower in AD patients as compared to healthy controls [31, 49], similar to Lee et al. [27] who employed closed-circuit rebreathing, while another two papers reported the BHI was only lower in a multi-infarct dementia group (not an AD group) as compared to healthy controls [36, 51]. Silvestrini et al. [48] used the BHI to investigate differences between patients with mild/moderate AD with/without carotid stenosis. They re-

ported that those with stenosis were more likely to develop severe dementia over 1 year, and this was related to the BHI ipsilateral to the stenosis. In another paper investigating progression, Silverstrini et al. [50] reported that, in a group diagnosed with AD, lower BHIs were associated with a more rapid cognitive decline.

Vicenzini et al. [32] used a gas mixture (with increased CO_2) to induce hypercapnia, followed by hyperventilation to induce hypocapnia. They reported that the vasomotor range (i.e. taking into account flow velocities during hyper- and hypocapnia) was reduced in AD and VaD patients. Ruitenberg et al. [15] reported no differences in cerebrovascular reactivity using the same protocol between demented (regardless of subtype) and non-demented individuals in a large population-based sample. However, in this case there were only 14 individuals diagnosed with dementia (as compared to 1,730 non-demented subjects). Interestingly, lower cerebrovascular reactivity in the non-demented group was found to be associated with preceding cognitive decline [15]. Anzola et al. [39] reported no differences in cardiovascular response to hypercapnia between MCI and control groups.

Gur et al. [21] and Likitjaroen et al. [37] investigated cerebrovascular reactivity via the administration of acetazolamide, which indirectly induces hypercapnia. Likitjaroen et al. [37] reported no significant differences in cerebrovascular reactivity between AD and VaD groups using this compound (there was no healthy control group). Gur et al. [21] reported no significant differences in cerebrovascular reactivity in individuals who did and did not convert to dementia 3–6 months after a first-ever ischaemic stroke.

Cognitive TCD/fTCD Measures

No article was identified using fTCD metrics to investigate changes over the age of 50 years. Four fTCD studies compared dementia subtypes and controls: two found that individuals with AD had an attenuated response to cognitive demand [35, 52], and two found no differences between AD patients and controls [26, 51]. Matteis et al. [51], however, reported that their AD group displayed a reduction in lateralised function, and Asil and Uzuner [26] reported an attenuated response only in their VaD group.

Discussion

This systematic review revealed 34 articles using TCD methods to investigate aging or dementia. This technique appears to be a feasible method of investigating cerebrovascular function during rest, hyper-/hypocapnia and cognition in old and demented individuals. Measures of vessel resistance and the presence of emboli as detected via TCD appeared the best discriminators of dementia from normal aging. There was also evidence for cerebrovascular reactivity to hypo- and hypercapnia.

Measures of vessel resistance during resting TCD, particularly the pulsatility index, were consistently associated with the presence of dementia, both in AD [20, 23, 29, 31, 32, 36, 40] and VaD or multi-infarct dementia [25, 32, 36]. Further, the pulsatility index appeared to discriminate between these dementia subtypes [18, 24, 28, 34]. Subjects with VaD appeared to have the highest pulsatility indexes (associated with high vessel resistance), controls the lowest and AD patients sitting in between. Another consistent discriminator between those with and without dementia was the presence of spontaneous cerebral emboli as detected via TCD, although all findings come from one participant group [42–47].

Cerebrovascular reactivity to hypo- or hypercapnia was also a good discriminator of dementia, using the BHI [31, 49], a gas [32] or closed-circuit rebreathing [27]. Effects may be stronger in VaD [36], similar to pulsatility index findings. Ruitenberg et al. [15] reported cerebrovascular reactivity was a good marker of future cognitive decline in non-demented

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individuals. However, they reported no differences in cerebrovascular reactivity between demented and non-demented groups using gas stimuli. The sample in this study was large and population based, however lacked the necessary power to detect effects as only 14 individuals were reported to have dementia. In contrast to measures of reactivity to hypo- or hypercapnia, the administration of pharmaceutical compounds to directly induce cerebrovascular reactivity was not as successful in the discrimination of dementia from normal aging and in predicting future decline [21, 37], possibly due to their indirect effect and intersubject metabolic differences.

Findings in relation to differentiating demented and non-demented groups using resting flow velocities were not consistent. Resting flow velocities including mean, systolic and diastolic velocities appeared similar [20–25] or lower in demented groups including AD patients [29–35], VaD/multi-infarct dementia patients [30, 32, 34, 36] or general dementia patients [15], as compared to healthy controls. There appeared to be no significant differences in blood flow velocities between dementia subtypes [18, 24, 30, 32, 34, 36, 37]. Resistance, emboli and cerebrovascular reactivity TCD measures appeared better discriminators of dementia. However, this may be due to the selection of non-optimal resting flow measures. For example, Rosengarten et al. [53] along with Rosengarten and Kaps [54] reported that systolic velocity is less prone to artefacts and more sensitive to the regulation of blood flow than mean flow velocity.

fTCD metrics showed that individuals with dementia had an attenuated response to cognitive load [26, 35, 52] or a reduction in lateralised function [51] which may reflect compensatory cognitive ability [55, 56]. Interestingly, a study of resting TCD reported that mean flow velocities were more asymmetric in an AD group as compared to controls [33] – opposite to that reported in the fTCD paper [51]. Future studies are needed to confirm these findings. There were no identified articles that assessed fTCD changes after 50 years of age.

Abnormalities in TCD measures in demented groups could reflect a number of pathological processes such as cerebral amyloid angiopathy [6, 49], arteriolosclerosis or endothelial dysfunction, particularly within the microvascular system [1]. Attenuations in the responsiveness of the cerebrovascular system during cognitive tasks in old and demented subjects may also be a function of surrounding neurons and astrocytes (not signalling for sufficient supply). This abnormal cerebral blood flow may be a cause or consequence of age- and dementia-related neuropathology such as cerebral atrophy. For example, it could simply be that reduced blood flow velocities represent the reduced metabolism of an atrophied brain. Alternatively, reduced blood flow velocities and thus flow may directly lead to cellular dysfunction and death in vulnerable areas such as the hippocampus [15, 57]. Ruitenberg et al. [15] found that there was a negative association between resting mean velocity and hippocampal/amygdala volume, and that cerebrovascular disease did not mediate this relationship. This suggests that cerebral blood flow velocity may be directly associated with the volume of brain structures.

Future studies need to investigate neuronal and vascular systems in parallel to assess neurovascular coupling. It is possible to simultaneously record electrical brain activity (via ERPs) and blood flow velocity (fTCD) to assess coupling [52, 53, 58, 59]. The combined ERP-TCD protocol provides an inexpensive, non-invasive method for measuring neurovascular coupling which has the potential to be significantly developed.

One limitation of the TCD method is the assumption that the artery diameter remains constant and therefore any change in velocity represses a change in flow. It has been reported, however, that the diameter of the MCA does not significantly change during moderate alterations in blood pressure (e.g. around 30 mm Hg) [60, 61] and therefore any change in velocity reflects a change in blood volume through the artery. Another potential limitation relates to the structure of the temporal window. With age, the temporal window where the

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TCD ultrasound probe is placed thickens, making recording more difficult. A population-based study reported 25% of participants were lost due to failure to obtain an adequate TCD signal, especially marked in older women [15, 17]. These failure rates should be taken into account when planning TCD-based studies. The technique is, however, well tolerated, portable, does not require participants to remain still and allows metal implants to remain in place, unlike expensive and high-spatial resolution cerebral blood flow imaging techniques such as positron emission tomography and single-photon emission computed tomography. Furthermore, TCD equipment is widespread in clinical and research facilities around the world.

Dementia appears to be associated with increased vessel resistance, the presence of spontaneous emboli and a reduced cerebrovascular response to increased/decreased environmental CO_2 using TCD methods. Blood flow velocities appear to decrease with age in late life. These patterns of TCD findings correspond to known structural vascular changes [16, 62]. TCD techniques stand to make a valuable contribution to the understanding of underlying cerebrovascular contributions to age-related cognitive impairment and dementia. Further, TCD measures may assist in the development of novel therapeutic strategies addressing cerebral vasoreactivity or may be reliable methods to differentiate between dementia subtypes or predict clinical progression of cognitive decline [15, 48, 50].

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